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Md. Shahidul Islam

Thrombosis and Embolism: from Research to Clinical Practice

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Editor

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Volume 1

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Preface

This book contains essential background information to cutting-edge research and state-of-the-art treatment options for the prevention, diagnosis, and treatment of thromboembolic disorders in different patient categories.

I thought of writing this book because I have been dealing with these problems in my every day clinical practice since many years during which period I have struggled hard to keep me updated and have watched the remarkable progresses made in these areas. I am a specialist in internal medicine, and my special interest in thromboembolism persisted over the years, during which I enjoyed working together with surgeons, orthopedicians, obstetricians, gynecologists, oncologists, cardiologists, nephrologists, and neurologists, in making crucial decisions in clinically challenging situations. The thought for a book on thromboembolism started to crystallize during this process.

The main purpose of this book is to compile a wide range of relevant information in one place. The target audience of this book is broad, from beginners to the experts, from scientists engaged in fundamental research to clinicians of essentially all medical sub-specialties. Every reader will probably not need to read every chapter of this book. I suggest that you start with the chapter that feels most relevant for you depending on what you are primarily interested in.

Thromboembolism is a subject close to my heart. I am not an expert, but I benefitted hugely from my interactions with local and international experts to whom I remain grateful for ever. Working on this book enriched me further, and I am better prepared to use the newly acquired knowledge in real life. It took almost three years to complete this book; it was hard work, but I enjoyed it. In the end, I am happy to see that the book contains substantial amount of old and new knowledge, critical thoughts, and in-depth analysis contributed by many authors with special interests for specific topics. There are many areas of controversies and important pieces of evidence are missing, but we still have to make important decision in our everyday clinical practice. I hope that the readers will benefit from the book. It is, however, no substitute for other sources of knowledge that the readers are likely to benefit from. In particular, it is important that clinicians follow the local and international guidelines and recommendations issued by different societies, in their clinical practice.

I am extremely grateful to all the authors who, in spite of their busy schedules, contributed chapters to this book, and to the referees who helped improve the chapters. I am grateful to Karolinska Institutet, my Alma mater, for providing an excellent platform for my academic activities, and to the Uppsala University Hospital (Akademiska Sjukhuset) for enriching me through real-life clinical challenges. I am grateful to Melania Ruiz of Springer, my long-term collaborator for making this and several previous publications possible. I thank Marleen Moore of Springer, for excellent practical helps for taking the book project to a completion.

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The Prevention of Venous Thromboembolism in Surgical Patients

Vivak Hansrani, Mustafa Khanbhai, and Charles McCollum

Abstract

Patients undergoing surgery are at an increased risk of VTE. Since the early 1990s the prevention of VTE has been dominated by the administration of low-molecular weight heparin during admission. New oral anticoagulants have been extensively researched and have increased in popularity. This chapter reviews why surgical patients are at increased risk of VTE and summaries both the pharmacological and mechanical methods of prophylaxis available.

Keywords

Deep vein thrombosis • Pulmonary embolus • Venous thromboembolism • Anticoagulation • Prevention

1 Introduction

Venous thromboembolism (VTE) is the formation of a blood clot (thrombus) in a vein that may dislodge from its origin and travel (embolus). The thrombus commonly originates in the deep veins of the leg (deep vein thrombosis, DVT) and can travel into the pulmonary circulation causing a pulmonary embolus (PE). Although often asymptomatic DVT can present with acute leg pain, swelling and erythema. Around 30 % of patients with DVT will go on to develop post-thrombotic syndrome, which is characterised by chronic lower limb swelling, discolouration, varicose veins and intractable venous ulcers (Prandoni et al. 1996). With an acute DVT often being asymptomatic, the first clinical signs of VTE manifest as PE presenting with acute chest pain, dyspnoea, haemoptysis or even death (Agnelli 2004).

VTE is the most common cause of preventable death in hospitalised patients in the United Kingdom (UK), accounting for 25,000–32,000 deaths per annum. This is more deaths than those attributed to breast cancer, AIDS and road traffic accidents combined. It is 25 times more than the number of people who die as a result of (methicillin-resistant

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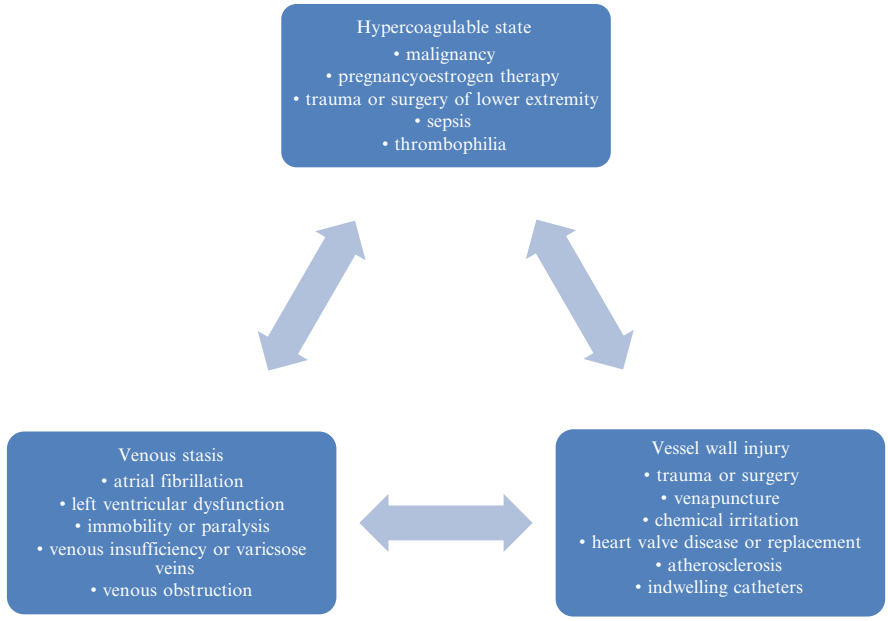

Fig. 1 Virchow's triad (Virchow's triad: thrombosis adviser)

staphylococcus aureus) MRSA infection (National Institute of Clinical Excellence (NICE) 2015). The treatment of VTE and management of its several consequences is associated with considerable cost to the health service; estimated to cost more than £1.4 billion per year in the UK (Sajid et al. 2006, 2012).

The risk of VTE in surgical patients is dependent upon factors inherent on the surgery taking place and individual patient-related risk factors. Rudolf Virchow first described a combination of three factors which increases the risk of thrombosis in the 1800's; he concluded that changes in the blood vessel wall, changes in blood flow and changes in the property of blood increased the risk of thrombosis (Fig. 1) (Sajid et al. 2006). Surgical patients often undergo at least one of these physiological increasing their risk. Immobilisation in hospital to due illness or surgery results in compression of the vessel wall and venous stasis. Decreased fluid intake during illness and excessive bodily fluid loss during surgery can lead to changes in haemo-concentration increasing the risk of thrombosis, and surgery or trauma itself can produce hypobaric hypoxia activating the coagulation system (Sajid et al. 2006; Bendz et al. 2000). Patient-related risk factors are highlighted in Table 1. The National Institute of Health and Care Excellence (NICE) regard patients at high risk of VTE if they have any of the following surgical risk factors:

Table 1 Risk factors for VTE (Rashid et al. 2005)

Over 60 years age
Critical care admission
Dehydration
Known thrombophilias
Obesity (body mass index [BMI] over 30 kg/m2)
One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; renal failure inflammatory conditions)
Personal history or first-degree relative with a history of VTE
Use of hormone replacement therapy
Use of oestrogen-containing contraceptive therapy
Varicose veins with phlebitis
Active cancer or undergoing treatment for cancer

undergoing a surgical procedure with a total anaesthetic and surgical time of more than 90 min (or 60 min if the surgery involves the pelvis or lower limb)

admitted acutely with inflammatory or intra-abdominal condition
expected significant reduction in mobility

More rapid mobilisation and improved perioperative care has reduced the risk of VTE events, but with over 9.5 million hospital admissions for surgical procedures taking place in the UK per annum, thromboprophylaxis methods in place need to be logistically acceptable and clinically effective (NICE Medical Technology Guidance (MTG19) (2014)). Patients admitted for surgery must be assessed for risk of VTE and this evaluation repeated regularly during the hospital stay as the condition of the patient changes. Currently there is no consensus on which thromboprophylaxis regimes should be used in particular patients and inconsistent use of prophylactic measures for VTE has been widely reported (Rashid et al. 2005). Thromboprophylaxis strategies for hospitalised patients includes pharmacological (such as unfractioned and low-molecular weight heparins, dabigatran, rivaroxaban, aspirin or warfarin), and mechanical (graduated compression stockings, intermittent pneumatic compression devices, venous foot pumps and electrical stimulation devices). Although mechanical devices have proven to be effective at reducing the risk of DVT against no intervention, in clinical settings they are often used in adjunction with pharmacological prophylaxis (Dennis et al. 2009; Howard et al. 2004). This chapter attempts to review the evidence for the use of both pharmacological and mechanical methods of VTE prophylaxis in surgical patients.

2 Pharmacological Thromboprophylaxis

Pharmacological agents form the staple method of thromboprophylaxis in high-risk surgical and medical patients. However they carry with them the risk of bleeding. Often major bleeding events are recorded in clinical trials, but some low volume bleeds can also result in major complication such as intracranial or intervertebral canal bleeding which can lead to death or permanent neurological damage. Risk factors for bleeding are shown in Table 2. The National Institute Care Excellence (NICE) formulates evidence-based recommendations on the prevention and management of a wide range of health conditions. NICE recommends the use of either: fondaparinux, low-molecular weight heparin (LMWH) or unfractioned heparin (for patients with renal failure) as the agent of choice for pharmacological prophylaxis. Treatment should be started as soon as possible after risk assessment has been completed and continued until the patient is no longer at increased risk of VTE.

Table 2 Risk factors for bleeding

Active bleeding
Acquired bleeding disorders (such as acute liver failure)
Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international normalized ratio [INR] higher than 2)
Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 h
Lumbar puncture/epidural/spinal anaesthesia within the previous 4 h
Acute stroke
Thrombocytopenia (platelets less than 75×10^9/l)
Uncontrolled hypertension (230/120 mmHg or higher)
Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)

3 Low-Molecular Weight Heparin (LMWH)

Low-molecular weight heparins (LMWH) such as enoxaparin, dalteparin and tinzaparin have been the staple prophylaxis agents in hospitalised patients over the last decade. They have been shown to be effective and safe but in high risk surgery (lower limb orthopaedic and pelvic cancer surgery) there is still a significant risk of VTE.

Compared with no prophylaxis, LMWH has been shown to reduce the risk of VTE in surgical patients by 60 % (Agnelli 2004). The introduction of pharmacological prophylaxis was primarily on the basis of their ability to

reduce the incidence of DVT detected using venography in clinical trials. The clinical relevance was highlighted in a meta-analysis which demonstrated that compared with placebo or no treatment, LMWH significantly reduced clinical PE (n = 5456, RR 0.25 (0.08–0.79) and clinical VTE (n = 4890, RR 0.29 (0.11–0.73) and trended towards a reduction in overall mortality rate. LMWH was favoured over low-dose unfractionated heparin as it was shown to be safer and just as effective (Mismetti et al. 2001).

4 Fondaparinux

Fondaparinux is a factor Xa inhibitor and like LMWH, it is administered once-daily subcutaneously. Fondaparinux has a half-life of 17–21 h and is eliminated by the kidneys contraindicating it in patients with a creatinine clearance less than 30 ml/min. Although there is no specific antidote to fondaparinux, in an emergency scenario recombinant factor VIIa can be used. Several large-scale phase III clinical trials have evaluated fondaparinux in major orthopaedic surgery. Meta-analysis has shown that fondaparinux significantly reduced the incidence of VTE experienced in 182 of 2682 patients (6.8 %) compared with enoxaparin-treated incidence of 371 of 2703 (13.7 %) patients) (Turpie et al. 2002). This beneficial effect was consistent across all types of surgery.

Although there were 2.7 % adjudicated major bleeding episodes in the fondaparinux-treated group compared with 1.7 % in the enoxaparin-treated group (p = 0.008), the incidence of clinically relevant bleeding (leading to death or reoperation or occurring in a critical organ) did not differ between groups (Turpie et al. 2002). In patients undergoing abdominal surgery, fondaparinux was found to be non-inferior to dalteparin, with VTE occurring in 47 of 1027 (4.6 %) patients treated with Fondaparinux compared with 62 of 1021 (6.1 %) patients treated with dalteparin (p = 0.144). The sub-group operated on for cancer had a significantly lower frequency of VTE when treated with fondaparinux (4.7 % compared with 7.7 %) (Agnelli et al. 2005).

5 Low Dose Un-Fractioned Heparin (UFH)

In a meta-analysis of randomised control trials, UFH was shown to significantly reduce the frequency of DVT compared with no prophylaxis or placebo. The use of UFH was however associated with an increased frequency of bleeding events (from 3.9 to 5.9 %) (Collins et al. 1988). Comparing efficacy with LMWH, at least nine meta-analyses and systematic reviews have compared the two regimes in surgical patients which taken together indicate that the two regimens are similar for efficacy and safer for the prevention of VTE. LMWH is more popular due to the ease of administration (Geerts et al. 2001).

6 Dabigatran

Dabigatran etexilate is a direct inhibitor of the enzyme factor IIa (thrombin). Also excreted primarily by the kidneys, dabigatran half-life is around 14–17 h. NICE recommend dabigatran for the primary prevention of VTE in adult patients who have undergone elective total hip or knee replacement surgery (NICE Technology Appraisal Guidance 157 (2008)).

Dabigatran had been investigated in three phase III clinical trials for the prevention of VTE comparing 220 mg daily dosing with enoxaparin; RE-NOVATE, RE-MODEL and the RE-MOBILIZE trial. Pooled together, no significant differences were detected between dibigatran and enoxaparin in any of the end-points analysed when all three trials were combined. Meta-analysis of the RE-MODEL and RE-NOVATE supported the conclusions of the individual trials that dabigatran is non-inferior to enoxaparin 40 mg. Major bleeding event frequency was similar in both Dabigatran and Enoxaparin groups (1.4 % respectively) (Wolowacz et al. 2009; Friedman et al. 2010).

7 Rivaroxaban

Rivaroxaban is an oral direct factor Xa inhibitor, which has also been recommended as an option for the prevention of VTE in adults having elective total hip and knee replacement surgery. Four phase III clinical trials (the RECORD program) have evaluated rivaroxaban in orthopaedic surgery compared with enoxaparin. RECORD 1 showed that rivaroxaban reduced the frequency of end-point DVT, PE or death but did not reduce the frequency of symptomatic VTE (0.3 % versus 0.5 %) (Lassen et al. 2008). RECORD 2 later showed that both total and symptomatic VTE was significantly lower in patients treated with 35 days of rivaroxaban compared with enoxaparin given for 12 days (Friedman et al. 2010). RECORD 3 and 4 demonstrated no significant difference was seen in non-major bleeding episodes with 81 of 1228 (6.6 %) patients treated with rivaroxaban having on-treatment bleeding compared with 68 of 1229 (5.5 %) patients treated with enoxaparin ($p = 0.25$) (Lassen et al. 2008; Turpie et al. 2009).

8 Apixaban

Abixaban is also an oral direct selective factor Xa inhibitor, thereby diminishing the conversion of prothrombin to thrombin. It has a half-life of 9–14 h and is primarily secreted via the gastrointestinal system. The ADVANCE 1 and 2 trials showed that apixaban was non-inferior to enoxaparin 30 mg given twice daily, but superior to enoxaparin 40 mg given once daily (Lassen et al. 2009, 2010a). On-treatment bleeding episodes were significantly lower in patients treated by apixaban. Meta-analysis of the ADVANCE 2 and 3 trials have shown apixaban to be superior to enoxaparin with similar safety profiles (Lassen et al. 2010b; Raskob et al. 2012).

9 Mechanical Thromboprophylaxis

Mechanical compression methods lower the risk of DVT by reducing venous stasis, increasing venous blood velocity, decreasing vein diameter and controlling oedema (Sajid et al. 2006). A recent systematic review determined that mechanical compression reduced the risk of DVT in surgical patients by about two-thirds when used on its own, and by half when added to a pharmacological method. This systematic review also determined that these reductions in VTE risk were similar irrespective of the particular method used (graduated compression stockings or intermittent pneumatic pumps) and were similar in each surgical group studied (Roderick et al. 2005). It is important to note that mechanical devices are the cornerstone of VTE prophylaxis in patients with contraindications to pharmacological agents.

10 Graduated Compression Garments

Of all the mechanical VTE prevention devices available, graduated compression stockings are the most widely used and have been shown to be effective at reducing VTE (Allan et al. 1983; Morris and Woodcock 2004). Graduated pressure is applied from the ankle to the calf level where the pressure exerted at the ankle is greatest and gradually decreases at the calf. The greater the graduated pressure, the greater the reduction in venous pressure from distal to proximal (Horner et al. 1980).

There is much debate regarding the use of thigh length or knee high compression garments. A recent Cochrane review found only three studies which investigated the two garments in 496 patients after surgery. No significant difference in the ability of the two modalities of leg compression to reduce the incidence of DVT was shown. Thigh length stockings present a unique problem that if applied incorrectly can roll down to above the knee creating a tourniquet effect that may lead to venous outflow obstruction from the calf that could increase the risk of DVT formation. Alternative when knee-high stockings roll down towards the ankle the pressure gradient is not reversed and pressure remains greatest at the level of the ankle. Knee high stockings are also reported to be more comfortable therefore increasing compliance (Dennis et al. 2009).

11 Intermittent Pneumatic Compression Devices (IPC)

IPC includes inflatable devices that wrap or are fixed around the lower limb. They can be applied to the calf alone or include the thigh and are inflated at customised pressures and timings. IPC is thought to reduce the risk of venous thrombosis by reducing venous stasis and stimulating the release of intrinsic fibrinolytic factors (Kohro et al. 2005). A large systematic review encompassing 2255 surgical patients demonstrated that IPC as monotherapy produced highly significant (66 %) reduction in DVT (112/1108 (10.1 %) IPC vs. 268/1147 (23.4 %) control ($p < 0.0001$). Foot pumps also appeared to a significant (77 %) reduction in DVT in these trials (Roderick et al. 2005).

12 Electrical Stimulation

Electrical stimulation has been shown to reduce the frequency of DVT in patients after surgery (Browse and Negus 1970; Moloney et al. 1972). Devices such as the Geko device (Fistkind Ltd) can be applied to the fibular head and delivers electrical impulses that stimulate the common peroneal nerve which in turn engages the venous muscle pumps of the lower limb; facilitating the emptying of veins in the lower limb by activating calf-muscle pump function. NICE currently recommends electrical stimulation devices in patients in which all current methods of prophylaxis (pharmacological or mechanical) would be contraindicated (NICE Medical Technology Guidance (MTG19) 2014), such as in patients with peripheral arterial disease.

13 Surgical Specialities and Optimal Duration of VTE Prophylaxis

The recommended VTE prophylaxis measures do not change amongst patients undergoing gastrointestinal, gynaecological, cardiothoracic, neurological and urological surgery. Typically, pharmacological VTE prophylaxis is continued until the patient no longer has significantly reduced mobility (5–7 days). In patients have had major cancer surgery in the abdomen or pelvis, it is recommended that pharmacological VTE prophylaxis should be extended to 28 days postoperatively. In patients with ruptured cranial or spinal vascular malformations, pharmacological VTE prophylaxis should be withheld until they are haemodynamically stable. In these cases mechanical prophylaxis measures would certainly be used where possible.

Patients undergoing orthopaedic surgery of the lower limb are at a particularly high risk of VTE. At admission for elective hip or knee replacement, it is recommended that patients are offered one form of mechanical VTE prophylaxis which is to be continued until the patient's mobility is no longer significantly reduced. Pharmacological prophylaxis should be offered 1–12 h after surgery (providing there are no contraindications) and continued for 28–35 days for hip replacements, and 10–14 days for knee replacements. The pharmacological agents currently recommended for lower limb arthoplasty are either dabigatran, fondaparinux, LMWH, UFH, apixaban or rivaroxaban.

In patients with hip fracture, again mechanical prophylaxis is advised to be worn as soon as possible. If the patient is on a pharmacological agent before surgery, this will need to be stopped either 24 h (if on fondaparinux) or 12 h (if on LMWH) before surgery and restarted 6–12 h after surgery (Venous Thromboembolism: Orthopaedic Surgery 2012). In patients with lower limb plaster casts, pharmacological prophylaxis can be continued until the cast is removed based on an evaluation of the individual risk and benefits.

14 Summary

Surgical patients are at great risk of VTE and surgeons have been central to researching methods of prophylaxis. It is clear that both pharmacological and mechanical methods of prophylaxis are effective at reducing the risk of

DVT and subsequent PE and combining the two methods when not contraindicated is common practice in the UK and abroad. Mechanical prophylaxis can be delivered in a variety of methods and electrical stimulation devices are recommended when graduated compression stockings are contraindicated.

Chemical thromboprophylaxis is strongly recommended in high-risk patients and is still frequently delivered using LMWH as has been the case for almost the last 20 years. Recent advances in new anticoagulants have introduced Fondaparinux, Dabigatran, Rivaroxaban and Apixaban to the markets= which have all been evaluated in large-scale clinical trial programs. The fact that there is no available antidote to dabigatran, rivaroxaban and apixaban is a concern for clinicians. However the redundancy of regular monitoring and availability in an oral form which can be easily extended for out-of-hospital prophylaxis makes them popular choices. These new agents have been extensively tested in orthopaedic surgery and have performed well under strict trial conditions. The few studies in non-orthopaedic surgical specialities have also shown promising results but it will be important to see how they perform in routine clinical settings. More experience is needed in managing patients with decreased renal function and pregnancy with these new agents.

There is a now clear indication for extending the duration of pharmacological prophylaxis to after discharge, in particular in lower limb orthopaedic surgery and those undergoing abdominal or pelvic cancer surgery. Further research is needed to determine the absolute risk of VTE among different groups of hospital patients, and whether the risk can reliably be estimated during the hospital admission and prophylaxis tailored accordingly.

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Thromboembolic Prophylaxis for Morbidly Obese Patients Undergoing Bariatric Surgery

Jaime Ruiz-Tovar and Carolina Llavero

Abstract

Obesity itself is associated with an increased risk of thromboembolic events. Moreover, most bariatric procedures actually are performed by laparoscopic approach, implying an increased intraabdominal pressure during the surgical procedure that may favor the development of thrombus. Therefore, bariatric surgery is considered a high-risk procedure for thromboembolic events. Actual recommendations are to include low molecular weight heparins (LMWH) and compression stockings in the primary prophylaxis of thromboembolic events. Following these measures, a routine screening of thromboembolic complications with imaging tests is not recommended.

Keywords

Obesity • Bariatric surgery • Venous thromboembolism • Prophylaxis • Low molecular weight heparin

1 Introduction

According to the World Health Organization (WHO), there are 1.6 billion overweight and 400 million obese people worldwide. Bariatric surgery has been demonstrated to be the most effective and sustainable method for the regulation of morbid obesity, superior to both pharmaceutical interventions and combinations of diet and lifestyle regimens. Therefore, the number of bariatric procedures performed, mainly in developed countries, is increasing every year [1, 2].

Obesity itself is associated with an increased risk of thromboembolic events. Moreover, most bariatric procedures are actually performed by laparoscopic approach, implying an increased intraabdominal pressure during the surgical procedure that may favor the development of thrombus. Therefore, bariatric surgery is considered a high-risk procedure for thromboembolic events [3, 4].

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2 Morbid Obesity as Risk Factor

It has been determined that obesity is associated with a hypercoagulability status. Morbidly obese patients present increased fibrinogen levels that may reach twofold the normal value. It has been proved that venous circulation flow is slower in the infradiaphragmatic territory and especially in the lower limbs. Both facts, associated with disorders in several coagulation factors, favor the appearance of venous thrombosis, thrombophlebitis, and thromboembolic events, mainly pulmonary thromboembolisms (PE), which are the first cause of mortality in obese patients.

Venous stasis and hypercoagulability improve with weight loss, mostly after bariatric surgery. This improvement is achieved several months after the surgical procedure, when an important weight reduction has been obtained. More than 90 % of patients undergoing any bariatric procedure present a relevant reduction of their hypercoagulability.

PE is also the most frequent cause of mortality in the immediate postoperative course of any kind of surgery in obese patients. Thus, they are considered as high-risk subjects, requiring intense prophylactic measures (mechanical and pharmacological) [5–7].

3 Laparoscopic Bariatric Surgery

Venous thromboembolism is the most common postoperative medical complication after bariatric surgery. The incidence of deep vein thrombosis (DVT) after laparoscopic bariatric surgery is about 3 % and that of pulmonary embolism (PE) is less than 1 %. However, mortality associated with PE is estimated to be between 50 % and 75 %[5, 7]. Venous thrombosis of the portal–mesenteric axis (PSMVT) is considered a rare event after bariatric surgery, but in past years an increased number of case reports of PSMVT after bariatric surgery has been published [8–10].

In laparoscopic abdominal surgery, the increase of intraabdominal pressure by the pneumoperitoneum, the prolonged operation time, and the anti-Trendelenburg position are considered risk factors for venous thromboembolisms. It has been demonstrated that the splanchnic flow is inversely proportional to the pressure of the pneumoperitoneum. Moreover, hypercapnia induces vasoconstriction. Obese patients require higher pneumoperitoneum pressures to obtain an adequate view. It has been also demonstrated that surgical dissection induces the release of procoagulant cytokines. Other causes of venous thromboembolism after bariatric surgery are splenectomy as a surgical complication, intraoperative portal vein lesion, and dehydration, especially after restrictive procedures, when patients hardly drink [11–14].

4 Clinical Manifestations and Diagnosis

Venous thromboembolisms are often a challenging issue for the medical staff. DVT is probably the most easily detected complication associated with venous thromboembolism, as it tends to appear with unilateral pain in the lower limb, associated with gastrocnemic edema and tenderness. DVT alone is not a life-threatening condition, but its main risk is migration of the thrombus and the development of PE. The gold standard method for the diagnosis of DVT is Doppler ultrasonography (US).

PE usually appears with sudden unexplained dyspnea without any relevant features at the physical examination and on X-ray plain films. Laboratory data may show increased levels of D dimers, which present high sensitivity but low specificity for the suspicion of PE. The gold standard test for the diagnosis is a contrast-enhanced thoracic computed tomography (CT) scan showing a filling defect in the pulmonary arteries or their branches.

PSMVT usually present subacutely, occurring between the 3rd and 30th postoperative day. However, chronic PSMVT are usually asymptomatic and unnoticed. Thus, patients can develop liver cirrhosis and their related complications. Between 5 and 15 % of all cases

of PSMTV develop a bowel ischemia, with mortality rates around 40 %. PSMVT symptoms are vague and nonspecific. In fact, 50 % are asymptomatic, especially after chronic thrombosis when collateral veins have been developed. Only abdominal pain seems to be a constant symptom. Contrast-enhanced abdominal CT is the gold standard method for the diagnosis of PSMVT, with an accuracy rate of 90 % [11, 13, 15].

5 Antithromboembolic Prophylaxis (Primary Prophylaxis)

Venous thromboembolisms are life-threatening conditions. Several measures, including prophylactic low molecular weight heparins (LMWH) and compressive stockings, are adopted to reduce their incidence. Up to the present there is no consensus about antithromboembolic prophylaxis for patients undergoing bariatric surgery. There is not even any consensus about the optimal dosage of LMWH. The dosage must be adjusted according to the weight of the patient, implying the need of administration of high preoperative doses. Intra- and postoperative bleeding is one of the main complications of bariatric surgery. Many surgeons fear these complications and administer lower doses of LMWH than that recommended by most groups (Enoxaparin 0.5 mg/kg/day or Bemiparin 5000 UI/day or Dalteparin 50 UI/kg/day or Nadroparin 4100 UI/day) [16–19]. However, other authors report that this dose is insufficient because these patients are at high risk of developing thrombotic events [20–22].

The postoperative prolongation of prophylaxis is also a debated issue as some authors defend that a prolongation of 5–7 days is enough, whereas others report the need for maintaining it during 1 month, considering laparoscopic bariatric surgery as a high-risk procedure performed in high-risk patients [23–25].

In our opinion, a preoperative dose of 0.5 mg/kg/day administered 12 h before surgery and maintained postoperatively for 1 month is an adequate scheme for pharmacological antithromboembolic prophylaxis. We also fear intraoperative bleeding, but at these doses, it is not especially relevant in our experience. However, a postoperative thromboembolic event is a life-threatening condition for us that, once established, could be very difficult to manage. Compression stockings must be maintained during the surgical event and postoperatively until the patient is able to make a proper ambulation [22, 26, 27].

6 Screening for Asymptomatic Venous Thromboembolism (Secondary Prophylaxis)

As has already been mentioned, venous thromboembolisms are asymptomatic in many cases. In DVT and PSMVT it is especially important to achieve an early diagnosis to avoid the development of life-threatening conditions, such as PE or chronic PSMVT and liver cirrhosis. With this aim, our group performed a prospective observational study of 100 consecutive patients undergoing laparoscopic sleeve gastrectomy as a bariatric procedure. DVT and PSMVT were investigated 3 months after surgery with Doppler US and contrast-enhanced abdominal CT scan. The results of this study revealed that 2 % presented unnoticed DVT and 1 % unnoticed PSMVT. All these patients were asymptomatic. According to these results, we concluded that a routine postoperative screening with Doppler US or contrast-enhanced CT seems to be unnecessary [28–30].

7 Summary and Recommendations

1. Morbidly obese patients are high-risk subjects to develop thromboembolic events, because obesity is associated with hypercoagulability status.
2. Venous thromboembolisms are often a challenging issue for the medical staff, as clinical manifestations are often unspecific. A high

degree of suspicion is necessary to achieve an early diagnosis.
3. Primary prophylaxis must include low molecular weight heparins and compressive stockings. The dosage of LMWH must be adjusted according to the weight of the patient.
4. Routine screening for venous thromboembolisms with Doppler US or CT scan is unnecessary.

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The Use of Surgical Care Improvement Projects in Prevention of Venous Thromboembolism

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Abstract

Venous thromboembolism (VTE) is a potentially mortal complication in patients undergoing surgery. Deep venous thrombosis and pulmonary embolism can be seen up to 40 % of patients who have no or inappropriate VTE prophylaxis during perioperative period.

In addition to the preoperative and intraoperative preventive measures, the standardization of postoperative care and follow-up are essential to reduce VTE risk. Modern healthcare prioritizes patient's safety and aims to reduce postoperative morbidity by using standardized protocols. Use of quality improvement projects with well-organized surgical care has an important role to prevent VTE during hospital stay. Present surgical care improvement projects have provided us the opportunity to identify patients who are vulnerable to VTE. Description and introduction of the quality standards for VTE prevention in the educational materials, meetings and at the medical schools will increase the VTE awareness among the health care providers. You are going to find the characteristics of the major surgical quality improvement projects and their relations with VTE in the chapter.

Keywords

World Health Organization (WHO) • The Safe Surgery Saves Lives Study Group • A Perioperative Surgical Safety Checklist (WHO-SSC) • American College of Surgeons • The National Surgical Quality Improvement Program (ACS-NSQIP) • The Surgical Care Improvement Project (SCIP) • The Surgical Patient Safety System (SURPASS) • The NICE (National Institute for Health and Care of Excellence) guideline • Prevention of Venous Thromboembolism

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1 Introduction

Venous thromboembolism (VTE) is a potentially mortal complication in patients undergoing surgery. Deep venous thrombosis (DVT) and pulmonary embolism (PE) can be seen up to 40 % of patients who have no or inappropriate VTE prophylaxis during perioperative period [1]. Thrombosis of the mesenteric and portal venous system may also complicate postoperative course and increase morbidity after surgery [2]. There are patient and disease related features increasing risk of VTE. Cancer, obesity, inflammatory bowel disease, old age, immobility and pelvic surgery are main factors associated with increased risk of VTE [3–7]. Advanced operative techniques and increased clinical experience are the main denominators of reduced perioperative morbidity. Recent reports showed that laparoscopic approach is associated with lower thromboembolic and hemorrhagic complications compared to open surgery [8].

Around 234 million operations are performed in the world annually. Modern healthcare approach prioritizes patient's safety and aims to reduce postoperative morbidity by using standardized protocols [9]. Perioperative mortality rate varies between 0.4 and 0.8 % and major complications may develop in 3–17 % of patients undergoing any type of surgical operation [10, 11]. Quality improvement projects have enabled to apply best practice parameters into clinical practice. As the most common preventable cause of inpatient death [12], VTE prophylaxis has become one of the major denominators of quality indicators [13]. Therefore overall improvement achieved with quality indicators almost always includes VTE related outcomes.

Patient positioning during surgery, pharmacologic and mechanical VTE prophylaxis, early ambulation, and increased vigilance of the entire health care team are denominators of prevention from VTE. In spite of the current precautions, VTE occurs in up to ten percentage of patients in the field of general surgery [3, 14, 15]. The operative techniques and instruments for patient care should be used in a way that they would be beneficial, easily applicable and cost effective. Development of VTE triggers a chain reaction increasing length of hospital stay, increased cost of care, and mortality [16]. The precautions in surgical care and quality improvement projects have improved perioperative outcomes [17]. "The Safe Surgery Saves Lives Study Group" of the World Health Organization (WHO) published the results of the perioperative surgical safety checklist, WHO-SSC, which has made a significant impact on postoperative complications and reduced major complications from 11 to 7 % such as pulmonary embolism [18]. In addition to the preoperative and intraoperative preventive measures, the standardization of postoperative care and follow-up are essential to reduce VTE risk. Majority of surgical complications and errors occur outside the operating room [19–21]. Importance of quality improvement projects standardizing all perioperative care has been well realized among the surgical societies. Major quality improvement programs are the WHO-SSC, the American College of Surgeons - the National Surgical Quality Improvement Program (ACS-NSQIP), the Surgical Care Improvement Project (SCIP), the Surgical Patient Safety System (SURPASS) and the NICE (National Institute for Health and Care of Excellence) guideline [19–21].

2 The World Health Organization Surgical Safety Checklist

The WHO published a safety checklist including multiple recommendations to secure patients' safety during perioperative period and to reduce rates of surgical errors [18]. First version of the WHO-SSC contains 19 items. The WHO-SSC mainly focuses on perioperative incidents occur in the operating room before induction of anesthesia, before skin incision, and before the patient leaves the operating room. Before the anesthesia induction, patient's identify and procedure type is confirmed, operation site is marked, any known allergies are documented and risk of massive blood loss are determined. Required back-up strategies are planned at this level based on the risks identified. Patient's

name, procedure type is reconfirmed, any anticipated critical events are announced and all the operating room staff is introduced before skin incision. The circulating nurse must verbally confirm the operation performed, completion of correct instrument and sponge counts, and appropriate specimen labeling before patient's leaving from the operating room.

The complication and mortality rates were significantly improved by using WHO-SSC [22, 23]. WHO-SSC reduced surgical-site infections development, reoperation requirement, and overall complications rates regardless of case characteristics and caseload of the healthcare center. It has been proposed that use of the checklists promotes healthcare providers to apply required measures and motivates all caregivers to act as a team. Having a checklist in front of the personnel in the operation room may significantly increase focusing on application of required medication in a timely manner, patient monitorization during surgery and management of operative instrument and materials. WHO-SSC has not been used universally and there are limited data about the impact of WHO-SSC on VTE related outcomes. We believe using a well-designed checklist and applying it in all required patients would reduce VTE risk.

3 The American College of Surgeons National Surgical Quality Improvement Program

The ACS-NSQIP has been planned in the mid-1980s as a government project of the US to improve surgical outcomes more than a hundred Veterans Administration (VA) hospitals which had high-rates of mortality and surgical complications [24]. This attempt showed the need for a risk-adjusted prospectively maintained nationwide database for surgical outcomes. Therefore the legislative act provided for the development of a risk-adjustment model that would take into account the severity of a patient's illness and thus enable more reliable comparisons of results from participating health centers. Following the National VA Surgical Risk Study conducted by the Department of Veterans Affairs between October 1st, 1991, and December 31st, 1993, parameters of risk adjustment were determined and the VA-NSQIP allowing risk-adjusted comparison of the VA hospitals was created in 1994 [25, 26]. This was constituted the birth of the ACS-NSQIP. The participation of the all VA hospitals was mandatory for the historical study. The program had been very successful, mortality and morbidity in the VA system was reduced to 27 % and 45 %, respectively. This quality improvement study has become the pilot study for the ACS NSQIP in a small number of academic medical centers and private hospitals [25]. In 2004, the ACS-NSQIP was initiated at the nationwide level and was designed to measure risk-adjusted outcomes of surgical interventions so as to compare results between hospitals [27]. This is achieved with a validated risk adjustment using a logistic regression model. This risk adjustment allows unbiased comparison of results between hospitals of different sizes serving different patient populations [28, 29]. Currently there are over 350 hospitals in the US and the Middle East are in the ACS-NSQIP.

The ACS-NSQIP has more than 130 variables of which numbers are increasing gradually. The ACS-NSQIP is one of the first national, validated, risk-adjusted, outcomes-based databases was created to evaluate the quality of care during perioperative and short-term (30-day) postoperative period. Trained personnel collect the data prospectively. Each hospital submits an average of 1600 major operations annually to the ACS-NSQIP. The variables are collected from the following categories; demographics, surgical profile, preoperative, intraoperative and postoperative outcomes. While there were nine categories of complications including overall mortality, overall complications, cardiac complications, postoperative pneumonia, intubations required within 48 h post-surgery (>48-h intubations), unplanned intubations, pulmonary embolism and deep venous thrombosis, renal dysfunction and surgical-site infections had been reported;

the parameters of the complications have been widened in the main dataset and a targeted datasets are added in last 2 years for specific type of operations such as colectomy. During the data abstraction, trained clinical nurses use well-determined, precise definitions for each parameter of the ACS-NSQIP. A comprehensive set of clinical and laboratory risk factors are assessed in every patient, and submitted data are externally audited to ensure their completeness and accuracy [30]. A well-validated risk-adjustment models gets the data from the registry randomly. Participating hospitals receive robust, risk-adjusted surgical outcomes, expressed relative to other hospitals as "observed to expected" (O/E) ratios. An O/E ratio <1 indicates that the hospital is performing better than expected or an O/E ratio >1 indicates that the hospital is performing poorer than expected. The comorbidities of their patient population and surgical case complexity are considered during the assessment (i.e., an O/E mortality ratio <1 means that fewer deaths occurred than anticipated in comparison with peer hospital performance). These biannual reports are blinded, allowing participating centers to compare their risk profiles and outcomes with those of peer medical centers and national averages [30]. Multiple studies have validated that institutions can improve their outcomes by directing performance improvement initiatives in areas where they seem to be outliers [31–33]. The ACS-NSQIP is not only documenting the VTE rates, it also allows us the perform risk analyses for VTE and enables to identify factors associated with high VTE risk in different operative setting and different type of patient populations [34]. Inflammatory bowel disease, emergent admission, open procedures, and stage 4 cancer patients have increased risk of DVT in setting of colorectal surgery [34, 35].

Even it is rare to develop VTE; obesity, inpatient status, venous catheterization, prolonged operative time, and immediate reconstruction were found to be independent risk factors for VTE [36]. The ACS-NSQIP outcomes allow us to determine the risk groups for VTE development.

4 The Surgical Care Improvement Project

The SCIP builds on the upgraded version of the Surgical Infection Prevention (SIP) project, which was created to reduce surgical site infections by promoting appropriate timing and selection of prophylactic antibiotics [37]. The SIP project, implemented by the Centers for Medicare and Medicaid Services (CMS) and the Centers for Disease Control and Prevention (CDC) in August of 2002, grew out of the CDC's extensive experience in surveillance of surgical site infections through the National Nosocomial Infection Surveillance system and in quality improvement and performance measurement [37].

The SCIP partner organizations coordinate their efforts through a steering committee including representatives from the American Hospital Association, American College of Surgeons, American Society of Anesthesiologists, Association of Registered Nurses, Joint Commission, Institute for Healthcare Improvement, Department of Veterans Affairs, Agency for Healthcare Research and Quality, CMS, and CDC [37]. There were three technical expert panels on infection, cardiac risk, and venous thromboembolism. Every panel has members from professional organizations, academic institutions, and government agencies to supplement the expertise of the partners. The expert panels ensure that SCIP quality measures are supported by evidence-based research. Partners in the SCIP point out that a remarkable reduction in surgical complications depends on surgeons, anesthesiologists, perioperative nurses, pharmacists, infection control professionals, and hospital executives. Teamwork is required for making surgical care improvement a priority. The motivation for the improvement of quality of care should be an organizational culture enabling collaborations among the healthcare centers. The SCIP quality measures include 10 quality parameters for prevention of postoperative complications from infection, myocardial ischemia and venous thromboembolism. The

CMS has endorsed the SCIP for providing better quality of care. In general surgery, the SCIP recommendations for VTE prophylaxis include both mechanical and pharmacologic prophylaxis for all patients, unless there is a contraindication. VTE preventative measures must be ordered in patients who meets the VTE-1 (Surgery patients with recommended venous thromboembolism prophylaxis ordered) criterion and must be administered based on VTE-2 (Surgery patients who received appropriate venous thromboembolism prophylaxis within 24 h prior to surgery to 24 h after surgery) criterion.

The CMS promotes transparency by publicly reporting hospitals' quality of care performance on the SCIP measures and other clinical quality parameters. These measures are aligned with measures required by the Joint Commission. An individual hospital's performance with surgical care patients may be accessed on the website (http://hospitalcompare.hhs.gov). Beginning in October 2007, hospitals' performance on VTE-1 and VTE-2 are also being publicly reported. The National Quality Forum has endorsed all of the publicly reported measures. Grades are given for individual hospitals and can be compared with the ratings of any hospitals in the US. The Cleveland Clinic study demonstrated that compliance with SCIP recommendations for pharmacologic VTE prophylaxis decreased the incidence of VTE after colorectal surgery with no increase in the use of perioperative transfusion [38].

5 The Surgical Patient Safety System

Development and validation of the SURPASS has been performed and it is a multidisciplinary checklist following the entire surgical pathway from admission to discharge [19]. The checklist is divided into parts that correspond to the stages of care in during surgical care (preoperative, intraoperative, recovery or intensive care, and postoperative). SURPASS is applied by a multidisciplinary team having doctor in the ward, nurse, surgeon, anesthesiologist, and operating assistant. All team members are responsible for completion of the checklist. Items on the checklist include; review of imaging studies, accounting of all necessary equipment and materials, marking the operation side, the hand-off the postoperative instructions, and provision of medication prescriptions to the patient at discharge [20]. In a comparative study of more than 3500 patients the total number of complications per 100 patients decreased from 27.3 to 16.7, for an absolute risk reduction of 10.6. The number of patients with one or more complications decreased remarkably from 15.4 to 10.6 %. 0.7 % decrease was observed in hospital mortality [absolute risk reduction of 0.7 percentage points (95 % CI, 0.2 – 1.2)] [39]. Further studies evaluating the impact of SURPASS on VTE related complications are required in well-defined group of patients undergoing specific type of operations.

In addition to creating quality measures, physician compliance with known prophylaxis strategies is also crucial to prevent VTE. Use of quality indicators also increased prophylaxis utilization [40]. Simplifying the coding systems for describing primary pathology, operation type and complications may improve effective use of outcome data stored in the quality improvement programs [41]. Combination of pharmacologic and mechanical prophylaxis is the key to minimize the incidence of postoperative VTE [6]. Acting as a unit should be the motto for reducing VTE events.

6 The NICE Guideline

The NICE guideline is another cornerstone in the field of VTE prevention. It was designed to examine the risk of VTE in adult inpatients undergoing elective orthopedic surgery, hip fracture surgery, general surgery, gynecological surgery (excluding caesarean section), cardiac surgery, thoracic surgery, urological surgery, neurosurgery (including spinal surgery) and vascular surgery. The evidence for the effectiveness of risk reduction measures was analyzed and recommendations on the most clinically and

cost effective measures to reduce the risk of VTE in inpatients having surgery were provided by the NICE guideline (http://www.nice.org.uk/guidance/CG046). While the percentage of patients for whom a VTE risk assessment was documented increased with use of the NICE guideline, administration of appropriate prophylaxis is still questionable [42]. The NICE guideline does not cover pediatric patients, adults who have a high risk VTE development but are not undergoing surgery and pregnant women. (http://www.nice.org.uk/guidance/CG046).

7 Comments and Conclusion

The use of surgical care improvement projects has an important role to prevent VTE during hospital stay. However obeisance on these indicators another issue which needs to be evaluated. Assessment of compliance on surgical quality of care measures is important to figure out our current status and requirements to achieve better outcomes. A pilot study on implementation of the quality improvement intervention with clerking proforma remarkably increased appropriate VTE prophylaxis rate form 37 to 88 % in acute admission patients [41]. Standardized VTE risk assessment, risk stratification to select appropriate prophylaxis from a prepared menu of proven options, identifying contraindications to VTE prophylaxis and collecting the protocol in a surgical clerking proforma provides a reliable strategy [41]. Hospitalization immediately prior to surgery is an independent risk factor for VTE and increases mortality after surgery [43]. Therefore, start of VTE prophylaxis should start at the time of hospital admission importance and this fact should be included in future projects on VTE prevention.

At the University of Michigan, Waits et al. conducted a study on training residents in the principles of quality improvement and providing practical experiences in developing and implementing improvement projects [44]. This is an important study bringing on the importance of educating future physicians by addressing the importance of quality improvement during their education. They included students, residents, and faculty in to quality improvement efforts and showed the deficiency in venous thromboembolism prophylaxis optimization related to sequential compression device compliance use [44]. These data shows necessity of education programs on VTE prophylaxis for every level of caregivers including faculty staff, nurse, fellows, residents and medical students. While no association was found between patient characteristics and patient quality score, elderly patients undergoing major surgery seems most vulnerable population requiring additional care for all measures of quality measures including VTE prevention [13]. Present surgical care improvement projects have also provided us the opportunity to identify patients who are vulnerable to VTE. New surgical care improvement projects on VTE prophylaxis are needed to eliminate lacks of current guidelines and quality projects.

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The Diagnosis and Management of Early Deep Vein Thrombosis

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Abstract

The diagnosis and management of an acute DVT is difficult and mistakes are often made. The cost to the National Health Service (NHS) of litigation arising from failure to diagnose and treat DVT early is substantial. Clinical diagnosis alone is often unreliable and a large proportion of DVT occurring in hospital are asymptomatic. In the United Kingdom, clinical scoring systems, D-dimer and ultrasound (US) imaging have all been adopted to aid diagnosis via DVT pathways. These pathways aim to exclude DVT only and often fail to actually address the cause of the symptoms once DVT is eventually cleared.

Keywords

Deep vein thrombosis • Venous thromboembolism • Swollen leg • Diagnostic pathway

1 Introduction

Acute leg swelling is a common presentation to Accident and Emergency (A&E) departments and General Practitioners (GP) in the United Kingdom. As well as a major concern for the patient, it is a difficult presentation to manage for clinicians and requires careful consideration to its aetiology and subsequent management. Lower limb swelling can often be a manifestation of a chronic underlying disease which has become symptomatic or represent a more acute problem which may be life threatening; therefore determining whether the swelling is acute or chronic should be the first step in assessing this common presentation.

Deep vein thrombosis (DVT) is a common cause of morbidity and mortality. The annual incidence of DVT of the leg is between 48 and 182 per 100,000 in the population (Khanbhai et al. 2015). It is the most worrisome of the aetiologies of acute leg swelling and prompt diagnosis and management is essential to minimise the risk of pulmonary embolus (PE) and post thrombotic syndrome (PTS).

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This chapter reviews the diagnosis and early management of DVT. It also describes common aetiologies for acute leg swelling once DVT has been excluded.

2 Pathophysiology

Virchow's triad describes three factors which increase the propensity to thrombogenesis (venous stasis, intimal damage and hypercoagulability). Many of the risk factors for DVT are related to venous stasis such as immobility, obesity, pregnancy, and trauma. Although direct intimal damage is rare, external trauma to a vein such as during pelvic or lower limb surgery can instigate thrombogenesis. Hypercoagulability is often suggested in young patients (<45 years) with a family history of venous thromboembolism.

Often beginning in the calf, the clot is free-floating within the vein and it is at this point that risk of pulmonary embolism is highest. The clot then becomes densely adherent to the vessel wall and incites an inflammatory reaction. It is at this point that the DVT becomes clinically apparent with leg swelling, dilated superficial veins and pain.

3 Diagnosis of DVT

The diagnosis of DVT of the leg can be difficult with clinical findings and history being unreliable. The National Institute of Health and Care Excellence (NICE) has evidence-based recommendations on the prevention and management of a wide range of health conditions. NICE published guidance on the detection and subsequent management of DVT and suggests the incorporation of a clinical prediction score (Wells score), d-dimer test and venous duplex ultrasound (Figs. 1 and 2) (Venous thromboembolic disease: the management of venous thromboembolic disease and the role of thrombophilia testing; Treating venous thromboembolism).

3.1 The Wells Score

NICE recommend the use of the two-level DVT Wells score to estimate the clinical probability of DVT as shown in Table 1. Patients with a score of 2 points or more should be offered a venous duplex ultrasound scan carried out within 4 h of being requested. If a venous duplex ultrasound scan is not available within 4 h of being requested, a D-dimer test and interim 24 h dose of parental anticoagulation is suggested.

3.2 Duplex Ultrasound

Venous duplex ultrasound has been widely adopted as the first line investigation for suspected DVT. It is able to identify DVT of the leg with a sensitivity of 96.5 % for proximal (above knee) DVT and 71.2 % for calf DVT, both with a specificity of 94 % (Goodacre et al. 2005).

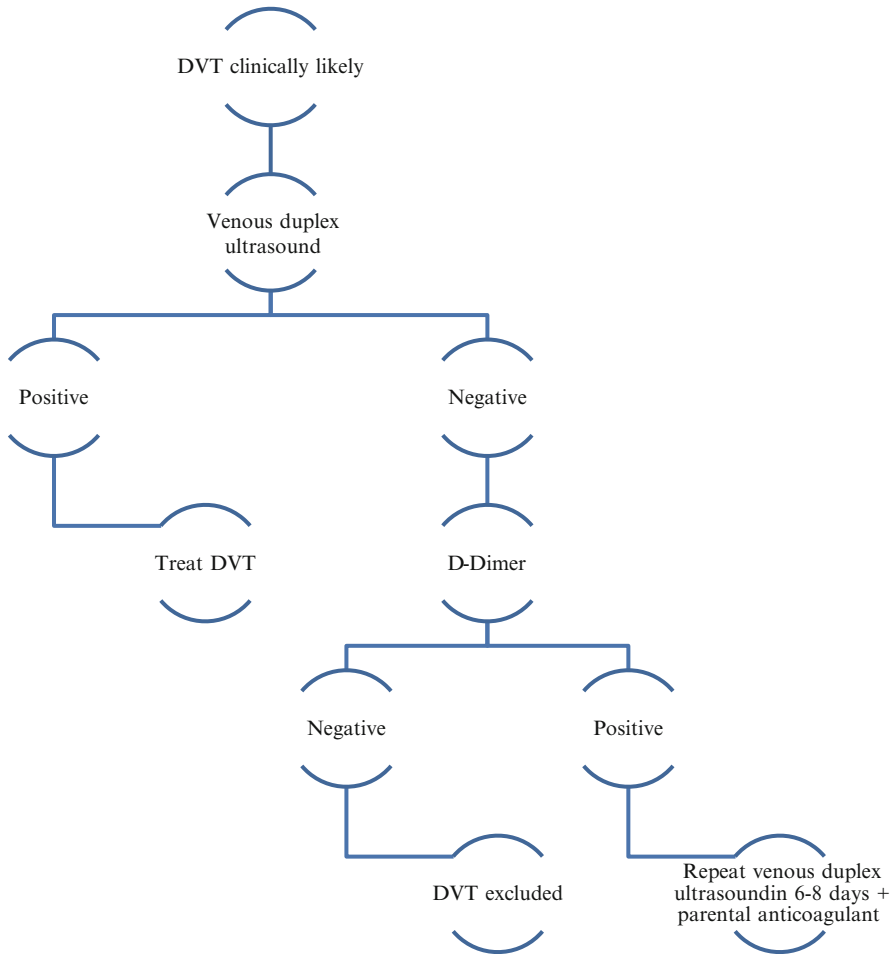
A screening two-point ultrasound is often used in clinical trials to detect the possibility of DVT in asymptomatic patients. Compressibility of the deep veins at two points (the common femoral and the popliteal veins) can characterise the scan as normal (fully compressible), abnormal (non-compressible) or non-diagnostic (due to poor images). This two-point screening test has been shown to be sensitive and specific (Robinson et al. 1998). However it will not detect below knee or non-occlusive proximal (iliac) DVT. Abnormal and non-diagnostic examinations are usually followed up by a complete diagnostic venous duplex ultrasound which includes B-mode imaging for compressibility and visualisation of the thrombus, spectral display to determine flow direction and respiratory phasicity and colour-flow imaging to determine flow. Virtually all vascular labs use the inability to collapse a vein with probe pressure as the primary diagnostic criteria for DVT. A recent RCT showed that the two-point and whole leg strategies are equivalent in identifying DVT in symptomatic patients but despite this screening two-point ultrasound is not routinely used in clinical practice (Bernardi et al. 2008).

The venous duplex ultrasound can be repeated 6–8 days later in patients with persistent swellings, a positive D-dimer and an initial negative duplex ultrasound. Most DVT algorithms and duplex ultrasound protocols for DVT only include initial ultrasound evaluation of the proximal leg veins only even in symptomatic patients. This is largely based on out-dated perceptions that ultrasound examinations of the calf veins are inaccurate and such strategies are inefficient and not cost-effective. With the commonest site for DVT being the muscular calf vein, scanning the proximal veins will invariably miss a large proportion of DVT (Yoshimura et al. 2012; Zierler 2004).

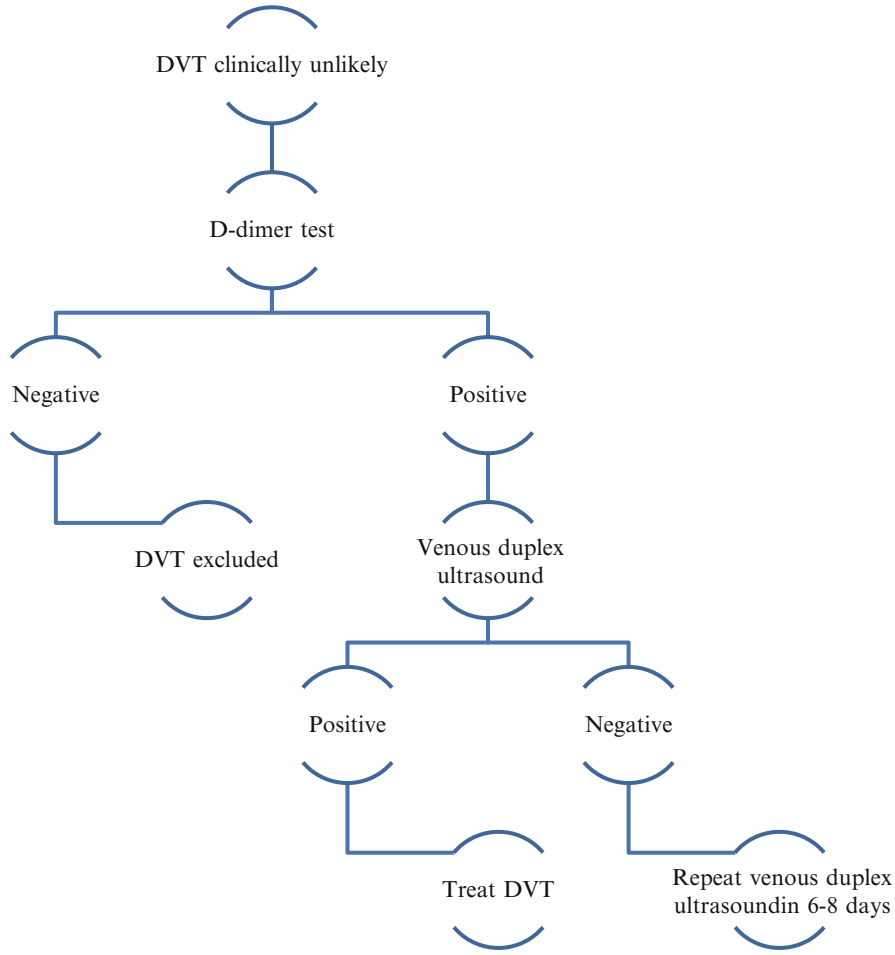
The duplex examination can also be useful to help determine the cause of leg pain and swelling when a DVT is excluded. Intramuscular hematomas, Bakers cysts and varicose vein disease can mimic DVT and be identified on duplex ultrasound.

3.3 D-Dimer Test

In patients in whom DVT is suspected and with a low Wells score, a D-dimer test is suggested. The use of the D-dimer test to rule out DVT and remove the need for more expensive testing has increased in popularity over the last decade.



Figs. 1 and 2 Illustration of diagnostic approach for suspected DVT



Figs. 1 and 2 (continued)

Table 1 Two-level DVT wells score (Wells et al. 2003)

Clinical feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic leg	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	−2
Clinical probability simplified score	
DVT *likely*	2 points or more
DVT *unlikely*	1 point or less

D-dimers are degradation products produced as a result of plasmin on cross-linked fibrin indicating the development of a thrombus. There are however several other conditions that can elevate D-dimer results such as infection, myocardial infarction, malignancy, trauma and pregnancy which make its interpretation difficult (Schumann and Ewigman 2007).

D-dimer test can reliably exclude DVT with a 99 % negative predictive value (Wells et al. 2003). Patients with a high Wells score with a negative venous duplex ultrasound scan are recommended to have a D-dimer test. A negative proximal ultrasound scan and D-dimer can reliably exclude DVT. In practice where a D-dimer test will not provide a reliable result, duplex ultrasound remains as the most robust diagnostic tool.

3.4 Venography

Catheter-based contrast venography had traditionally been accepted as the reference diagnostic test for DVT before the widespread introduction of duplex ultrasound. Contrast venography was up until recently still widely used in clinical trials investigating anticoagulant therapies (Eriksson and Quinlan 2006). Because of its invasive nature, technical difficulty and cost it is not deemed suitable for routine clinical evaluation of suspected DVT (Zierler 2004). It is however still used for suspected pelvic and iliac vein DVT.

Magnetic resonance venography (MRV) is an alternative to catheter-based venography and has been shown to be highly accurate with sensitivies of 97 % and specificity of 100 % with excellent inter-observer variability for iliac, femoral and below knee DVT (Fraser et al. 2002; Spritzer et al. 2001). Compared with conventional catheter-based contrast venography, it is non-invasive and avoids ionising radiation. It is however expensive compared to venous duplex ultrasound and not available to patients with metal implants.

Computerised tomographic (CT) venography is similarly advantageous as MRV over duplex ultrasound but does involve ionising radiation and the use of intravenous contrast. It is reported to be 97 % sensitive and 100 % specific at determining lower limb DVT compared with duplex ultrasound (Frankel and Bundens 2014).

4 Management of Early DVT

4.1 Anticoagulation

The aim of treatment for DVT is to relieve the acute symptoms whilst reducing the risk of recurrent thrombosis and post-thrombotic syndrome. The initial anticoagulant regime for DVT can be a choice of either intravenous or subcutaneous un-fractionated heparin (UFH), low molecular weight Heparin (LMWH), Fondaparinux, Rivaroxaban and Apixaban. Vitamin K antagonists such as Warfarin can be initiated simultaneously with heparin to a target international normalised ratio (INR) of 2.0–3.0 In the UK LMWH in the form of Enoxaparin, Dalteparin or Tinzaparin are most frequently used in hospitalised patients whilst the target INR is reached. It is favoured because it can be administered by a single daily subcutaneous injection and is less likely to produce heparin related thrombocytopenia when compared to UFH. There are several LMWH on the market some of which are licensed for treatment and pharmacological VTE prophylaxis; prescribers must review local hospital guidance on which agent to use.

New oral anticoagulants such as Rivaroxaban and Apixaban are now recommended for use in the treatment of acute VTE in adult patients after review by NICE in 2012 and 2015 respectively. Both drugs have been shown to be clinically more effective and cheaper for patients requiring anticoagulation for longer than 12 months as they remove the need for regular monitoring and blood tests (Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism). A recent meta-analysis of new oral anticoagulants (Dabigatran, Rivaroxaban, Apixaban and Edoxaban) showed that they significantly reduced the risk of stroke or systemic embolic events by 19 % when compared with warfarin (RR 0.81, 0.38–0.64, $p < 0.0001$) but was associated with greater risk of gastrointestinal bleeding (Ruff et al. 2014). No clinically

Table 2 Recommended duration of anticoagulation (Kearon et al. 2008)

Patients	Modifier	Recommendation
1st episode distal DVT	Idiopathic or unprovoked	3 months
1st episode proximal DVT	Idiopathic or unprovoked	Consider Long term (indefinite) therapy
1st episode DVT	Transient risk factor (long travel, post-operative, lower limb immobilisation)	3 months
2nd episode (distal or proximal) DVT	Idiopathic or unprovoked	Consider Long term (indefinite) therapy
1st episode DVT	Cancer	LMWH for 3–6 months and anticoagulation as long as cancer is active
1st episode DVT	Antiphospholipid antibody or $\geq$2 thrombophilic conditions	Indefinite anticoagulation
Recurrent DVT		Indefinite anticoagulation

relevant increases in major bleeding events were noted in the RE-COVER, RE-MEDY and the EINSTEIN trials that established the efficacy of dabigatran and rivaroxaban for the prevention of VTE (Sarrazin 2015).

Vitamin K antagonists include substances with a short (acenocoumarol), intermediate (warfarin, fluindione), or long (phenprocoumone) half-life. Because of the variable vitamin K content of food, a narrow therapeutic index, and several interactions with other drugs, treatment with vitamin K antagonists needs close monitoring. The safety their use can be increased by encouraging compliance, avoiding use of concurrent drugs with potential interactions, and restricting alcohol intake.

The duration of oral anticoagulant depends upon patient presentation, history of prior venous thromboembolism and condition of the patient after 6–12 months of therapy. The American College of Chest Physicians (ACCP) recommendations for duration are summarised in Table 2 but the optimal duration is still uncertain. Co-morbidities, family history, BMI and gender all need to be taken into account before stopping anticoagulation. Serial D-dimer testing to determine the risk of recurrent DVT has been shown to produce promising results in large cohort studies. Patients with abnormal D-dimer levels 1 month after discontinuation of anticoagulation were shown to have significantly higher incidence of recurrent VTE compared to patients with persistently negative D-dimers after stopping anticoagulation (Palareti et al. 2006, 2014).

4.2 Post Thrombotic Syndrome

Post thrombotic syndrome (PTS) is a chronic condition that develops in 25–50 % of patients after DVT. Often presenting with leg pain, chronic oedema, skin discolouration and ulcers it is associated with significant health and economic burden as reduces quality of life. PTS develops due to either valvular incompetence or residual outflow obstruction with eventual calf muscle pump failure after DVT. Therefore treatment of the primary DVT should be aimed not only at preventing thrombus propagation and PE, but also on preventing venous damage and restoring venous function. This may include limb elevation, elastic compression therapy and in some cases thrombolysis.

All patients who have had a DVT should be considered for long-term elastic compression hosiery, in particular those who are on their feet all day or travel long journeys. They should also be encouraged to take regular exercise to stimulate the calf muscle pump. Graduated elastic compression stockings (ECS) applied after initiating coagulation is thought to reduce the development of PTS is not associated with increased risk of PE. Previous studies have demonstrated that wearing ECS could reduce post-thrombotic morbidity by up to 50 % (Partsch 2005; Brandjes et al. 1997) but a recent multicentre randomised control trial showed ECS did not prevent the development of PTS when compared to a placebo; incidence of PTS 14.2 % in patients with ECS compared with 12.7 % in

placebo ECS (Kahn et al. 2014). Although the development of post thrombotic syndrome may not be prevented by ECS it may still be effective in the management of its symptoms and warrants further assessment in future studies.

4.3 Severe or Complicated DVT

iliofemoral DVT, vena cava, phlegmasia or recurrent thrombosis may be considered for thrombolysis or caval filter insertion. Catheter-directed thrombolysis can rapidly clear the thrombotic segment in patients with extensive proximal DVT. It is considered in patients who have a high proximal DVT, good functional status, a life expectancy of 1 year or more and a low risk of bleeding as it has been shown to be associated with more frequent adverse events and bleeding but no difference has been shown in mortality when compared with anticoagulation alone (Enden et al. 2012). Accepted indications for caval filter insertion include cases where it can be proved that PE is still occurring despite adequate anticoagulation or where anticoagulation is contra-indicated. Filters are inserted under local anaesthesia percutaneous through the jugular or femoral vein.

4.4 Unprovoked DVT

Patients who have developed an unprovoked DVT or PE who are not already known to have cancer should be offered further investigations. This includes a physical examination, a chest X-ray, blood tests and urinalysis to identify undiagnosed malignancy. Further investigations using abdomino-pelvic CT scan in patients over 40 years may also be warranted.

Thrombophilia testing should be offered in patients with an unprovoked DVT or PE. In particular if it is planned to stop anticoagulation. Hereditary thrombophilia testing in patients who have a first degree relative with DVT or PE is also suggested by NICE (Treating venous thromboembolism).

5 Alternative Causes of Acute leg Swelling

Common causes of both acute and chronic leg swelling are shown in Table 3. A careful and systematic history and physical examination will point to the likeliest aetiology.

5.1 Chronic Venous Insufficiency (CVI)

CVI is the most common cause of lower limb swelling in the elderly, often due to primary valvular incompetence or secondary to DVT, but almost invariably associated with obesity or poor mobility. Sitting for prolonged periods of time they are exposed to almost continuously raised venous pressure at the ankle. This venous hypertension leads to oedema which is initially pitting but can progress to subcutaneous fibrosis and induration. In the obese, the femoral vein and lymphatics in the groin are compressed between the fat of the lower abdomen and the thigh on sitting. This compression alone may cause prolonged swelling and even ankle ulceration, even in patients with healthy veins.

Table 3 Shows the causes of swelling of the lower limb

Acute	Chronic
Deep vein thrombosis (DVT)	Venous disease: post thrombotic syndrome, lipodermatosclerosis, chronic venous insufficiency, venous obstruction
Cellulitis	
Superficial thrombophlebitis	Lymphedema: cancer treatment, infection, tumour, trauma, pretibial myxoedema
Joint effusion or heamarthrosis	
Haematoma	Congenital vascular abnormalities: haemangioma, klippel-trenaunay syndrome
Musculoskeletal	Others: heart failure, reflex sympathetic dystrophy, idiopathic oedema in women, hypoproteinaemia in cirrhosis or nephrotic syndrome, armchair legs, lipoedema

5.2 Lymphedema

Lymphedema is a condition in which excessive amounts of protein-rich fluid accumulates in peripheral tissues. The lymphatic system removes excess water and protein from the interstitial space. Intrinsic lymphatic contractions and endothelial valves direct flow centrally, with lymph entering the venous system through the thoracic duct. Lymphoedema is a chronic condition which can be managed effectively if a careful treatment program is followed.

Early or new onset lymphedema can present with pitting oedema. Swelling often commences distally on the foot and extending proximally either uni- or bilaterally. Often difficulties with footwear is the first sign that patients notice. It is often reversible at this stage and may be managed by high leg elevation and compression hosiery. Focal pain is not a characteristic of lymphedema, although patients may complain that the limb is heavy.

5.3 Cellulitis

Painful, erythematous, red unilateral leg oedema with increased warmth suggests cellulitis. A careful search often reveals a break in the skin integrity allowing bacterial ingress. Predisposing factors should be sought, such as foot blisters, skin excoriation and previous episodes of cellulitis.

5.4 Musculo-Skeletal

Sudden intense pain of the posterior lower leg is often suggestive of a musculoskeletal cause. If pain was associated with sudden dorsiflexion of the foot, rupture of the tendinous portion of the gastrocnemius or plantaris muscle should be suspected. Localised swelling in the mid-calf area is also common. Ecchymotic discolouration can follow 2–5 days later.

Popliteal cyst rupture can present with sudden severe pain and swelling of the calf. Popliteal cysts are composed of a fibrous wall communicating with the joint space and lined by synovia and often develop as a result of degenerative arthritis, trauma and gout. Popliteal cysts are can cause chronic symptoms of discomfort. Symptoms include posterior knee pain and swelling, tenderness on palpation with a palpable mass. The diagnosis is uniformly made with a duplex ultrasound examination.

Treatment of musculo-skeletal pain is symptomatic, applying cold packs or ice, anti-inflammatory medications reduced weight bearing and treatment directed at the underlying condition.

6 Conclusion

The acutely swollen limb is a common presentation with several causes, the most worrisome being DVT. This chapter has highlighted the pathway used to diagnose and manage early DVT. It is imperative that duplex ultrasound is used almost primarily to diagnose or exclude DVT. Once DVT is excluded, patients with persistent symptoms an alternative diagnosis should be sought.

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Symptomatology, Clinical Presentation and Basic Work up in Patients with Suspected Pulmonary Embolism

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Abstract

Basic knowledge of pulmonary embolism is relevant to most practicing physicians. Many medical specialties care for patients with increased risk of pulmonary embolism, why recognition of relevant symptoms, a thorough medical history, assessment of the clinical condition of the patient and possibly referral to a relevant facility should be a part of the skills of all clinicians. Sudden onset dyspnea, chest pain, syncope and hemoptysis are essential symptoms of pulmonary embolism, and in most of these patients basic investigations like arterial blood gas analysis, electrocardiogram, chest x-ray and biochemical analyses are appropriate. In addition, lung ultrasound and echocardiography are indicated in many of these patients. The information available from the medical history, clinical assessment and basic investigation form the basis on which the decision about further diagnostic imaging and intensity of treatment and monitoring can be made. These decisions can be guided by clinical scoring systems like the Wells score, revised Geneva score and the PESI.

Keywords

Pulmonary embolism • Diagnosis • Prognosis • Clinical presentation • Symptomatology

1 Introduction

Even in the age of widespread prophylaxis against venous thromboembolism (VTE), physicians in virtually every field of clinical medicine will have to care for patients with suspected pulmonary embolism (PE). Inherently, the occurrence of PE varies largely among different specialties, and some clinicians in large centers are primarily

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dedicated to PE management. Other clinicians only face these patients infrequently. This means that almost all physicians must be familiar with the risk factors for PE in the specific patient population they care for, and in addition, must be capable of identifying relevant symptoms.

When managing patients with suspected PE, different aspects have to be addressed besides diagnosis and treatment. Firstly, the clinician must suspect that PE can be the cause of the present symptoms. This assessment is based on clinical presentation, risk factors, and available investigations. Afterwards, a diagnostic strategy must be planned to confirm or rule-out PE, and in this case, also determine alternative diagnoses. In addition, risk stratification must be completed to guide intensity of monitoring and treatment. Depending on the skills of the individual physician, local facilities and referral practices, some patients can benefit from care at another facility. The initial work-up must also clarify this.

This chapter deals with these topics with focus on the practical approach to the patient with symptoms and clinical features compatible with pulmonary embolism. It should not be considered a comprehensive review, and often references are given to such comprehensive and contemporary reviews in which more details can be found. In addition, major international societies like the European Society of Cardiology have published guidelines for the management of PE (Konstantinides et al. 2014). Even though PE does occur in children, it is far more frequent in adults, and this chapter only deals with adult PE (Patocka and Nemeth 2012). Clinical characteristics and basic examinations can be crucial not only to decide whether further evaluation with imaging modalities like CT-angiography or ventilation-perfusion scintigraphy (V/Q-scan) for PE is warranted, but also to decide which modality is most suited. For example, V/Q-scan is less appropriate in patients with COPD as it often turns out to be non-diagnostic (Lesser et al. 1992). On the other hand, V/Q-scan is very appropriate e.g. when minor peripheral emboli have to be ruled out in a non-critically ill patient with no preexisting pulmonary disease in which a normal V/Q-scan rules out PE with very high negative predictive value. In addition, the different modalities have the benefit of revealing differential diagnosis; e.g. V/Q-scan can detect shunting, and CT-angiography can detect pneumonia (Madsen et al. 2010; Perelas et al. 2015). Pros and cons of the different imaging modalities are covered in details in other chapters.

2 Identification of the Patient with Possible Pulmonary Embolism

2.1 Overall Clinical Presentation

Even though the clinical spectrum, both regarding symptoms and severity, for a wide variety of diseases is broad, this is particular pronounced in PE. Indeed, PE has been quoted one of the great imitators of medicine (Sharma et al. 1976). In the cause of time, however, the disease presentation has changed.

Nowadays, PE is often found on CT scans performed on suspicion of completely different conditions, for example when staging extrapulmonary cancers. A recent meta-analysis of 35,990 cancer patients found that unsuspected PE was seen in 552 patients corresponding to a mean weighted prevalence of 1.8 % (Donadini et al. 2014). However, when retrospectively reviewing symptoms almost half of these patients with unsuspected PE actually had symptoms like dyspnea that was attributable to PE. Even though patients with unsuspected PE in general have fewer symptoms and less severe clinical presentation, the prognosis is worse, probably due to underlying disease like malignancy (Shteinberg et al. 2012).

In other patients, PE presents dramatically as sudden cardiac arrest without any prodromes. Around one third of patients presenting with pulseless electrical activity cardiac arrest turns out to have unsuspected PE (Comess et al. 2000). These two clinical scenarios (the asymptomatic patient and the patient presenting in cardiac arrest) define the extremities of the clinical spectrum of PE, with every possible presentation in between.

2.2 Symptoms

Even though some patients are asymptomatic, the patient with PE generally presents with symptoms from the cardiopulmonary system. As described above, the symptoms will vary according to the severity of the clinical presentation. However, several large reviews have demonstrated that dyspnea, most often of sudden onset, is the most common finding in PE (Pollack et al. 2011; Miniati et al. 1999; Stein et al. 1991a; Miniati et al. 2012). Other typical symptoms are seen in Table 1.

As discussed below, although these symptoms are often due to serious disease, they are non-specific and thereby non-diagnostic. A study comparing symptoms in patients with (n = 1880) and without (n = 528) PE found no relevant differences in symptoms between the groups. The results are seen in Table 2.

Another study found significant differences in the frequency of sudden onset dyspnea, gradual onset dyspnea, orthopnea, pleuritic and substernal chest pain and fainting when studying 202 patients with, and 298 patients without PE. However, this is not clinically significant, as all symptoms can be present and absent in patients with PE. The results are seen in Table 3.

The pathophysiology of dyspnea in PE is probably multifactorial and includes hypoxemia and stimulation of pressure receptors in the right atrium (Manning and Schwartzstein 1995). When present, chest pain in PE is often pleuritic, i.e. worsening during inspiration, and is thought to be caused by lung infarction and pleural irritation (Stein and Henry 1997). This is also the background for alveolar hemorrhage and hemoptysis seen in PE. However, chest pain in PE can also mimic acute myocardial infarction. In these cases the pain probably originates from right ventricular strain with pressure overload and decreased coronary perfusion. Syncope is often a sign of reduced cardiac output and massive PE.

Four main symptoms of PE (acute onset dyspnea, chest pain, syncope, and hemoptysis) are almost always present, either alone or in combination, if the patient is not asymptomatic. In Table 4, this is summarized.

Table 1 Symptoms of PE (Miniati et al. 2012)

Acute onset dyspnea	80 %
Gradual onset dyspnea	3 %
Orthopnea	0.4 %
Chest pain	49 %
Syncope	24 %
Hemoptysis	6 %

Table 2 Symptoms in patient with and without PE (Pollack et al. 2011)

Symptom	PE proven (%)	PE not proven (%)
Dyspnea	50	51
Pleuritic chest pain	39	28
Cough	23	23
Substernal chest pain	15	17
Fever	10	10
Hemoptysis	8	4
Syncope	6	6
Unilateral leg pain	6	5
Signs of deep vein thrombosis	24	18

Table 3 Symptoms in patient with and without PE (Miniati et al. 1999)

Symptom	PE proven (%)	PE not proven (%)
Dyspnea (sudden onset)	78	29
Dyspnea (gradual onset)	6	20
Orthopnea	9	9
Chest pain (pleuritic)	44	30
Chest pain (substernal)	16	10
Fainting	26	13
Hemoptysis	9	5
Cough	11	15
Palpitations	18	15

Table 4 Constellation of symptoms in PE (Miniati et al. 2012)

Only one of four symptoms	42 %
Any two of four symptoms	41 %
Any three of four symptoms	11 %
At least one of four symptoms	94 %
Other symptoms	2 %
Symptoms and signs of deep vein thrombosis only	3 %
No symptoms at all	1 %

When interviewing the patient suspected of PE, the focus must be on these symptoms and the duration, but in addition the interview must clarify risk factors for PE and possible contraindications to treatment.

2.3 Clinical Findings

In all patients with acute cardiopulmonary symptoms, vital signs like heart rate, blood pressure, arterial oxygen saturation, and respiratory frequency, should be recorded immediately, as these are fundamental during initial resuscitation and in risk stratification if PE is confirmed. However, no clinical important differences in vital signs are found between patients with or without PE (Goldhaber 2010).

Likewise, no physical findings are reported to either confirm or rule-out PE, although signs of deep vein thrombosis are found more frequently in patients with PE than patients without PE (Kline et al. 2004; Wells et al. 2000; Perrier et al. 2004; Le Gal et al. 2006). Clinical findings like wheezing and high fever are found more often in patients without PE, and suggest other diagnosis (Miniati et al. 2008; Stein et al. 2000; Kline et al. 2002; Kabrhel et al. 2006). Table 5 presents findings from 202 patients with and 298 patients without PE; differences in the frequency of leg swelling, high fever and wheezing between the two groups were statistically significant, but have limited clinical significance.

Table 5 Clinical findings in patients with and without PE (Miniati et al. 1999)

Clinical finding	PE proven (%)	PE not proven (%)
Tachycardia > 100/min	24	23
Cyanosis	16	15
Hypotension < 90 mm Hg	3	2
Neck vein distension	12	9
Leg swelling (unilateral)	17	9
Fever > 38 °C	7	21
Crackles	18	26
Wheezes	4	13
Pleural friction rub	4	4

2.4 Differential Diagnosis

In general, patients presenting to the emergency room with respiratory impairment like tachypnea and hypoxemia most commonly suffers from one of the conditions seen in Table 6 (Ray et al. 2006). By nature, the distribution of these conditions will vary in different patient populations, e.g. children or very specialized centers.

Other, common and uncommon, diseases with symptoms and clinical findings mimicking PE by causing dyspnea are lung malignancies, cardiac or intrapulmonary shunt states, pneumothorax, interstitial lung diseases, pulmonary hypertension and tracheobronchial foreign bodies. In addition, non-cardiopulmonary conditions like severe anemia, obesity and certain neuromuscular diseases can result in dyspnea.

In the patient presenting with chest pain, syncope and hemodynamic instability, acute myocardial infarction, malignant cardiac arrhythmias, aortic dissection, ruptured aortic aneurism, and other forms of shock must be included as possible differential diagnosis (Finfer and Vincent 2013).

2.5 Risk Factors for PE

Even though Virchow's Triad (consisting of abnormal blood composition, vessel wall abnormalities and stasis) has been used for

Table 6 Common causes of acute respiratory impairment (Ray et al. 2006)

Cardiogenic pulmonary edema	43 %
Community acquired pneumonia	35 %
Acute exacerbation of obstructive pulmonary disease	32 %
Pulmonary embolism	18 %
Acute asthma	3 %

Table 7 Risk factors for PE (Anderson and Spencer 2003)

Strong risk factors (odds ratio >10)	Moderate risk factors (odds ratio 2–9)	Weak risk factors (odds ratio < 2)
Fracture (hip or leg)	Arthroscopic knee surgery	Bed rest > 3 days
Hip or knee replacement	Central venous lines	Immobility due to sitting (e.g. prolonged car or air travel)
Major general surgery	Chemotherapy	Increasing age
Major trauma	Congestive heart or respiratory failure	Laparoscopic surgery (e.g. cholecystectomy)
Spinal cord injury	Hormone replacement therapy	Obesity
	Malignancy	Pregnancy/antepartum
	Oral contraceptive therapy	Varicose veins
	Paralytic stroke	
	Pregnancy/postpartum	
	Previous venous thromboembolism	
	Thrombophilia	

more than a century to describe risk factors for VTE, the clinical value of this has recently been questioned and additional details and interactions between the three components have been suggested (Wolberg et al. 2012). In some patients, it is not possible to establish any obvious risk or disposing factors for PE (White 2003).

However, if one or more risk factors are demonstrated, it is important if these are temporary (like recovery from surgery) or permanent (like incurable cancer). In other words, it must be decided whether the patient has secondary/provoked or primary/unprovoked/idiopathic PE. The thrombophilias constitutes a separate entity, and are covered in details in another chapter.

Table 7 (modified from (Anderson and Spencer 2003)) shows important relative risk factors for PE.

In recent years more focus has been on VTE and arterial thrombosis sharing the same risk factors, and this has to be taken into account when assessing the patient with PE; both during diagnosis, treatment and prophylaxis of PE (Piazza 2015). The traditional risk factors for arterial thrombosis which are also recognized as risk factors for VTE and PE, are seen in Table 8 and are based on a metaanalysis of 63,552 patients (Ageno et al. 2008; Goldhaber 2010) (Table 9).

Table 8 Risk factors for VTE and PE traditionally seen as risk factors for arterial thrombosis (Ageno et al. 2008)

Diabetes mellitus
Hypercholesterolemia
Hypertension
Obesity
Smoking

Table 9 Susceptibility to PE, according to hospitalization status modified from (Goldhaber 2010)

In-patient population	Out-patient population
Major surgery	Advancing age
Cancer	Cancer
Congestive heart failure	Prior VTE
Chronic obstructive pulmonary disease	Venous insufficiency
Chronic kidney disease, especially nephrotic syndrome	Pregnancy
	Trauma
	Frailty and immobility

2.6 PE in Different Medical Specialties

In 2011, almost 200,000 patients in the United States were admitted with PE (LaMori et al. 2015), and every year 300,000 and 600,000 patients with PE are diagnosed in Europe and United States, respectively (Cohen et al. 2007; Garcia et al. 2005).

However, these numbers are not of direct utility to the individual clinician, as the incidence varies widely across medical specialties. In some fields of practice, PE is very common. For example, some studies suggest that 20 % of patients admitted with exacerbation of chronic obstructive pulmonary disease in fact have PE (Rizkallah et al. 2009; Kim et al. 2014). Also patients with liver cirrhosis and different autoimmune diseases have increased risk of PE (Ng et al. 2015; Tamaki and Khasnis 2015). In the emergency department, up to 1/400 will be diagnosed with PE (Kline and Kabrhel 2015a). Even though PE in pregnancy, and especially in the postpartum period (Meng et al. 2015), is fairly uncommon with 0.1 % of pregnant woman developing PE (Neuberger and Wennike 2013; Simpson et al. 2001), the risk is increased (Heit et al. 2005), and PE is a leading cause of maternal mortality in developed countries (Khan et al. 2006). In addition, the impact of PE in this patient category is often more complex with ethical and legal aspects in addition to the tragic nature of the situation. In surgery, increased risk of PE has to be taken into account in many specialties – e.g., 5 % of patients undergoing urooncological surgery will develop PE (Kukreja et al. 2015), in orthopedic surgery, 1 % of patients undergoing lower extremity surgery developed PE (Park et al. 2015; Wahlsten et al. 2015; Dixon et al. 2015) and the same is the case in patients with severe trauma and spine surgery (Lichte et al. 2015; Hamidi and Riazi 2015). Even in psychiatry, increased risk of PE is found in schizophrenic patients with a twofold risk of PE (Hsu et al. 2015). The examples above are by no means exhaustive, but meant as illustrations that clinicians in every field of medicine must have some knowledge of PE.

3 Basic Work Up

When assessing patients with acute cardiopulmonary symptoms, a range of investigations is indicated. In most patients, arterial gas analysis, chest x-ray, electrocardiogram (ECG) and venous blood samples are performed. In the following, the usefulness of these examinations in suspected PE will be reviewed.

Recently, focused point-of-care ultrasonography of the lungs, heart and deep vein have gained popularity in some centers, and seems utterly applicable in patients with respiratory symptoms and hypoxemia, increasing the number of patients with correct diagnosis at 4 h from admission from 64 to 88 % (Laursen et al. 2014). Ultrasonography of the lungs, heart and deep veins in the primary evaluation of these patients have several advantages in addition to establishing differential diagnoses to PE. Firstly, lung ultrasound has, in a recent meta-analysis, been found to have sensitivity of 87 % and specificity of 82 % for the diagnosis of PE (Squizzato et al. 2013). In addition, ultrasonography of the heart (echocardiography) will aid in risk stratification (as described later) and ultrasound of the deep vein can reveal deep venous thrombosis which will increase the possibility of PE in patients with relevant symptoms. However, while lung ultrasound has obvious benefits, is radiation free and can be used bedside, important limitations, primarily concerning training issues and interobserver variability exists (Touw et al. 2015).

3.1 Arterial Gas Analysis

Arterial blood gas measurements are fundamental when evaluating patients with acute respiratory impairment. Hypoxemia is present in most patients with PE, but is also present in many other conditions. The same is true for hypocapnia and abnormal (A–a) DO2 gradient (Rodger et al. 2000). Thus, the arterial blood gas is generally not helpful in making or excluding the diagnosis, but is important in determining severity and emergency treatment in patients with respiratory distress. However, some papers have demonstrated a lower PaCO2 in patients with COPD and PE, than in patients with COPD exacerbation without PE. Therefore, unsuspected hypocapnia in a patient with COPD exacerbation could be a clue that PE is present (Akpinar et al. 2014).

3.2 Chest X-Ray

Most patients with PE present with some abnormalities on the chest x-ray. These are, however, almost always non-specific and classical findings in PE like the Westermark sign (distal oligemia due to PE) are, although with varying frequency, only seen in a minority of patients (Miniati et al. 1999; Elliott et al. 2000; Stein et al. 1991b). Table 10 presents findings from the ICOPER study which studied around 2300 patients with PE.

When pleural effusion is present, it is present only as blunting of the costodiaphramatic angle in the large majority of patients (Stein et al. 1991a). A large pleural effusion should therefore not be contributed to PE, but investigated further to exclude other diagnosis like e.g. malignancy even though PE has been confirmed.

In general, the chest x-ray is important as an initial investigation in patients with clinical features of PE, as important differential diagnosis, like pneumothorax, can be diagnosed this way and typically leaves other more advanced diagnostic modalities redundant.

Table 10 Chest x-ray findings in patients with PE (Elliott et al. 2000)

Chest x-ray finding	% of patient with PE with finding	No. of patient with finding/no. interpreted
Cardiac enlargement	27	622/2315
Pleural effusion	23	523/2319
Elevated hemidiaphragm	20	457/2316
Pulmonary artery enlargement	19	443/2305
Atelectasis	18	410/2310
Infiltrate	17	400/2317
Pulmonary congestion	14	330/2316
Oligemia	8	196/2315
Pulmonary infarction	5	117/2312
Overinflation	5	121/2319

3.3 ECG

Multiple ECG changes in PE have been reported, and most patients with PE, depending on severity, have abnormal ECG (Stein et al. 1991b). Although some findings, like signs of right ventricular overload, are significant more frequently present in patients with PE than without (49.5 % vs. 12 %, $P < 0.00001$) (Miniati et al. 1999) the findings cannot by themselves either rule in or out PE. The ECG therefore serves primarily as an important tool in differential diagnostics. Conditions like acute coronary syndrome and ventricular arrhythmia can clinically mimic PE and can be diagnosed by ECG. Table 11 outlines findings on ECG in documented PE (from Stein et al. 1975).

Table 11 ECG findings in PE

ECG finding	% of patients with massive or submassive PE with finding
Normal electrocardiogram	13
Rhythm disturbances	
Premature atrial beats	2
Premature ventricular beats	3
Atrio-ventricular conduction disturbances	
First degree A-V block	1
P pulmonale	6
QRS abnormalities	
Right axis deviation	7
Left axis deviation	7
Clockwise rotation (V s)	7
Incomplete right bundle branch block	6
Complete right bundle branch block	9
Right ventricular hypertrophy	6
S1S2S3 Pattern	7
S1Q3T3 Pattern	12
Pseudoinfarction	11
Low voltage (frontal plane)	6
Primary RST segment and T wave abnormalities	
RST segment depression (not reciprocal)	26
RST segment elevation (not reciprocal)	16
T wave inversion	42

When signs of right heart strain are present on ECG, it is associated with worse prognosis (Hariharan et al. 2015). For example, in one study 29 % of patients with PE and ECG changes died during the admission, whereas this was only the case in 11 % of patients without ECG changes (Geibel et al. 2005).

3.4 Biochemical Analyses

Presently, three biochemical analyses have gained interest in the work-up of pulmonary embolism. These are fibrinogen d-dimer, (N-terminal-pro)-brain-natriuretic peptide (BNP) and the cardiac troponins T and I (TNT and TNI).

Different d-dimer assays are available, with different diagnostic performance. When using a high sensitivity-assay like the the quantitative enzyme-linked immunosorbent assay (ELISA) or ELISA-derived assays, the sensitivity and negative predictive values are very high (Stein et al. 2004). However, many agree that a negative d-dimer should not rule out PE when the clinical probability is high.

No d-dimer assay has sufficient specificity to confirm PE, as increased d-dimer is a non-specific marker of activation of the coagulation system. A recent review have summarized conditions described to cause elevated d-dimer, and of notice is that many of these conditions are also present in patients typically suspected of PE which can render d-dimer testing in these patients useless. The factors that, among others, can cause false-positive d-dimer are increasing age, cocaine use, immobility, hemoptysis, hemodialysis, malignancy, rheumatoid arthritis, systemic lupus erythematosus, sickle cell disease, pregnancy, postpartum state and surgery (Kline and Kabrhel 2015b).

BNP is released in right ventricular pressure overload as seen in more severe PE (Henzler et al. 2012). The test is not useful in the diagnosis or exclusion of PE, but a low value is useful to identify patients with low risk of adverse events and thereby candidates for early discharge and out-patient management (Coutance et al. 2011; Klok et al. 2008; Vuilleumier et al. 2009; Hardeman et al. 2010).

TNI and TNT are released in myocardial infarction. Right ventricular infarction can occur in PE, and is a sign of severe PE. The use of TNI and TNT has been studied in PE, and most reports have shown a connection between the release of TNI and TNT and a worse prognosis and higher risk of adverse events. As an example, a recent study showed that negative high sensitivity TNT has a very high negative predictive value of adverse events like mortality (Lankeit et al. 2011).

4 Compilation of History, Symptoms, Clinical Findings and Basic Workup

Not all patients with symptoms and clinical features suggestive of PE should be tested with diagnostic imaging. This would result in enormous overuse of CT-angiography, V/Q-scan or whatever diagnostic imaging modality is available.

Generally, when symptoms and clinical findings compatible with PE are present in a patient without any other obvious explanation testing for PE should be commenced. This balance is difficult, thus, multiple clinical decision tools have been developed and validated.

To aid the clinical decision, multiple clinical prediction scores have been suggested, of which the Wells score (Wells et al. 2000) and revised Geneva score (Le Gal et al. 2006) are widely used. Although proposed before the millennium, these two scoring systems continue to attract research interest (Guo et al. 2015). Other clinical prediction models have been suggested, e.g. the Pisa-models which have been derived from 1100 patients (Miniati et al. 2003, 2008). The Pisa-models have some obvious advantages compared to the Wells score and revised Geneva score. In particular, the prevalence of PE in patients with high clinical probability is higher using the Pisa-models. However, the Pisa-models have not been

validated to the same extent as the other scoring systems. In addition, the Pisa-model from 2008 requires ECG and a computer or similar hand held device to calculate the clinical probability which may limit the use of this clinical prediction system. In general, the clinical prediction scoring systems is more helpful in ruling out than ruling in PE, and a high clinical probability will almost always have to be confirmed by diagnostic imaging.

4.1 The Wells Score

The Wells score was derived from data from more than 1.000 patients and later validated in other patient populations (Douma et al. 2011; Wolf et al. 2004). The Wells score is found in Table 12.

One of the most notable weaknesses of the Wells score is the subjective judgment of "An alternative diagnosis less likely than PE". This has been criticized, as it leads to some degree of begging the question. However, the Wells score have stood the test of time, and in the original study it was rather predictive both in the derivation and validation group, as seen Table 13. In addition, the Wells score (in its modified version) have been validated in pregnancy and found useful to exclude PE (O'Connor et al. 2011).

Table 12 The Wells score

Clinical signs and symptoms of deep vein thrombosis (DVT)	3
An alternative diagnosis less likely than pulmonary embolism (PE)	3
Heart rate greater than 100	1,5
Immobilization or surgery in the previous 4 weeks	1,5
Previous DVT or PE	1,5
Hemoptysis	1
Malignancy	1

4.2 The Geneva and Revised Geneva Score

The Geneva score overcomes the subjective judgment in the Wells score, namely "An alternative diagnosis less likely than PE" (Wicki et al. 2001). However, the Geneva score requires arterial blood gas values while on room air which is not always available. The revised Geneva counteracts the problems with the Wells score and the original Geneva score cf. Tables 14 and 15.

4.3 Practical Impact of the Clinical Probability Scoring Systems

Based on the basic investigations, clinical presentation, symptoms, d-dimer and clinical probability score (e.g. Wells or revised Geneva scoring systems), it is possible to determine whether the patient needs focused diagnostic imaging to clarify the diagnosis. In hemodynamically stable patients, current guidelines (Konstantinides et al. 2014) suggest that patients with a high clinical probability should undergo diagnostic imaging like CT-angiography without further testing. However, in patients with low or intermediate clinical probability diagnostic imaging for PE can be withheld in patients with a negative d-dimer. This strategy is supported both by the original studies described above and later investigations (van Belle et al. 2006).

Table 13 Probability of pulmonary embolism according to the Wells score

	Derivation group			Validation group		
	Negative d-dimer	Positive d-dimer	All patients	Negative d-dimer	Positive d-dimer	All patients
Low probability (<2)	1.5	8.6	3.6	2.7	0	2.0
Intermediate probability (2–6)	7.6	36.1	20.5	2.9	37.3	18.8
High probability (>6)	20	79.6	66.7	20	60	50

Table 14 The revised Geneva score

Age > 65 years	1
Previous deep vein thrombosis or pulmonary embolism	3
Surgery (under general anaesthesia) or fracture (of the lower limbs) within 1 month	2
Active malignant condition (solid or hematologic malignant condition, currently active or considered cured < 1 year)	2
Unilateral lower-limb pain	3
Hemoptysis	2
Heart rate 75–94 beats/min	3
Heart rate ≥ 95 beats/min	5
Pain on lower-limb deep venous palpation and unilateral oedema	4

Table 15 Probability of pulmonary embolism according to the revised Geneva score

	Derivation group	Validation group
Low (0–3)	9.0	7.9
Intermediate (4–10)	27.5	28.5
High (>10)	71.7	73.7

4.4 Limitations of the Clinical Probability Scores

The clinical scoring systems are used primarily to guide whether further work up for PE is appropriate, and in many circumstances they do indeed provide guidance. However, as shown in the table below, this is not always the case, and then a gestalt clinical judgment is crucial and has to incorporate other parameters than those in the Wells and revised Geneva scores.

The three examples in Table 16 are fictional, but every day examples of comparable patients, i.e. a 68 year old male with symptoms which could be caused by PE. The first patient has intermediate probability of PE both by Wells score and revised Geneva score. Most clinicians however, will probably have an *a priori* feeling that the clinical probability is indeed very high. The symptoms, risk factors, clinical presentation, and basic work up is compatible with PE, and no major sign of infection, or other cardiac-pulmonary cause is obvious. The d-dimer level in this patient should probably not be used to decide whether further work-up is warranted or not.

The second patient has discrepancies between the Wells score and revised Geneva score which are low and intermediate, respectively. The d-dimer analysis could, according to the algorithms, be appropriate, as the Wells score is of low probability. However, many clinicians would probably without hesitation find the overall clinical presentation compatible with pneumothorax, and not find indication for diagnostic imaging on suspicion of PE even though the d-dimer level is abnormal.

The third patient is categorized as intermediate probability (like the first patient) by both Wells score and revised Geneva score. However, the overall clinical presentation in this patient would by most clinicians probably not be judged obviously, as PE could be the cause of the symptoms, but they could also be attributed to infectious exacerbation of COPD. The d-dimer in this setting adds little value, as it would be expected to be elevated in all circumstances due to ongoing inflammation or infection, as judged by the abnormal CRP level.

4.5 Risk Stratification

Aside from guiding whether specific diagnostic imaging is advisable in suspected PE, the history, symptoms, clinical findings and basic workup is also helpful in risk stratification of patients with an established diagnosis of PE. Obviously, patients presenting in cardiac arrest due to PE have a high risk of death, even though resuscitation with good clinical outcome is indeed possible with prompt and evidence-based treatment (Logan et al. 2014). These patients will intuitively receive aggressive emergency treatment, monitoring, and observation in an intensive care environment. In other patients, risk stratification is less obvious. Multiple studies have addressed this issue, and especially one study, the pulmonary embolism severity index (PESI) study, has gained universal use, as it is based on 15,000

Table 16 Examples of three patients presenting with the same symptoms

#	Preexisting disease	Present history	Symptoms	BP/mmHg HR/min SpO2/% RR/min Temp/°C	Clinical findings	ECG	Chest x-ray	ABG	D-dimer	CRP	Wells score	Revised Geneva score
1	None	3 days ago hip replacement	Shortness of breath, Left-sided pleuritic chest pain	125/85 105 88 % 25 37.9	Lungs clear No signs of DVT	Sinus tachycardia	Discrete left pleural effusion	Hypoxemia Hypocapnia	2.09	11	6	8
2	None	3 days ago hip replacement	Shortness of breath, Left-sided pleuritic chest pain	125/85 105 88 % 25 37.9	Decreased left sided sounds No signs of DVT	Sinus tachycardia	Left PTX	Hypoxemia Hypocapnia	2.09	11	3	8
3	Severe COPD	None	Shortness of breath Left-sided pleuritic chest pain	125/85 105 88 % 25 37.9	No signs of DVT	Sinus tachycardia	Discrete infiltration left lower lobe	Hypoxemia, Normocapnia	2.09	35	4.5	6

ABG arterial blood gas analysis, *BP* blood pressure, *COPD* chronic obstructive pulmonary disease, *CRP* C-reactive protein, *DVT* deep venous thrombosis, *ECG* electrocardiogram, *HR* heart rate, *PTX* pneumothorax, *RR* respiration rate, *SpO2* peripheral capillary oxygen saturation

Table 17 The PESI for risk stratification of PE

Clinical feature	Point	
Age	Age in years	
Male sex	+10 points	
Cancer	+30 points	Class I $\leq$ 65 points
Chronic heart failure	+10 points	Class II = 66–85 points
Chronic pulmonary disease	+10 points	Class III = 86–105 points
Pulse rate > 110/min	+20 points	Class IV = 106–125 points
Systolic blood pressure <100 mm Hg	+30 points	Class V $\geq$ 125 points
Respiratory rate >30 breaths per minute	+20 points	
Temperature <36 °C	+20 points	
Altered mental status	+60 points	
Arterial oxygen saturation <90 %	+20 points	

Table 18 In-patient mortality according to PESI-score (%)

	Derivation group	Internal validation group
Class I	0.8	1.1
Class II	1.8	1.9
Class III	4.2	4.7
Class IV	5.9	7.0
Class V	15.8	17.2

patients with PE (Aujesky et al. 2005), and later validated in other settings (Chan et al. 2010; Donze' et al. 2008). The PESI calculation and derived risk stratification are seen in the Tables 17 and 18, respectively.

Right heart dysfunction due to PE is found in a subgroup of patients with otherwise stable systemic circulation. This finding is caused by both obstruction of the pulmonary vasculature and release of pulmonary vasoactive substances secondary to PE. The result from this is pulmonary hypertension, right ventricular dilatation, tricuspid valve insufficiency and intraventricular septal shift towards the left ventricle. These consequences leads to left heart dysfunction, decreased myocardial perfusion and in some cases right ventricular infarction and can be visualized by e.g. echocardiography and result in the release of BNP, TNT and TNI measurable in the blood as earlier described. In addition, left heart dysfunction due to intra-ventricular septal shift and decrease in left ventricular preload, can lead to a fall in cardiac output, systemic hypotension, shock and increased mortality (Kreit 2004). These pathophysiological consequences have been clinically confirmed in numerous studies which have demonstrated increased mortality in patients with right heart dysfunction (Coutance et al. 2011).

When PE is diagnosed, risk stratification is warranted. This stratification is, depending on local guidelines and facilities, based on clinical information (like the PESI), the presence or absence of shock and signs of right heart dysfunction or infarction on echocardiography and biochemical analyses. The result of this risk stratification is important both in prognostication, choosing site of treatment (out-patient, in-patient, intensive care) and when selecting appropriate therapy. For example, studies have shown that low-risk patients without signs of right heart dysfunction can safely be discharged to out-patient care (Squizzato et al. 2012), and other studies have shown that patients with shock and selected patients with right heart dysfunction benefit from fibrinolytic therapy (Aujesky et al. 2011; The PEITHO Steering Committee 2012). However, further discussion of these topics is found in other chapters.

5 Conclusions

- Symptoms of PE (like dyspnea, chest pain, hemoptysis and syncope) are non-specific, but inevitably warrants further diagnostic work-up
- Point-of-care ultrasonography of the lungs and deep veins seems appropriate when

evaluating patients with acute symptoms compatible with PE

- Basic work up in patients with symptoms of PE comprises, in part, of arterial blood gas analysis, ECG, chest x-ray and venous blood sampling and these investigations are primarily important in establishing differential diagnosis and in risk stratification
- Clinical prediction score systems like the Wells score and revised Geneva score can, along with d-dimer, be used to guide if diagnostic imaging like CT-angiography or V/Q-scan on suspicion of PE is warranted
- When the diagnosis of PE is established, risk stratification is warranted e.g. using the PESI-score and assessment of right heart function by echocardiography to guide location of treatment, monitoring, treatment and prognosis
- When the diagnosis of PE is established, identification of risk factors for PE is warranted to guide duration of therapy and prevent further PE

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Radionuclide Diagnosis of Pulmonary Embolism

Søren Hess and Poul Henning Madsen

Abstract

Diagnostic imaging plays an integral role in the diagnostic workup of suspected pulmonary embolism, and several modalities have been employed over the years. In recent years, the choice has been narrowed to either computer tomographic or radionuclide based methods, i.e. computer tomographic angiography (CTA) and ventilation-perfusion scintigraphy (V/Q-scan). Both methods display advantages and shortcomings, and while we provide some insights into CTA and alternative methods, the paper's main focus is a review of the V/Q-scan. We discuss basic considerations, interpretation criteria, clinical value, and controversies of conventional planar lung scintigraphy as well as the more contemporary 3-dimensional imaging technique of single photon emission tomography (SPECT) with or without CT.

Keywords

Pulmonary embolism • Diagnosis • Radioisotope • Lung scintigraphy • Ventilation-perfusion scintigraphy • V/Q-scan • SPECT • Molecular imaging

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1 Introduction

Accurate diagnosis of pulmonary embolism (PE) is imperative to institute correct treatment in a timely fashion, not only to reduce morbidity and mortality, but also to limit the number of patients subjected to the risks of potentially dangerous side effects from PE therapy. Over

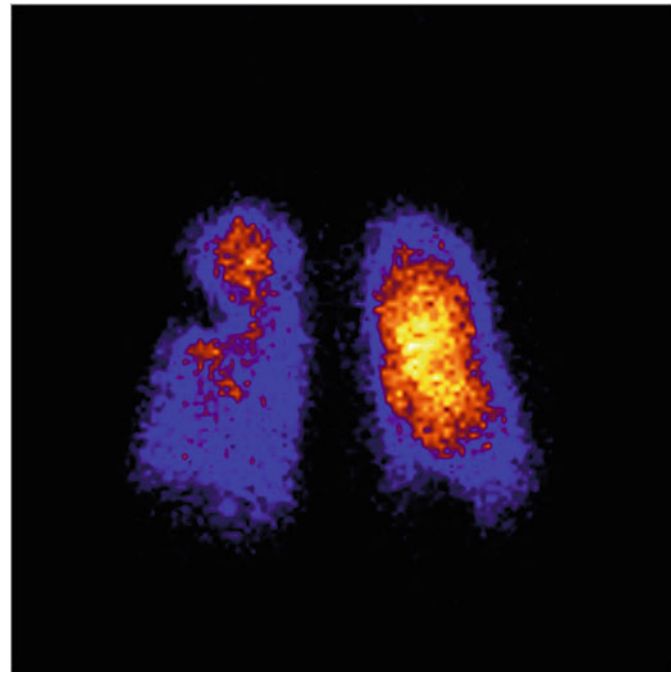

Fig. 1 Planar perfusion scintigraphy in anterior-posterior projection showing a classic segmental wedge-shaped perfusion defect

the years, several imaging modalities have been employed in the diagnostic workup of patients suspected of PE, i.e. conventional pulmonary angiography, magnetic resonance imaging, computer tomography angiography (CTA), and radionuclide ventilation-perfusion scintigraphy (V/Q-scan). In recent years, the choice has been narrowed and now stands between CTA and V/Q-scan both with advantages and shortcomings (Hess et al. 2005; Madsen et al. 2005). This chapter focuses on basic considerations and clinical value of V/Q-scan.

Radionuclide assessment of suspected pulmonary embolism was introduced 50 years ago: In 1964, Wagner et al. presented the first lung perfusion scans based on intravenous injection of Iodine-131-labelled microparticles (Ueda et al. 1964). The rationale is simple; the tracer is transported to the pulmonary circulation where the microparticles are distributed evenly before they wedge in the precapillary arterioles. The gamma rays from the radioisotope are registered by a gamma camera and hereby produce an image of the pulmonary perfusion. However, if blood supply to part(s) of the lung is blocked by an embolus, the microparticles do not reach the capillaries distal to the embolus and an area devoid of radioactivity appears as a perfusion defect in the scintigraphic image. As a result of the anatomy of the pulmonary vascular bed and the segmental morphology of the lungs, the ensuing perfusion defects are often near-wedge shaped and limited by segmental anatomy (Bajc et al. 2009a) (Fig. 1).

Only a few years after the introduction of perfusion scintigraphy supplemental ventilation scintigraphy was introduced (Wagner et al. 1968): The patient inhales a radiolabelled gas or aerosol which distributes throughout the ventilated parts of the lungs to depict the ventilation distribution. The method was developed to help differentiate perfusion defects caused by PE (i.e. perfusion defects with retained ventilation; *mismatch*) from perfusion defects secondary to parenchymal lung disease (i.e. *matched* defects due to regional hypoxic vasoconstriction causing perfusion defects secondary to ventilation defects) (Fig. 2). Thus, the combined perfusion and ventilation study potentially improves the diagnostic specificity for pulmonary embolism.

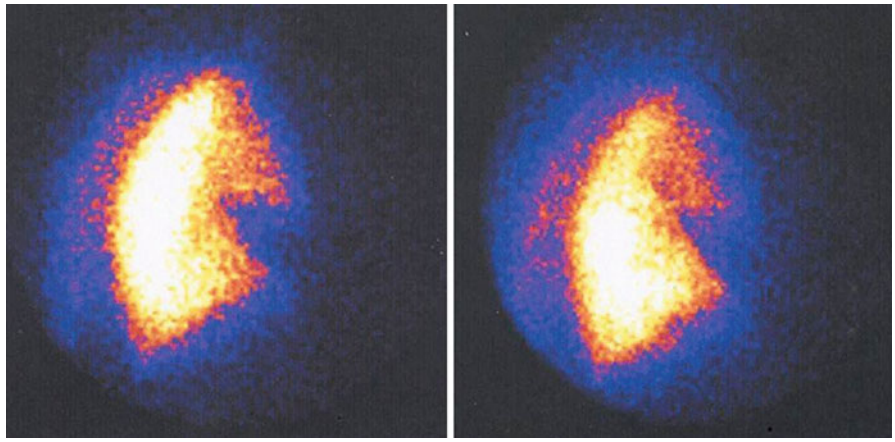

Fig. 2 Planar V/Q-scan in lateral projections showing matched perfusion (*left*) and ventilation (*right*) defects

1.1 Tracers and Imaging Technique

Today, technetium-99m-labelled macroaggregated albumin (^{99m}Tc-MAA) has replaced the iodine-based perfusion tracers, but otherwise the technique has remained virtually unchanged since 1964. Usually, 200,000–500,000 particles are injected intravenously with the patient in the supine position to limit the effect of gravity on regional pulmonary arterial blood flow. The particles mix uniformly with venous blood and are subsequently distributed homogenously in the pulmonary circulation. The caliber of precapillary arterioles is usually < 15 μm, while ^{99m}Tc MAA particles measure between 10 and 90 μm. They cause transient blockage of about 0.1 % of the capillary bed; the biologic half-life of the particles is usually 3–4 h before they are hydrolyzed to smaller particles by enzymatic hydrolysis and cleared by phagocytosis. The administered dose of radioactivity is usually 100–200 MBq yielding an effective dose of 2–3 mSv (mean annual background radiation constitutes ca. 3 mSv worldwide). The dose should be reduced in pregnant women, while the number of particles should be reduced according to weight in children (<35 kg) and may be reduced in patients suspected of right-to-left shunt (to minimize the risk of systemic emboli) or pulmonary hypertension (to reduce the risk of severe pulmonary deterioration as the particles lodge more centrally due to reduced lumen) (Bajc et al. 2009a; Ciofetta et al. 2007).

Ventilation tracers are either gaseous or aerosols. Of the former, the preferred tracer is krypton-81m, a noble gas with a 13 s physical half-life. Thus, is has to be breathed continuously by mask during image acquisition which most patients with impaired respiration can accommodate. However, krypton-81m is produced from rubidium-81 with a physical half-life of 4.7 h, and the generator lifetime is therefore only 1 day which may limit availability due to relatively high costs. Particularly in Europe, an aerosol labelled with technetium-99m (^{99m}Tc-Technegas®) is now replacing krypton-81m. It is produced by nebulizing the radiopharmaceutical into a fine mist for inhalation. In contrast to krypton-81m, technetium-99m is widely available and relatively inexpensive. Both have ideal energies for gamma camera imaging, but the aerosols are not always uniformly distributed as their regional distribution in the lungs reflects local ventilation. Furthermore, the ultrafine particles may be caught in mucus in the central airways of COPD patients, and not all patients can cooperate to the relatively deep inhalations required (Bajc et al. 2009a, 2010).

In suspected PE, most centers routinely combine perfusion and ventilation images in corresponding projections (Figs. 3, 4, and 5).

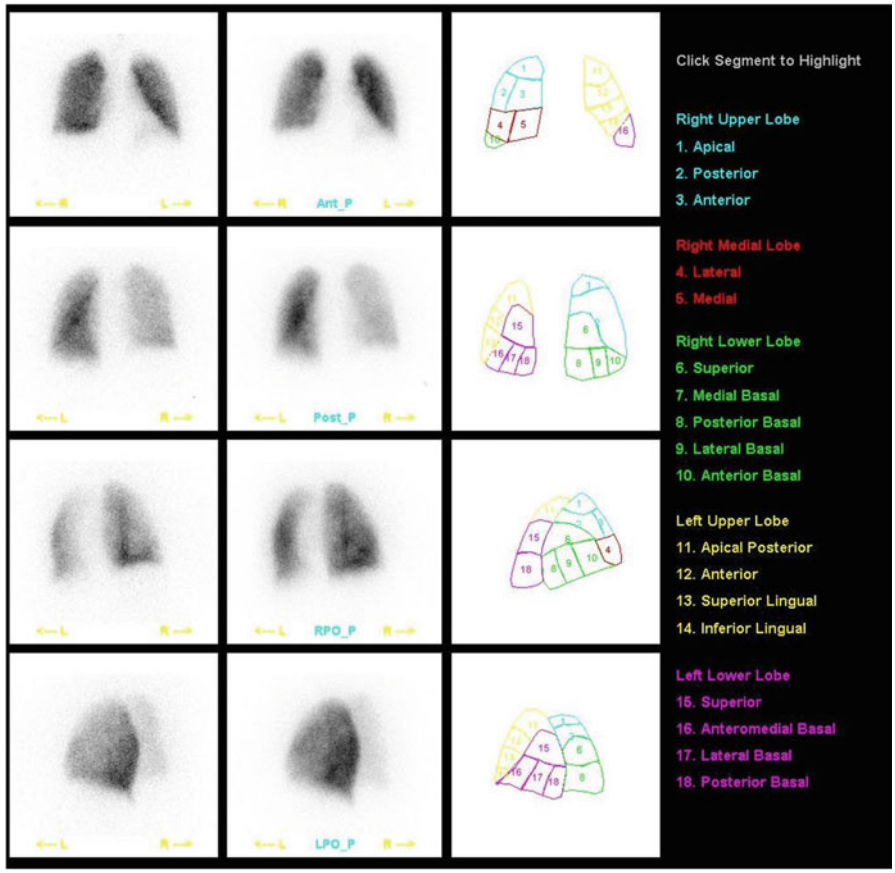

Fig. 3 Normal planar V/Q-scan. Normal distribution of ventilation (*left column*) and perfusion (*right column*) with no defects in either scan

Images may be acquired as planar (two-dimensional) in which case they should include 4–8 views of the lungs, i.e. anterior and posterior views, right and left lateral views, and right and left posterior oblique views. However, despite numerous projections, planar perfusion imaging may not be sufficient to clearly visualize all segments of the lungs; especially solitary segmental defects in the basal medial segments of the right lower lobe may go undetected. Segments devoid of radioactivity in these regions will be obscured by the radioactivity in the surrounding segments that completely encompass it. Thus, in recent years single photon emission computed tomography (SPECT) imaging has become much more widespread: SPECT enables three-dimensional image acquisition by rotation of the gamma camera around the patient. Images are subsequently reconstructed to be displayed in three projections (i.e. transaxial, sagittal, and coronal), much like conventional CT (Fig. 6).

SPECT images may even be co-registered with CT (SPECT/CT) to combine the physiological data from the radiotracer distribution with the radiological (structural) information from CT. The downside of SPECT is longer acquisition time of ca. 30 min for a complete ventilation/perfusion scintigraphy, which may be rather lengthy to lay still and flat for patients with respiratory impairment. The CT acquisition only takes a few minutes.

2 The Value of Planar V/Q-Scan in Suspected Pulmonary Embolism

To date, the comprehensive multicenter *Prospective Investigation of Pulmonary Embolism*

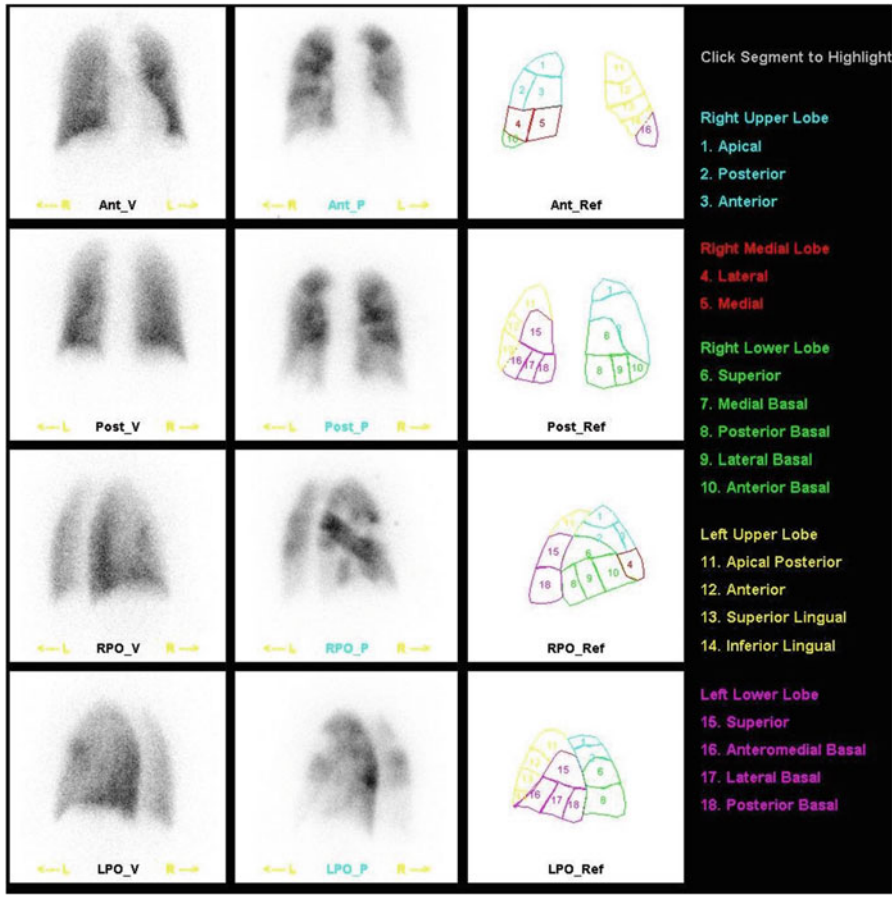

Fig. 4 Multiple pulmonary emboli. Normal ventilation (*left*) but multiple perfusion defects in both lungs (*right column*), i.e. V/Q mismatch

Diagnosis (PIOPED) study from 1990 remains the landmark study on combined V/Q-scan in suspected PE (PIOPED Investigators 1990). It included 933 consecutive patients of which 755 underwent both V/Q-scan and the reference standard pulmonary angiography. V/Q-scans were reported probabilistic, i.e. scan results were divided into four categories based on comprehensive, but somewhat cumbersome interpretation criteria, i.e. high, intermediate, or low probability for PE or normal scans (Table 1).

The results clearly stated that, in conclusive cases, sensitivity and specificity was high: If all abnormal scans (high, intermediate, or low) were considered indicative of PE, sensitivity was 98 %, but specificity only 10 %; which means all PE would be diagnosed and a normal scan would safely rule out the diagnosis. If on the other hand only high probability scans were considered diagnostic for PE, sensitivity was only 41 %, but specificity increased to 98 %; which means not all PE would be diagnosed but a positive scan would be very specific for PE. Thus, a high probability scan accurately diagnoses PE, whereas normal scans safely rules out the diagnosis. Unfortunately, less than half of the scans were in either category with the remainder being intermediate or low probability scans, and both categories are considered non-diagnostic as PE is present in 31 % and 12 % of cases, respectively. The combination of clinical pretest probability and V/Q-scan results could to some extent mitigate these numbers, i.e. in patients with low-probability V/Q-scans and low clinical

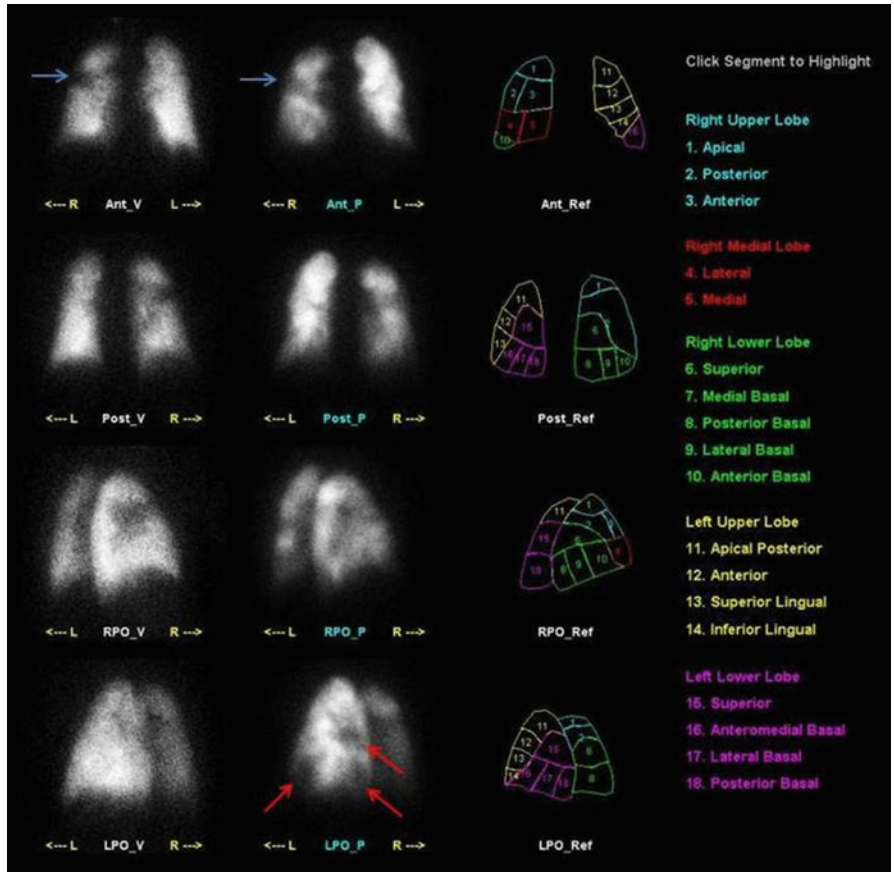

Fig. 5 Suspected pulmonary embolism in a lung cancer patient. Planar V/Q-scan shows segmental ventilation defect with corresponding matched perfusion defect consistent with the known tumor (*blue arrows*), but also several perfusion defects (*red arrows*) in areas with normal ventilation consistent with pulmonary embolism

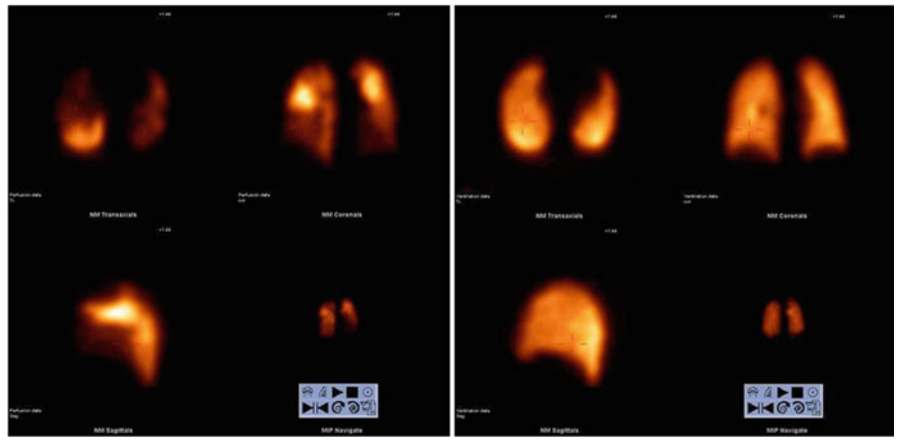

Fig. 6 SPECT V/Q-scan with classic appearance of pulmonary emboli, i.e. multiple perfusionsdefects (*left*) with normal ventilation (*right*)

Table 1 Original and *revised* PIOPED interpretation criteria (PIOPED Investigators 1990; Freeman et al. 2008)

High probability
≥2 Large (>75 % of a segment) segmental perfusion defects without corresponding ventilation or roentgenographic abnormalities or substantially larger than either matching ventilation or chest roentgenogram abnormalities
≥2 Moderate segmental (≥25 % and ≤75 % of a segment) perfusion defects without matching ventilation or chest roentgenogram abnormalities and 1 large mismatched segmental defect
≥4 Moderate segmental perfusion defects without ventilation or chest roentgenogram abnormalities
Intermediate probability (indeterminate)
Not falling into normal, very-low-, low-, or high-probability categories
Borderline high or borderline low
Difficult to categorize as low or high
Single moderate mismatched segmental perfusion defect with normal chest roentgenogram (low probability in the original criteria)
Low probability
Nonsegmental perfusion defects (eg, very small effusion causing blunting of the costophrenic angle, cardiomegaly, enlarged aorta, hila, and mediastinum, and elevated diaphragm)
Single moderate mismatched segmental perfusion defect with normal chest roentgenogram (*intermediate probability in the revised criteria*)
Any perfusion defect with a substantially larger chest roentgenogram abnormality (*very low probability in the revised criteria*)
Large or moderate segmental perfusion defects involving no more than 4 segments in 1 lung and no more than 3 segments in 1 lung region with matching ventilation defects either equal to or larger in size and chest roentgenogram either normal or with abnormalities substantially smaller than perfusion defects
>3 Small segmental perfusion defects (<25 % of a segment) with a normal chest roentgenogram (*very low probability in the revised criteria*)
Very low probability
≤3 Small segmental perfusion defects with a normal chest roentgenogram
Nonsegmental perfusion abnormalities. These are enlargement of the heart or hilum, elevated hemidiaphragm, linear atelectasis, or costophrenic angle effusion with no other perfusion defects in either lung
Perfusion defect smaller than corresponding radiographic lesion
>2 matched V/Q defects with regionally normal chest radiograph and some areas of normal perfusion elsewhere in the lungs
1–3 small segmental perfusion defects (<25 % of a segment)
Solitary triple matched defect (defined as a matched V/Q defect with associated matching chest radiographic opacity) in the middle or upper lung zone confined to a single segment
Stripe sign, which consists of a stripe of perfused lung tissue between a perfusion defect and the adjacent pleural surface (best seen on a tangential view)
Pleural effusion equal to one third or more of the pleural cavity with no other perfusion defect in either lung
Normal
No perfusion defects present
Perfusion outlines exactly the shape of the lungs as seen on the chest roentgenogram (hilar and aortic impressions may be seen, chest roentgenogram and/or ventilation study may be abnormal)

(continued)

pretest probability of PE, the negative predictive value was 96 %, but this combination only occurred in a minority of patients. Thus, the conclusions of the study, which still stands today at its 25-years anniversary, were those already mentioned, i.e. in conclusive patients V/Q-scans reliably established and ruled out PE, but in many patients further imaging is necessary. Some additional shortcomings of PIOPED study need to be mentioned. First and foremost, the interpretation criteria are themselves relatively complicated and may therefore seem cumbersome to use in daily clinical practice. They are not based solely on mismatched defects, but a rather intricate assessment which to some extent seems arbitrarily outlined and prone to subjectivity. This is to some extent evident from the inter-observer variability in scan interpretation. As expected, agreement among readers was excellent for normal and high probability scans (92–95 %), but not as good for intermediate and low probability studies. Furthermore, since pulmonary angiography (PA) was omitted for ethical reasons in 176 patients with low probability or normal V/Q-scans, selection bias may have been introduced towards patients with intermediate or high probability scans leading to overestimation of sensitivity and underestimation of specificity (Stein and Gottschalk 1994).

2.1 Later Modifications of Planar V/Q Scan Interpretations

In acknowledgement of the less-than straight forward results obtained in the PIOPED study, the ensuing decades have seen several attempts to optimize the results, by revising interpretation algorithms, or the interpretation criteria themselves. The former include some more or less esoteric findings such as the "triple match" and the "stripe sign". According to PIOPED, triple matched findings (i.e. matching perfusion, ventilation, and findings on chest x-ray) caries varied prevalence of PE based on location, e.g. 11–12 % in the upper or middle zones of the lung (low probability of PE) and 33 % in the lower zones (intermediate probability of PE) (Worsley et al. 1993). The "stripe sign" (i.e. a rim of perfused lung between the perfusion defect and adjacent pleural surface) was considered low-probability in PIOPED. It was later re-categorized as very low probability (a novel category introduced in 2007 with PPV less than 10 %) and, thus, considered to rule out PE if present as the only finding (Sostman and Gottschalk 1992). Conversely, some findings were later upgraded from low to intermediate probability, e.g. a single, segmental V/Q-mismatch which has been shown to be positive for PE in 36 % of cases (Gottschalk et al. 1993). Nonetheless, these modifications changed little with regard to the overall shortcomings of planar V/Q-scans. Several studies have assessed the interpretative challenges to the clinicians by way of questionnaires; Siegel et al. found the clinician's interpretation of the probability of PE in patients with intermediate probability ranging from 5 to 75 % (Siegel et al. 2004), whereas Kemper et al. found the clinical significance of intermediate probability misinterpreted in 39 % of patients, and only 11 % was investigated further (Kember et al. 1997). We found similar results in a retrospective survey at our institution as only 14 % of patients with intermediate probability V/Q-scans were further investigated (Marmolin et al. 2009). These results are in opposition to the literature which state the probability of PE in intermediate probability scans to be 30 %, and the various guidelines recommend further investigations in all patients with intermediate probability scans.

Table 2 PIOPED II interpretation criteria (Sostman et al. 2008a)

PE present (high probability)
Two or more segments of V/Q mismatch
PE absent (normal perfusion or very low probability)
Nonsegmental perfusion abnormalities; these were enlargement of the heart or hilum, elevated hemidiaphragm, costophrenic angle effusion, and linear atelectasis with no other perfusion defect in either lung
Perfusion defect smaller than corresponding radiographic lesion
Two or more matched V/Q defects with regionally normal chest radiograph and some areas of normal perfusion elsewhere in the lungs
One to three small segmental perfusion defects (<25 % of segment)
Solitary triple-matched defect (defined as a matched V/Q defect with associated matching chest radiographic opacity) in the mid or upper lung zone confined to a single segment
Stripe sign (a stripe of perfused lung tissue between a perfusion defect and the adjacent pleural surface; best seen on a tangential view)
Pleural effusion of one-third or more of the pleural cavity with no other perfusion defect in either lung
Nondiagnostic (low or intermediate probability)
All other findings

The original PIOPED interpretation criteria were revised for the PIOPED II trial (Table 2), which aimed at comparing V/Q-scans with computer tomography angiography (CTA) (Sostman et al. 2008a).

CTA was shown to have an overall sensitivity, specificity, PPV, and NPV for PE of 83 %, 96 %, 86 %, and 95 %, respectively. However, the results of CTA were highly influenced by PE location (i.e. PPV of 97 % in main or lobar arteries, 68 % in segmental arteries, and 25 % in subsegmental arteries) as well as clinical pretest probability (i.e. PPV of a positive CTA was > 92 % for high or intermediate clinical probability, but only 58 % in patients with low clinical probability). Likewise, NPV of negative CTA was 96 % in patients with low clinical probability, 89 % with intermediate clinical probability, but only 60 % in patients with high clinical probability. Also, inconclusive CTA due to technically inadequate scans (comprising 51 patients

or 6 %) were excluded from data analysis. If these scans were included, the overall sensitivity and specificity would have been 78 % and 90 %, respectively (Goodman et al. 2007). The overall results of CTA were generally comparable to overall results for V/Q-scans, i.e. sensitivity of 78 % (high probability V/Q-scans) and specificity of 98 % (normal scans). Furthermore, based on retrospective analysis of PIOPED II data, Gottschalk et al. introduced the aforementioned very low probability category with overall PPV less than 10 %, a limit considered acceptable by clinicians. Not least thanks to this category, the number of non-diagnostic intermediate probability scans was less than the original PIOPED (74 % had a conclusive V/Q scan); in fact, 56 % of PIOPED II patients was interpreted as very low probability with only 8 % (36 of 440) of these patients having PE and only 3 % (8 of 62) in conjunction with a low clinical pretest probability (Freeman et al. 2008; Gottschalk et al. 2007).

Another approach was the return to earlier practices of assessing perfusion scans only. The PISA-PED study included 890 patients (Miniati et al. 1996) and based their criteria on the shape of the perfusion defect only and comprised few, simple criteria (Table 3).

Table 3 PISA-PED interpretation criteria (Miniati et al. 1996)

Abnormal PE+ (PE present)
Single or multiple wedge-shaped perfusion defects with or without matching chest-roentgenographic abnormalities. Wedge-shaped areas of overperfusion usually coexist
Abnormal PE− (PE absent)
Single or multiple perfusion defects other than wedge-shaped, with or without matching chest-roentgenographic abnormalities. Wedge-shaped areas of overperfusion are usually not seen
Near-normal (PE absent)
Perfusion defects smaller or equal in size and shape to the following roentgenographic abnormalities: cardiomegaly; enlarged aorta, hila and mediastinum; elevated diaphragm; blunting of the costophrenic angle; pleural thickening; intrafissural collection of liquid
Normal (PE absent)
No perfusion defects of any kind

PE was considered present in PE+ scans and absent in PE-, near-normal, and normal scans, which yielded sensitivity and specificity of 92 % and 87 %, respectively, and there were no non-diagnostic results. At the same time, the patients' clinical likelihood of PE was categorized as very likely, possible, and unlikely. Combining a PE+ scan with clinically very likely PE, PPV was 99 %, whereas the combination of clinically unlikely PE with a PE- scan yielded a NPV of 97 %. As part of the aforementioned PIOPED II, perfusion scans were reinterpreted using either PIOPED II criteria or PISA-PED criteria. The fraction of non-diagnostic results was 21 % using revised PIOPED II criteria, compared to none when using PISA-PED criteria. The sensitivity of "PE present" reached 85 %, and the specificity of "PE absent" 93 % (modified PIOPED II criteria), whereas PISA-PED criteria yielded sensitivity of 80 % and specificity of 97 %. The authors concluded that perfusion scintigraphy combined with chest radiography is as accurate as CTA with lower cost and lower radiation dose (Sostman et al. 2008b). However, the results of PISA-PED have never been reproduced in any similar setting, and the results rely heavily on skilled chest x-ray interpretation in conjunction with V/Q-scans. Nonetheless, the results indicate that perfusion scans may be viable in patients incapable of performing an adequate ventilation scan.

As mentioned earlier, the patients pretest probability is highly influential on the diagnostic performance of V/Q scans (as well as CTA). This prompted the use of so-called "gestalt interpretation", that is, experienced nuclear medicine physicians' subjective estimate of PE likelihood sans specific interpretation criteria. This is in essence an integrative composite pathway taking into account all available data, including overall image interpretation algorithms, clinical data, ancillary findings, and pathophysiological features of PE. Gestalt interpretation correlated well with proven PE in the PIOPED study with good-to-excellent intra- and inter-observer variability (Hagen et al. 2002, 2003). Thus, experienced readers may be able to provide accurate estimates of the clinical PE likelihood, but the

method is difficult to use for inexperienced readers of V/Q-scans.

2.2 Additional Interpretive Pitfalls

Co-morbidity severely influences the diagnostic performance of V/Q-scans, especially chronic obstructive pulmonary disorder (COPD). Thus, a novel chest X-ray is pivotal in the setting of suspected PE, not for the diagnosis per se, but to assist in the interpretation of ventilation abnormalities. The challenge with V/Q-scans in patients with COPD was addressed by Lesser et al. based on PIOPED data; in the subgroup of patients with COPD intermediate and low probability scans occurred in 60 % (22 % had PE) and 30 % (6 % had PE), respectively. In the remaining patients with either high probability scans or normal scans, PE was present in 100 % and 0 %, respectively. Thus, the diagnostic value is exactly the same as in patients with no pulmonary co-morbidity, but the proportion of non-diagnostic scans is severely increased (Lesser et al. 1992).

Other interpretative pitfalls include false positive readings. These may be caused by older, unresolved PE: About 75 % of perfusion defects are dissolved completely within 3 months to a year while the remainders persist and these unresolved or only partly lysed emboli may give rise to persistent perfusion defects in later scans if the patients are suspected of recurrence (Sasahra 1973). Thus, some advocate follow up scans after 6–12 months to serve as new baseline scans in case of suspected recurrence (Bajc et al. 2009b) (Fig. 7).

Other false positive readings are the results of various conditions causing external compression of the pulmonary vasculature (e.g. tumors or lymphadenopathy), abnormalities in the vessel wall (e.g. vasculitis), or congenital abnormalities (e.g. pulmonary artery agenesis or hypoplasia). Unilateral V/Q mismatch, especially hypoperfusion in an entire lung with normal contralateral

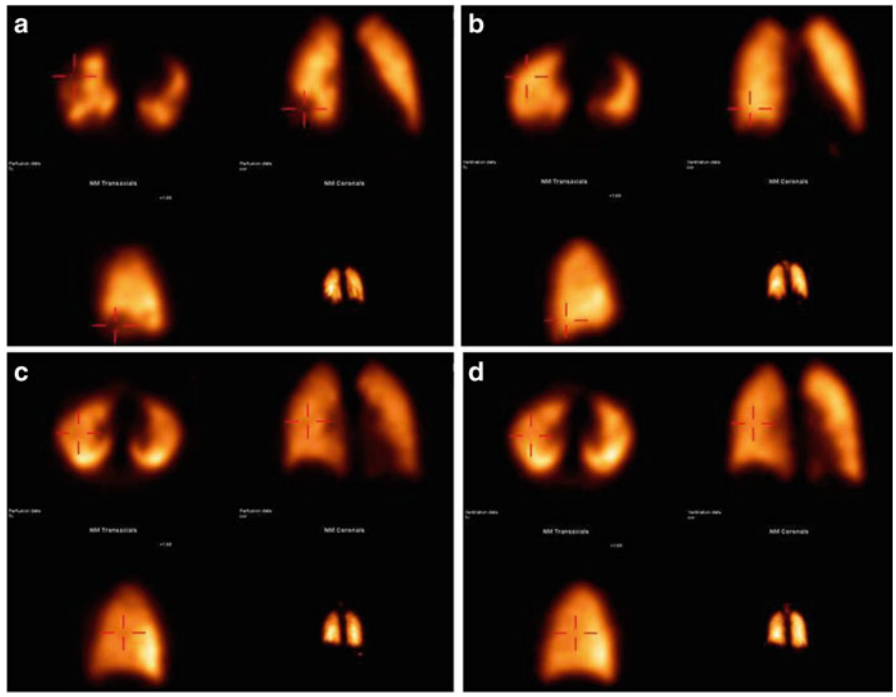

Fig. 7 Resolution of perfusion defects. (**a**–**b**) SPECT V/Q-scan at baseline; perfusion (**a**) with right-sided segmental defect and normal ventilation (**b**). (**c**–**d**) SPECT V/Q-scan in the same patient 3 months later; normalized perfusion (**c**) and normal ventilation (**d**)

perfusion should raise suspicion of external (tumorous) compression, congenital abnormalities, or proximal PE. However, emboli are usually bilateral (in 85 % of cases), so if such a finding is caused by proximal PE, it is often accompanied by multiple peripheral and wedge-shaped perfusion defects as a result of dispersed emboli.

3 The Value of SPECT V/Q-Scan in Suspected Pulmonary Embolism

As presented above there are inherent problems with planar V/Q-imaging. These are to some extent owing to the 2-dimensional assessment of a moving 3-dimensional organ and include: (1) overlap of anatomic regions which may hamper correct assignment of defects to the correct anatomic segments, (2) "shine-through", i.e. normal perfusion from underlying segments may obscure perfusion defects, and (3) - non-visualization of some segments, especially the medial basal ones. However, all may be alleviated by using SPECT, and in recognition of this, SPECT V/Q-scans have gained more widespread use in the past decade, especially in European centers and in Australia and New Zealand. The less implementation in the United States is in part due to the fact that the most widely used ventilation tracer, ^{99m}Tc-Technegas, is currently only on the brink of becoming commercially available in the United States. The abundant ventilation tracer in the United States, Xenon-133, is less than ideal for SPECT imaging owing to its relatively low energy and suboptimal spatial resolution both of which is enhanced in SPECT imaging. Krypton-81m is a viable alternative, and due to a different energy than that of ^{99m}Tc-MAA, the V/Q-scan can be performed as a simultaneous dual-isotope scan which reduces the risk of misalignment due to patient movement between scans. However, as already mentioned the isotope is less cost-effective (Roach et al. 2010).

Overall, studies on accuracy of SPECT V/Q-scans report sensitivities of 79–100 %, specificities of 83–100 %, and accuracies of 80–98 % (Stein et al. 2009; Mortensen and Gutte 2014). These results were recently summed up in a meta-analysis of the available literature; three retrospective studies and six prospective ones comprising 36–1,785 patients with PE-incidences ranging 20–38 %. Pooled sensitivity and specificity of SPECT V/Q-scan were 96 % and 97 %, respectively (Kan et al. 2015).

When direct comparison between planar and SPECT V/Q-scans are performed, corresponding values of planar V/Q-scans have been reported as 64–85 % sensitivity, 72–100 % specificity, and 70–96 % accuracy. In general, SPECT is considered to increase sensitivity, specificity, and accuracy with 21 %, 6 %, and 7 %, respectively – thus, SPECT identifies a larger number of defects as well as smaller defects, and it increases the confidence of the reader (Stein et al. 2009; Mortensen and Gutte 2014). Perhaps the most important gain from SPECT is the marked reduction in non-diagnostic scans which is consistently reported to be < 4 % of cases (compared with 72 % low or intermediate probability planar V/Q-scans in the original PIOPED) (Stein et al. 2009).

3.1 Controversies

Although the advantages of SPECT over planar images are irrefutable, generally as well as in PE diagnostics, some controversies remain. The choice of interpretation criteria is the most important one, and whereas the interpretation criteria for planar V/Q-scan are well-established and extensively validated, the optimal schemes for V/Q-SPECT are a lot less defined. It is worth noting that in the abovementioned meta-analysis, the studies on SPECT with poorest performance with regard to sensitivity and specificity were the ones employing PIOPED-based criteria (revised PIOPED or PIOPED II), they had sensitivities of 79 %, 83 %, and 94 %, respectively. The poorest specificity (83 %) was also found in a study using PIOPED-based criteria (Kan et al. 2015). Furthermore, one of these studies reported a rate of non-diagnostic scans of 25 % (Miles et al. 2009). Thus, novel and simpler criteria have been

Table 4 European Association of Nuclear Medicine's recommended interpretation criteria for SPECT or SPECT/CT V/Q-scans (Bajc et al. 2009a)

PE present
Mismatch of at least 1 segment or 2 subsegments that conforms to the pulmonary vascular anatomy
PE absent
Normal perfusion pattern conforming to the anatomic boundaries of the lungs
Matched or reversed mismatch defects of any size, shape or number in the absence of mismatch
Mismatch that does not have a lobar, segmental or subsegmental pattern
Non-diagnostic
Multiple abnormalities not typical of specific diseases

proposed to overcome the challenges of probabilistic interpretation. Most are simply based on the presence or absence of mismatched defects albeit with variable cut-offs. The European Association of Nuclear Medicine recommends $\geq$ 1 segmental or 2 subsegmental mismatched perfusion defects to be considered positive for PE if they conform to the pulmonary vasculature, whereas normal perfusion, any matched defects, or any mismatched defects not conforming to pulmonary vasculature anatomy is to be reported as negative for PE (Roach et al. 2010) (Table 4).

This approach was also endorsed in a recent study by Le Roux et al. which investigated several different interpretation schemes. They found one segmental mismatched defect or 2 subsegmental mismatched defects to be the best cut-off yielding sensitivity and specificity of 92 % and 91 %, respectively (Le Roux et al. 2014).

In the past two decades since the first studies on CTA emerged, the debate has raged back and forth between radiologists and nuclear medicine physicians as to which is the better modality in suspected PE (Mortensen and Gutte 2014; Roach et al. 2013; Laurence et al. 2012). Much of the debate was caused by the abovementioned shortcomings of planar V/Q-scans which drove many clinicians towards the more dichotomous CTA. Although CTA is outside the scope of this chapter a few remarks are in order. Several studies have shown that the initial overenthusiastic diagnostic accuracies of CTA were somewhat premature when the whole pulmonary vasculature (and not just larger branches) was assessed – sensitivity falls significantly with decreasing size of the included vessels for analysis, whereas specificity remains relatively high (Hess et al. 2005; Stein et al. 2006). Recent studies including some with head-to-head comparisons have established sensitivities at the same level or lower than SPECT V/Q-scans, i.e. 68–94 %, with specificity generally higher at 94–100 %. Furthermore, the radiation dose in previous studies was at least 2–3 times higher than with V/Q-scans (irrespective of it being planar or SPECT) although novel developments in instrumentation may reduce the radiation from CTA significantly (Mortensen and Gutte 2014; Mamlouk et al. 2010; Gutte et al. 2009). Especially the absorbed doses to the female breast has been worrisome with estimated doses as high as 20–80 mSv (Freeman et al. 2008). Finally, the use of intravenous contrast may preclude a substantial number of patients from undergoing CTA; in fact 25–50 % of patients are routinely excluded from prospective CTA studies in PE because of kidney disease or risk factors for developing it (Mortensen and Gutte 2014). That said, CTA has the obvious advantages of being very fast (seconds) and therefore tolerable by most patients, it is available in most centers (also out-of-hours), and it frequently provides clinically important differential diagnoses.

As it is recommended to interpret V/Q-scans in conjunction with a recent chest x-ray, an obvious way of enhancing SPECT V/Q-scans is by combination with CT as it is the case with most other uses of SPECT imaging, e.g. bone or tumor scintigraphies. Protocols with low-dose CT allow for crude assessment of structural lung appearance but keep the additional radiation to the patient at an acceptable, almost negligible, level (Mortensen and Gutte 2014). In the Danish study by Gutte et al. (2009), adding low-dose CT to the SPECT V/Q-scan increased specificity from 88 to 100 % and accuracy from 91 to 99 % without affection sensitivity (97 %). Thus, the added value of CT relates to increased specificity and reader confidentiality, i.e. the number of false-positives and inconclusive scans was

reduced to 0 % because CT offered alternative explanations for small, ambiguous perfusion defects. Similarly, Ling et al. (2012) examined 106 patients and SPECT/CT V/Q-scan yielded a NPV of 97 % while CT suggested alternative diagnoses to PE in 27 % of cases.

Following the promising results of perfusion scan only in the PISA-PED study and the PIOPED II as mentioned above along with developments in SPECT and SPECT/CT it has been debated whether ventilation studies are still necessary or if perfusion imaging in conjunction with CT is sufficient. A recent study by Bajc et al. (2013) assessed this in 152 patients, and the authors found high sensitivity (90 %), specificity (95 %), PPV (91 %), and NPV (94 %) when evaluation was performed by a single reader who was highly experienced in reading perfusion scans according to PISA-PED criteria. There were no non-diagnostic scans. However, in the SPECT/CT study by Gutte et al. (2009) specificity as well as accuracy decreased substantially with perfusion scans only combined with CT compared with combined SPECT/CT V/Q-scans, i.e. from 100 % to 51 % and from 99 % to 68 %, respectively. Furthermore, the rate of non-diagnostic scans was significantly higher with perfusion scans only combined with CT (17 %) compared with combined SPECT/CT V/Q-scans (0 %). Thus, routine use of perfusion SPECT only, with or without accompanying CT, cannot be recommended per se, but may be a viable compromise if patients are unable to ventilate sufficiently, or in order to reduce radiation burden in pregnant patients with a lower pre-test probability and therefore a more favorable NPV. Thus, a recent study found high NPV (>90 %) of perfusion SPECT/CT only in 127 pregnant patients (with a PE prevalence of 9 %) (Bajc et al. 2015).

A major problem with comparative diagnostic imaging in PE is the lack of a true reference standard. Earlier, conventional PA was considered the gold standard against which new modalities were tested, but this is no longer considered lege artis – compared to novel techniques PA is probably both less sensitive and less specific, it is invasive with a risk, albeit small, of adverse, potentially fatal complications, and the radiation dose is substantial compared to CT angiography and V/Q-scans. Thus, most studies on SPECT V/Q-scans employ a composite reference standard based on follow up and available patient data including imaging and often even including the method being tested itself. This renders protocols less standardized (i.e. the information included in the composite reference standard varies considerably), inter-study compare is more difficult, and the risk of bias is apparent. Furthermore, the conclusions based on the composite data are most often consensus decisions by a mixed project group and patient data may have to be omitted from data analysis, if consensus cannot be reached. This is presumably more prevalent in the most difficult cases and therefore those most prone to affect the overall results of a given study. For instance, in the study by Gutte et al. (2009), an otherwise very well-executed study, 5/86 (6 %) patients had to be omitted as no diagnosis could be reached, and this rate was at the same level as the numbers of patients excluded due to technically suboptimal V/Q-scans (8 %) or CTA (6 %), or the rate of non-diagnostic V/Q-scans (5 %).

This has also implications for the impact a novel methodology may have on patient outcome, a factor to be considered along with the assessment of mere diagnostic performance. Due to the lack of a true reference standard it is difficult to establish if the more sensitive method of SPECT causes an over-diagnosis of smaller, and potentially clinically insignificant, PE. Conversely, the reliability of a negative scan is equally important, but easier to address in a strict follow-up setting. The aforementioned study by Le Roux et al. (2014) did in fact consider this and found a 3-months thromboembolic risk of 0.38 % (one event in 262 patients with negative scans and not treated with anticoagulants). However, further outcome studies are desirable.

4 Radionuclide Molecular Imaging of Pulmonary Embolism

Regardless if the V/Q-scan is performed as planar, SPECT or SPECT/CT the rationale is rather simplistic or mechanistic. As opposed to this

approach, a multitude of more elaborate, cellular or molecular based radiolabeled probes targeting the components of clot formation directly have been proposed and tested with more or less promising results, usually less. These include tracer molecules targeting fibrinogen, fibrin or fibrin derivatives (i.e. labeled fibrinogen or various monoclonal or polyclonal antibodies against fibrin, fibrin-binding peptides, D-Dimer, or fibronectin), clotting factors, platelets and its receptors (i.e. radiolabeled platelets, GPIIB/IIIA platelet receptor antibody), P-Selectin (a platelet adhesion molecule in activated platelets), or plasmin and its derivatives (i.e. plasminogen and tissue-type plasminogen activator). In general, none of these techniques have translated into clinically useful methods for various reasons, e.g. unfavorable radiation burden due to long blood circulation time, accumulation in undesirable organs, or low target-to-background ratios or signal-to-noise ratios with resulting low sensitivity and specificity. Furthermore, the probes were generally more successful for deep venous thrombosis and less useful for PE (Houshmand et al. 2014).

4.1 Positron Emission Tomography/ Computer Tomography (PET/CT)

This is also the case with the molecular imaging method with perhaps the most potential, PET/CT with a flour-18 labelled glucose analog (FDG). The modality has gained widespread use in the past decade and the rationale is known to most clinicians: Hypermetabolic cells (e.g. cancer cells) take up glucose (or FDG) in larger amount than normal cells and due to certain enzymatic intricacies FDG is accumulated and trapped inside these cells. The radiation from FDG is detectable and quantifiable from outside the patient using PET/CT scanners which are hybrids like SPECT/CT combining the molecular or (patho)physiological information from the distribution of the PET-tracer with the high resolution anatomic data from a modern CT scanner. Thus, FDG-PET/CT offers whole-body scans with very high sensitivity for locating hypermetabolic cells or tissues. Although much focus has been on its use in oncology, there is an increasing interest towards the use for non-malignant hypermetabolic cells, e.g. inflammatory cells such as leucocytes and macrophages (Hess et al. 2014). Since there is a significant inflammatory component to venous thromboembolism (VTE), several cases have reported increased FDG-uptake in thrombosis or emboli throughout the body, not only in the traditionally metabolically active thrombi such as tumor thrombosis or septic thrombophlebitis, and this has prompted further investigations towards its potential for routine use in VTE (Hess et al. 2012; Ravina et al. 2014; Nielsen et al. 2013).

We have previously summarized what we believe constitutes the potentially added value of FDG-PET/CT in VTE: DVT and PE are just two manifestations of VTE, which may occur throughout the body, and an underlying disease is often a key factor in developing VTE. Thus, although conventional imaging techniques as mentioned above may have a good diagnostic accuracy, only FDG-PET/CT addresses the other important aspects of the disease, i.e. screening of the entire body for VTE (including the pelvis and upper extremities, where conventional imaging fail), differentiating acute (metabolically active) from chronic (non-FDG-avid) VTE which may have implications for treatment strategy, and early diagnosis of underlying disease (e.g. cancer, with the possibility of early treatment) (Hess et al. 2012). And our points have to some extent been corroborated by recent human studies. Thus, in a small proof-of-concept study, we included 15 patients with suspected DVT and/or PE to undergo FDG-PET/CT within 24 h of the diagnosis being confirmed or ruled out. FDG-PET/CT correctly diagnosed or ruled out DVT in all patients, whereas FDG-PET/CT was only positive for PE in 2 out of 6 PE patients (Hess et al. 2015). Rondina et al. (2012) included 12 patients with confirmed proximal thrombosis of the leg and FDG-PET/CT detected thrombosis with sensitivity of 88–100 % and specificity of 88–100 % depending on the cut-off thresholds for a simple quantitative measure of the tracer

uptake in active lesions (i.e. maximum standard uptake value (SUVmax)). Furthermore, the maximum metabolic activity in thrombosed veins was inversely related to the time span from onset of DVT symptoms and this may suggest a steady decrease over time. The authors extrapolated a proposed time to normalization of FDG-uptake to be approximately 3 months, a prerequisite for differentiation between old and new thrombi and for response evaluation. We have also assessed the value of volumetric FDG-PET/CT parameters in the same group of patients as (Hess et al. 2015). We found several quantitative parameters to be robust predictors of DVT with areas under the receiver operating characteristic (ROC) curve of 0.94–0.96 with statistical significance ($p = 0.005–0.007$) yielding sensitivity and specificity of 84 % and 100 %, respectively. Finally, further unpublished data from our group suggest FDG-PET/CT is sensitive in detecting early VTE, even in pre-symptomatic patients: We reviewed sequential FDG-PET/CT scans in multiple myeloma patients from before and after a diagnosis of VTE was established. We found FDG uptake consistent with VTE not only in scans performed at the time of the clinical VTE diagnosis but also in all FDG-PET/CT performed prior to the clinical VTE diagnosis in 9 out of 10 cases. Thus, FDG-PET/CT seems promising as a tool for greater insight into the natural history and pathophysiology of VTE, but it remains to be seen if its role becomes more clinically oriented in the future.

5 Concluding Summary

Radionuclide-based techniques have played an important role in VTE for decades and especially the V/Q-scan remains an important modality. Bases on the above some summary recommendations can be put forth:

(1) V/Q-scan is a valid method for suspected PE
(2) SPECT or SPECT/CT is preferred over planar imaging
(3) Whenever possible, reporting should be dichotomized; i.e. “PE present” or “PE not present” (with the remaining being “non-diagnostic”).
(4) Clinical pretest probability assessment is important – and if imaging results are discordant with clinical probability further testing is recommended
(5) A normal V/Q-scan virtually excludes PE (regardless of technique)
(6) A patient with a positive V/Q-scan and high clinical likelihood of PE requires treatment
(7) Combined V/Q-scan is preferable, but perfusion only is viable if this is the only option
(8) In most cases, PE can be excluded on the basis of a normal perfusion pattern, so in pregnant women a sequential protocol is suggested to minimize fetal radiation. Perfusion-only scans should be performed on day 1 using a reduced dose of ^{99m}Tc MAA.
(9) Follow-up scans to serve as new baselines may be considered in patients with persistent risk factors and, thus, a relative higher risk of suspected recurrence
(10) V/Q scan is preferred over pulmonary CTA for follow-up of PE particularly in young women in order to avoid the excessive breast radiation exposure associated with CTA.

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Thrombolytic Therapy by Tissue Plasminogen Activator for Pulmonary Embolism

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Abstract

Clinicians need to make decisions about the use of thrombolytic (fibrinolytic) therapy for pulmonary embolism (PE) after carefully considering the risks of major complications from bleeding, and the benefits of treatment, for each individual patient. They should probably not use systemic thrombolysis for PE patients with normal blood pressure. Treatment by human recombinant tissue plasminogen activator (rt-PA), alteplase, saves the lives of high-risk PE patients, that is, those with hypotension or in shock. Even in the absence of strong evidence, clinicians need to choose the most appropriate regimen for administering alteplase for individual patients, based on assessment of the urgency of the situation, risks for major complications from bleeding, and patient's body weight. In addition, invasive strategies should be considered when absolute contraindications for thrombolytic therapy exist, serious complications arise, or thrombolytic therapy fails.

Keywords

Thrombolytic therapy • Tissue plasminogen activator • Pulmonary embolism • Embolism and thrombosis

1 Introduction

Most patients with pulmonary embolism (PE) treated in hospitals are at low risk for mortality (less than 1 %) and can be successfully treated with unfractionated heparin, low molecular weight heparins (LMWH), fondaparinux, or one of the new oral anticoagulants (NOACs). About 4 % of acute PE patients are at high risk for mortality, and for these patients, treatment by

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thrombolytic agents save lives [1]. Whether to treat a patient with thrombolytic agents is an important decision that must be made promptly, carefully taking into consideration the severity of the condition and the risks for major complications related to bleeding. This chapter is written primarily for clinicians who are likely to treat PE patients by human recombinant tissue plasminogen activator (rt-PA).

2 Indications for Systemic Treatment by Thrombolytic Agents in PE

1. In *high-risk PE*, systemic treatment by thrombolytic agents increases survival. PE patients who present with hypotension or cardiogenic shock are those most likely to benefit from thrombolytic treatment, compared to treatment with unfractionated heparin alone [2]. Persistent hypotension in patients with confirmed PE is, thus, an accepted indication for immediate treatment by thrombolytic agents. A fall in the systolic blood pressure by more than 40 mmHg, or a systolic blood pressure less than 90 mmHg for more than 15 min, caused by PE, is usually accepted as an indication for thrombolytic treatment. It is not essential to confirm the presence of right ventricular dysfunction in such patients. For best results, thrombolytic treatment should be started within 2 days of the onset of the symptoms, but patients with symptoms for as long as 2 weeks can still benefit from the treatment [3].

Some patients with high-risk PE will not benefit from thrombolytic therapy. These patients may need urgent surgical embolectomy, and it may be risky to first try thrombolytic therapy in such patients. Surgical embolectomy is usually recommended in case of strong contraindications for, or failure of, initial thrombolytic therapy (rescue surgical embolectomy). However, rescue surgical embolectomy after initial unsuccessful thrombolysis is associated with higher mortality compared to primary surgical embolectomy [4]. There is no consensus about the criteria for identification of high-risk PE patients who are more likely to benefit from primary surgical embolectomy rather than from thrombolysis. One study proposes that patients with a computer tomography-based right ventricular to left ventricular diameter ratio of more than 1.5 should be allocated to primary surgical embolectomy rather than to thrombolysis [4].

2. *Intermediate-risk PE* patients are those with signs of right ventricular dysfunction detected by echocardiography, computed tomography, elevated troponin T, or troponin I, brain natriuretic peptide (BNP), or N-terminal proBNP, but with normal blood pressure. In this group of patients, systemic treatment with thrombolytic agents prevents different degrees of hemodynamic decompensation but increases the risk of stroke and major bleeding [5]. Randomized controlled trials with power to detect the differences in the rates of death in this group of patients are lacking. In one study, thrombolysis improved right ventricular function at 12 h, but after 1 week there was no difference in right ventricular function between the group treated by thrombolysis and the group treated by heparin alone [6]. In patients treated with tenectplase plus heparin, or placebo plus heparin, stroke occurred in 2.4 % in the tenectplase group and 0.2 % in the placebo group [5]. Thus, great caution is needed in making decisions about thrombolytic treatment in the intermediate-risk group of PE patients. In case of doubt about whether to treat by thrombolysis, start treatment with heparin infusion.

3. *Cardiac arrest caused by PE*. About 5 % of cardiac arrest could be attributed to PE, as revealed from autopsy studies [7]. Some guidelines recommend that if cardiac arrest is suspected to be the result of PE, then thrombolytic therapy, early during cardiopulmonary resuscitation should be considered [8–10]. There is some evidence, mostly from case reports, that this approach saves lives, but this remains an area of controversy [11]. Patients in whom the cause of cardiac arrest is unclear do not benefit from thrombolytic therapy [12].

In practice, it is difficult to know whether cardiac arrest is the result of PE. In some clinical situations cardiac arrest may be presumed to be

caused by PE. For instance, if a patient with known deep vein thrombosis or PE develops imminent or actual cardiac arrest, it may be from PE. In one series about 95 % of the patients with cardiac arrest caused by PE had pulse-less electrical activity or electromechanical dissociation, and only about 5 % had ventricular fibrillation [13]. ECG recorded before cardiac arrest or after successful cardiopulmonary resuscitation showed right bundle branch block in 67 % of the cases. Echocardiography performed by trained personnel during ongoing cardiopulmonary resuscitation can be helpful in determining if PE is the cause of cardiac arrest [13].

3 Contraindications for Thrombolysis

Risk for major bleeding or intracranial bleeding is a contraindication for treatment by thrombolytic agents. According to one meta-analysis, the incidence of major bleeding in patients treated with thrombolytic agents was 9.24 % compared to 3.24 % in those treated with anticoagulants alone [odds ratio (OR), 2.73; 95 % confidence interval (CI), 1.91–3.91, and number needed to harm (NNH), 18] [14]. The incidence of intracranial bleeding was 1.46 % in the thrombolysis group compared to 0.91 % in anticoagulation group (OR, 4.63; 95 % CI, 1.78–12.04; NNH, 78) [14]. It should be noted that bleeding complications tend to be lower in prospective trials because of the use of strict exclusion and inclusion criteria. In real life, such complications are likely to be higher.

Some commonly accepted contraindications for thrombolytic therapy are listed in Table 1. Clinicians need to judge the relative benefits of thrombolytic therapy in the presence of contraindications on a case-by-case basis. For instance, pregnancy is considered a relative contraindication for thrombolysis, but pregnant women with PE and hypotension should be treated by thrombolysis, whereas those without hypotension should not be treated by thrombolysis. In case of life-threatening PE, many of the absolute contraindications become relative. If the patient has high-risk PE and absolute contraindications for treatment by thrombolysis, then the patient should be treated by other approaches, for example, by extracorporeal membrane oxygenation (ECMO), surgical embolectomy, or catheter embolectomy.

Table 1 Contraindications for thrombolytic treatment in pulmonary embolism (PE)

"Absolute" contraindications:
Ongoing bleeding or recent severe bleeding
Known bleeding diseases
Intracranial bleeding or previous intracranial bleeding
Structural intracranial cerebrovascular diseases that increase risk for bleeding (e.g., aneurysm)
Some malignant intracranial tumor (depends on type of tumor) [15]
Aortic dissection
Recent intracranial or spinal surgery
Severe closed-head or facial trauma within 3 months
Recent (<3 months) ischemic stroke
Recent head or facial trauma with brain injury or bone fracture
Recent major surgery (within 1 week) [15]
Relative contraindications or cautions:
Recent major surgery or trauma (within 2–3 weeks) [15]
Internal bleeding within 2–4 weeks
Severe uncontrolled hypertension (i.e., systolic >200 mmHg or diastolic >110 mmHg)
Ischemic stroke or transient ischemic attack during past 3–6 months [15]
Severe liver diseases
Active gastrointestinal ulcers during past 3 months
Acute pancreatitis
Bacterial endocarditis or pericarditis
Traumatic or prolonged cardiopulmonary resuscitation (>10 min)
Pregnancy
Peripartum period [15]
Age >75 years
Dementia
Diabetic retinopathy

4 Benefits of Thrombolytic Therapy and the Risks of Bleeding Complications

A 2014 meta-analysis of 15 randomized controlled studies involving 2057 patients reveals

that systemic thrombolysis is associated with reduction of overall mortality only when high-risk PE is included in the studies (OR, 0.59; 95 % CI, 0.36–0.96) [16]. Thrombolytic treatment is also associated with reduction in the combined endpoint of death or treatment escalation (OR, 0.34; 95 % CI, 0.22–0.53), mortality related to PE (OR, 0.29; 95 % CI, 0.14–0.60), and recurrence of PE (OR, 0.50; 95 % CI, 0.27–0.94). On the risk side, systemic thrombolysis is associated with fatal or intracranial hemorrhage (OR, 3.18; 95 % CI, 1.25–8.11), and major bleeding (OR, 2.91; 95 % CI, 1.95–4.36) [16].

5 Thrombolytic Drugs

For most practical purposes it will be sufficient for most readers of this review to have a thorough knowledge of alteplase. These drugs activate plasminogen by different mechanisms to form plasmin, a natural proteolytic enzyme that breaks the crosslinks between the fibrin molecules in a thrombus. Plasmin can also cleave fibrinogen, factor V, and factor VIII, giving rise to generalized coagulopathy. There are two groups of fibrinolytic drugs: fibrin-specific agents, e.g., tissue plasminogen activator (tPA), and non-fibrin-specific agents, e.g., streptokinase and urokinae.

tPA is naturally present in the vascular endothelial cells. It shows considerable affinity and specificity for fibrin. Alteplase is recombinant human tPA (rt-PA) and is identical to human tPA. rtPA binds selectively to fibrin on the surface of the thrombus and thereby activates fibrin-bound plasminogen. This event favors local fibrinolysis at the site of the thrombus, leading to a lower incidence of major bleeding [17]. The half life of alteplase is about 5 min, and it is therefore usually used as a continuous infusion. In contrast to streptokinase, it is not antigenic. Alteplase is the lytic agent most commonly used for thrombolysis in PE.

Retaplase is a second-generation recombinant human tPA that contains 355 of the 527 amino acids of native tPA. It is more potent and rapid acting than alteplase. The half-life of reteplase is about 15 min, and it is usually given as intravenous bolus injection. Desmoteplase has higher fibrin specificity and a longer half-life (4 h). Reteplase and desmoteplase have similar effect as rtPA in PE [18, 19], but these drugs are still not widely used or recommended for the treatment of PE.

Tenecteplase is a third-generation rtPA, a 527-amino-acid glycoprotein with several modifications in the amino acid molecules. The result of these modifications is that it binds with fibrin with a higher affinity than alteplase and is associated with fewer bleeding complications. It has a longer half-life and, therefore, can be administered as a bolus injection. It has been used in the treatment of PE [5].

Stretopkinase is less expensive and is still used in many developing countries. In the developed countries it is used less and less because of its high antigenicity and many adverse effects, and because it causes systemic fibrinolysis rather than fibrin-specific fibrinolysis.

6 Administration of Thrombolytic Drugs

In this section, I mainly discuss the use of alteplase. In emergency situations, thrombolytic treatment should be started without delay. In addition to the treatment by thrombolytic agents, patients in severe hypotension or shock will need parallel resuscitation and stabilization. In this context, it should be noted that many aspects of fluid therapy and treatment by vasoactive drugs in PE remain controversial. One should order baseline blood tests for prothrombin time, activated partial thromboplastin time (APTT), full blood count, fibrinogen, serum creatinine, and liver function tests before starting thrombolytic therapy.

If the patient has already received LMWH or fondaparinux, warfarin, or one of the NOACs, and you decide to treat by thrombolytic agents, you can still start treatment by alteplase immediately. You can do this irrespective of the dose or time of the last dose of heparin, LMHW, fondaparinux, warfarin, or the novel oral

anticoagulants. If the patient is receiving unfractionated heparin infusion, this can be continued during the infusion of altiplase (if you are going to use streptokinase or urokinase, then stop the heparin infusion during the infusion of streptokinase or urokinase). Adjust the rate of heparin infusion to keep the APTT between within 1.5 and 2.5 times the normal reference values.

For patients who weigh less than 65 kg, the total dose must not exceed 1.5 mg/kg. Regimens for treatment by alteplase vary depending on the urgency of the situation, bleeding risks, guidelines from major societies or regulatory authorities, and even local traditions. There are insufficient data to compare the effectiveness of specific types of regimes. There is some evidence that alteplase infusion is more effective than bolus dose alteplase in the treatment of PE in most situations [20].

The most commonly used regimen is to infuse 100 mg alteplase continuously over 2 h [21, 22].

We usually give 10 mg altiplase i.v. as a bolus injection in 2 min, and then 90 mg as an infusion over 2 h.

An alternative regime is to give alteplase 50 mg as an infusion during 30 min, and then another 50 mg during 90 min.

In critical conditions, give alteplase 0.6 mg/kg (maximum, 50 mg) as an i.v. bolus injection over 5–15 min, and then 50 mg as an infusion over 90 min.

The British Thoracic Society recommends giving 50 mg alteplase as a bolus injection to patients with imminent cardiac arrest suspected to be caused by PE [10].

If the risk of bleeding is considered high, then give 50 mg as an infusion over 1–1.5 h, and then, if there is no improvement, give 0.6 mg/kg (maximum, 50 mg) as an infusion over another 1 h.

According to one study, infusion of 50 mg alteplase in 2 h has a similar effect as infusion of 100 mg alteplase in 2 h [23]. In this study, there was less bleeding tendency in the 50 mg regimen compared to the 100 mg regimen, especially in patients with body weight <65 kg (14.8 % vs. 41.2 %).

7 Care of the Patients During and After Thrombolysis

When possible, the patient should be transferred promptly to a unit that has experience and resources for administering such treatment and for appropriate monitoring. We usually transfer our patients to an intermediate care or intensive care unit. Patients should be under strict bed rest. Blood pressure and pulse should be monitored continuously for up to 24 h after administration of alteplase. Patients should be monitored frequently for signs and symptoms of bleeding and for neurological symptoms. Neurological status should be checked every 15 min during infusion of alteplase, then every 30 min for 6 h, and then hourly for 24 h.

Do not give intramuscular or subcutaneous injections during and 4 h after thrombolysis. After intravenous injections or blood sampling, use a compression bandage for at least 10 min to reduce bleeding from the puncture site. Refrain from eventual insertion of a urinary catheter and venous or arterial punctures during the first 24 h after administering alteplase.

8 Treatment After Thrombolysis

If you stopped heparin infusion during infusion of alteplase, then restart heparin infusion, without a bolus dose, after the end of the alteplase infusion. Check APTT and adjust the rate of heparin infusion (or stop heparin infusion temporarily) to maintain the APTT within 1.5 to 2.5 times the upper limit of normal. If the patient received LMWH or fondaparinux once or twice daily, before the start of alteplase, then start heparin infusion 24 h or 12 h, respectively, after the last injection.

Heparin infusion should be continued for at least 4 h, or often longer, after the end of the alteplase infusion. We usually continue heparin infusion for 1 day and then switch to LMWH, or fondaparinux, if the patient is hemodynamically stable, and if there is no clinically significant

bleeding. If the latest APTT is less than 140 s, you can stop the heparin infusion, and switch to LMWH, or fondaparinux at full dose, immediately after stopping the heparin infusion. If the latest APTT is more than 140 s, then start LMWH, or fondaparinux, 2 h after stopping the heparin infusion.

9 Thrombolysis for PE During Pregnancy

Pregnancy is usually listed as a relative contraindication for thrombolytic therapy, but such treatment must not be withheld in high-risk PE patients. There are many case reports and series in which thrombolytic agents have been used in pregnancy. rtPTA does not cross the placenta. The complication rate of thrombolytic therapy during pregnancy is not higher than in large randomized trials of PE [25, 26]. In one review of 172 pregnant women treated by thrombolytic agents (mostly streptokinase), there was no maternal death. The rate of nonfatal bleeding was 2.9 % and that of fetal deaths was 1.7 %. Thrombolysis should be followed by heparin infusion, which can be switched on to LMWH. Vitamin K antagonists and the NOACs are contraindicated in pregnancy.

10 Complications of Thrombolysis

Although the elimination half life of alteplase is short, some of its effects on coagulation activity after its discontinuation can last for up to 48 h [27]. Bleeding complications occurring during alteplase infusion, or within 48 h of discontinuation of alteplase, can be attributed to the thrombolytic agent.

Intracranial Bleeding The most serious complication of thrombolysis is intracranial bleeding, which needs early detection and treatment [28]. Headache, reduced consciousness, seizures, or neurological deterioration should raise the suspicion of intracranial bleeding. When intracranial bleeding is suspected, stop the infusion of thrombolytic agent and of heparin (and all other antithrombotic drugs). Obtain a non-contrast computed tomography scan of the brain immediately. Order laboratory tests for prothrombin time, activated partial thromboplastin time, fibrinogen, full blood count, and blood group.

If intracranial bleeding is confirmed by CT, it should be treated aggressively. Administer fresh frozen plasma 12 ml/kg [27]. Consider administering 6–10 units (bags) of cryoprecipitate, especially if fibrinogen concentration is less than 1 g/l [27]. Administer intravenous tranexamic acid, 1 g three times daily, especially to patients who would not accept blood products [27, 29]. Some clinicians prefer to administer fresh frozen plasma and cryoprecipitate, and others prefer to administer all three.

Extracranial Bleeding Look for evidence of blood loss, e.g., melaena, hematuria, bleeding from puncture sites, drop in blood pressure, or shock. Minor bleeding from vascular puncture sites can be controlled by prolonged manual pressure followed by a pressure dressing. In such cases, concomitant anticoagulation by heparin infusion should be stopped, and alteplase infusion may be continued, perhaps at a reduced rate of infusion.

In case of major or refractory bleeding, stop alteplase and heparin infusions, and resuscitate the patient by cautious administration of intravenous fluids. Give tranexamic acid 1 g and repeat at 8 h, if needed. Consider administering fresh frozen plasma and cryoprecipitate as already mentioned for intracranial bleeding. If blood loss has been extensive, administer packed red blood cells.

Further treatment of PE in patients who develop alteplase-induced bleeding complications needs to be decided on a case-by-case basis. In intermediate-risk PE patients who develop bleeding complications, thrombolysis should be discontinued, and they should be treated by anticoagulation alone. High-risk PE patients who develop alteplase-induced severe bleeding complications should be treated by invasive procedures.

11 Unsuccessful Thrombolytic Therapy

About 8 % of patients do not respond to initial thrombolytic therapy. Failure of thrombolytic therapy can be suspected from persistent hemodynamic instability and residual right ventricular dysfunction as assessed by echocardiography. During and after thrombolysis, it is essential to evaluate clinically the response of the patient to thrombolysis. Patients who fail to respond to thrombolysis should be treated by rescue surgical embolectomy or catheter-directed approaches, rather than by repeat thrombolysis [30]. When available, patients should be urgently treated by ECMO, either alone or as an adjunct to the definitive treatment by surgical embolectomy or catheter embolectomy [24]. (see the chapter on "Surgical Treatment of Acute Massive Pulmonary Embolism," in this book). No comparative data exist to support the choice of surgical embolectomy or catheter-directed approaches; the choice depends on local availability of expertise in cardiothoracic surgery or catheter-based therapy. Preoperative thrombolytic therapy increases bleeding risk but is not an absolute contraindication for surgical embolectomy.

12 Final Remarks

Thrombolytic therapy for PE needs an individualized approach that weighs the risk of severe deterioration or death against the adverse effects of thrombolysis. Many elements of uncertainties exist in the use of thrombolytic therapy in PE. Clinicians must assess the relative chances of success and the risks of bleeding complications on a case-by-case basis. They have to make such decisions by processing the information they obtain and, to some extent, by their intuition. There may be no single right way for choosing the types and strategies of treatment for a particular case of PE, but the clinical decision-making process can be improved by experience of treating PE patients through a multidisciplinary approach. Ideally, hospitals should have pulmonary embolism response teams consisting of specialists from multiple disciplines for rapid evaluation, formulation of treatment plans, and mobilization of resources for optimal treatment of high-risk and intermediate-risk PE patients [31].

Conflicts of Interest None

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Surgical Treatment of Acute Massive Pulmonary Embolism

Ziv Beckerman and Gil Bolotin

Abstract

Massive pulmonary embolism (MPE) is a life-threatening condition. The management of MPE has changed over the course of the last few years. Since the emergence of thrombolytic therapy, only a few patients remain amenable for surgical treatment. Currently, surgical embolectomy is advised only in very specific indications. This chapter will review the background, history, indications, surgical technique and results of surgical pulmonary embolectomy in patients with MPE.

Keywords

Massive • Pulmonary embolus • Embolectomy • Surgery • Thrombolysis • Hemodynamic

1 Definition

Acute MPE is the sudden entrapment in pulmonary arteries of a dislodged thrombus, usually from the deep veins of the legs, pelvis, or arms. It is life threatening and can result in right heart failure, low cardiac output, and sudden cardiac death (Kirklin/Barratt-Boyes Cardiac Surgery: Expert Consult.

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2 History

The first pulmonary embolectomy was performed by Trendelenburg in 1908, with a dismal prognosis. Long-term survival using his technique was not achieved until 1924. Dr. John Gibbon, the inventor of the cardiopulmonary bypass (CPB), performed the first successful operation for removal of a pulmonary embolus in 1953. The first successful pulmonary embolectomies performed with use of CPB were reported by Cooley and colleagues in l961 and by Sharp in 1962 (Kirklin/Barratt-Boyes Cardiac Surgery: Expert Consult).

3 Epidemiology

Pulmonary embolism (PE) leads to at least 630,000 clinically symptomatic episodes in the United States yearly, making it about half as common as acute myocardial infarction, and three times more common than cerebrovascular accidents (Dalen and Alpert 1975).

Acute PE is the third most common cause of death (after heart disease and cancer). These estimates are probably low, because approximately 75 % of autopsy-proven PE are not detected clinically (Landefeld et al. 1988). Of all hospitalized patients who develop PE, 12–21 % die in the hospital, and another 24–39 % die within 12 months (Kniffin et al. 1994; Martin 1993; Carson et al. 1992). Thus, approximately 36–60 % of patients who survive the initial episode live beyond 12 months.

The main source (>90 %) for clinically detected pulmonary emboli is lower extremity deep vein thrombosis (DVT). However, DVT is frequently under-diagnosed since it is asymptomatic in two-thirds of patients with DVT and PE (Clagett et al. 1992; Anderson and Wheeler 1995; Greenfield 1994).

Isolated calf vein thrombi pose a much lower risk for massive PE, compared to pelvic vein thrombosis or proximal leg DVT (resulting in PE in approximately 50 % of patients) (Harrison's Principles of Internal Medicine).

For the most part, DVT and acute pulmonary embolism are managed medically.

4 Pathology, Physiology and Pathogenesis

As the most frequent origin of a pulmonary embolus is DVT, it is also the most studied and described in the literature. The only firm attachment of leg thrombus is at the site of origin, usually a venous saccule or venous valve pocket. (Robertson et al. 1972) The degree of organization within the thrombus varies, but recent clots are more likely to migrate than older thrombi that are more firmly attached to the vessel wall. Detached venous thrombi are carried in the bloodstream through the right heart into the pulmonary circulation (Finlayson 2008).

The majority of pulmonary emboli lodges in the lower lung lobes, (Godleski 1985) and are slightly more common in the right lung than the left.

Simple mechanical obstruction of one or more pulmonary arteries does not entirely explain the often-devastating hemodynamic consequences of major or massive emboli. Humoral factors, specifically serotonin, adenosine diphosphate (ADP), platelet-derived growth factor (PDGF), thromboxane from platelets and others are also involved. (Malik and Johnson 1989; Huval et al. 1983) Anoxia and tissue ischemia downstream to emboli inhibit endothelium-derived relaxing factor (EDRF) production and enhance release of superoxide anions by activated neutrophils. The combination of these effects contributes to enhanced pulmonary vasoconstriction. (Malik and Johnson 1989)

The main pathophysiological outcomes include: (1). Gas exchange abnormalities leading to hypoxemia (decreased arterial Po2) and increased alveolar-arterial O2 tension gradient. (2). Increased pulmonary vascular resistance. (3). Increased airway resistance due to constriction of airways distal to the bronchi. (4). Decreased pulmonary compliance due to lung edema, or lung hemorrhage (Harrison's Principles of Internal Medicine).

Progressive right heart failure is the usual cause of death from PE. As pulmonary vascular resistance increases, right ventricular (RV) wall tension rises and causes further RV dilation and dysfunction. The interventricular septum bulges into and compresses an intrinsically normal left ventricle (LV). Diastolic LV impairment develops, attributable to septal displacement, and results in reduced LV distensibility and impaired LV filling during diastole. Increased RV wall tension also compresses the right coronary artery, diminishes subendocardial perfusion, limits myocardial oxygen supply, and may precipitate myocardial ischemia. Eventually, circulatory collapse and death may ensue (Harrison's Principles of Internal Medicine).

5 Natural History

The mortality rate of untreated PE is 18–33 %. (Carson et al. 1992; Barritt and Jordan 1960; The Urokinase Pulmonary Embolism Trial 1973) Seventy-five to ninety percent of patients who die of pulmonary emboli do so within the first few hours of the primary event. (Bell and Simon 1982) In patients who have sufficient cardiopulmonary reserve and right ventricular strength to survive the initial few hours, autolysis of emboli occurs over the next few days and weeks (Dalen et al. 1969).

In an unknown but small percentage of patients with acute pulmonary embolism, the clot will not lyse and chronic thromboembolic obstruction of the pulmonary vasculature develops. The reasons for failure of emboli to dissolve are unknown.

6 Clinical Presentation

Acute massive pulmonary artery embolism may lead to sudden dyspnea, tachypnea, tachycardia, diaphoresis, hypoxemia and, occasionally, loss of consciousness. Symptoms and signs vary with the extent of blockage, the humoral response, and the pre-embolus reserve of the cardiac and pulmonary systems of the patient.

Stigmata of low cardiac output may present, with weak peripheral pulses and oliguria. Jugular venous pressure is elevated, often with a prominent A wave, and neck veins may be distended. Cardiac examination may demonstrate tachycardia, a prominent RV impulse, a loud pulmonary component of the second heart sound, and a gallop rhythm. (Hirsh et al. 1986) An ejection or pansystolic murmur is often present that may represent tricuspid valve regurgitation.

7 Diagnosis

Methodology of the diagnostic workup depends mainly on the patient's clinical status. In patients presenting with cardiogenic shock, performing diagnostic studies is often not possible, and diagnosis is made based on presenting symptoms and signs (Gulba et al. 1994).

The main diagnostic tools available are:

1. **Electrocardiogram** (ECG) may demonstrate T-wave inversion in the anterior leads, reflecting inferoposterior ischemia from pressure overload, a pseudo infarction pattern, or an S1Q3T3 pattern (Ferrari et al. 1997).
2. **Transthoracic echocardiography** (TTE) is particularly useful, and can identify RV pressure overload (Come 1992; Goldhaber 1998).
3. **Transesophageal echocardiography** (TEE) can demonstrate pulmonary artery thrombi as well as RV overload. (Pruszczyk et al. 2001) See Fig. 1a, 1b, 1c and 1d.
4. **Computed tomography** (CT) of the chest with contrast medium is the mainstay of the diagnostic workup when clinically possible to perform, and it can accurately diagnose and define the extent of the thrombotic/embolic event. (See Fig. 2, 3 and 4)
5. **Gadolinium-enhanced magnetic resonance imaging** (MRI) can identify pulmonary thromboemboli and RV wall motion abnormalities, although rarely performed in the acute setting due to technical difficulties.
6. **Contrast pulmonary angiography** is a definitive diagnostic study but is infrequently performed in hemodynamically unstable patients. (Goldhaber 1998)

8 Surgical Indications

Current guidelines published by both the European Society of Cardiology (ESC 2014) and by the American Heart Association (AHA 2011) discuss the indications for pulmonary embolectomy in clinical practice. The ESC guidelines recommend the use of pulmonary embolectomy for patients in whom thrombolysis is contraindicated or have failed as class I, level of evidence C indication, (Konstantinides et al. 2014) whereas the AHA guidelines describe surgical pulmonary embolectomy as reasonable

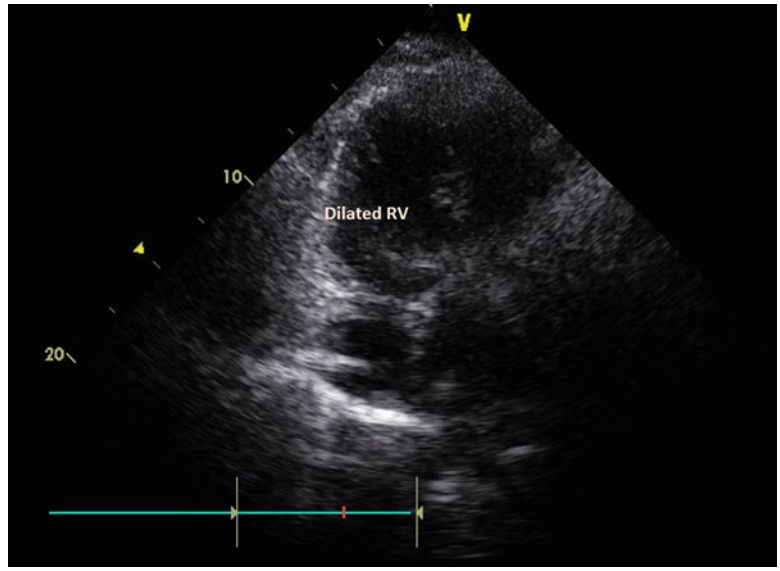

Fig. 1a Dilated right ventricle in the setting of acute massive PE

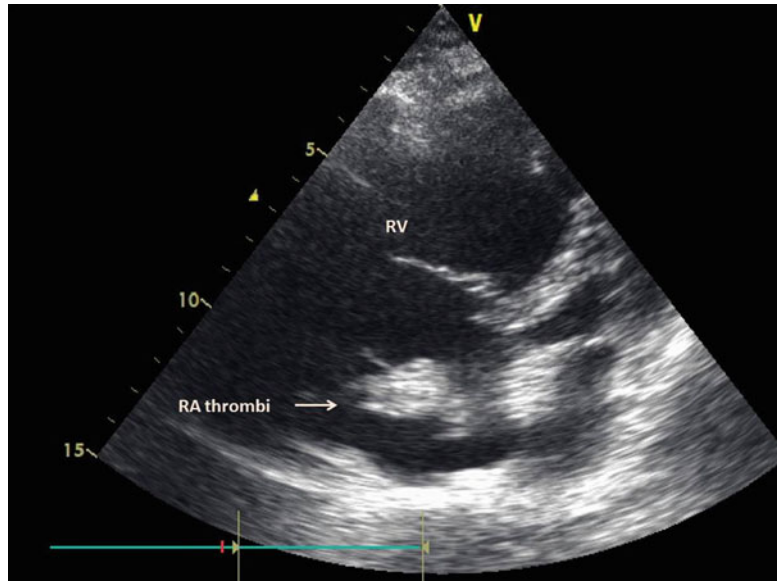

Fig. 1b Dilated right ventricle with large right atrial thrombi

for patients who failed or for those in whom fibrinolysis is contraindicated. (Jaff et al. 2011)

As described in both the ESC and the AHA guidelines, primary reperfusion treatment, particularly systemic thrombolysis, is the treatment of choice for patients with high-risk PE. In patients with contraindications to thrombolysis—and in those in whom thrombolysis has failed to improve the hemodynamic status—surgical embolectomy is recommended if surgical expertise and resources are available. (Konstantinides et al. 2014)

Additional indications may include echocardiographic evidence of an embolus trapped within a patent foramen ovale, or present in the right atrium, or right ventricle (Bloomfield et al. 1988; Ruiz-Bailen et al. 2008).

Proximal emboli are amenable to surgical removal (i.e., right ventricle, main pulmonary artery [PA], and extrapulmonary branches of

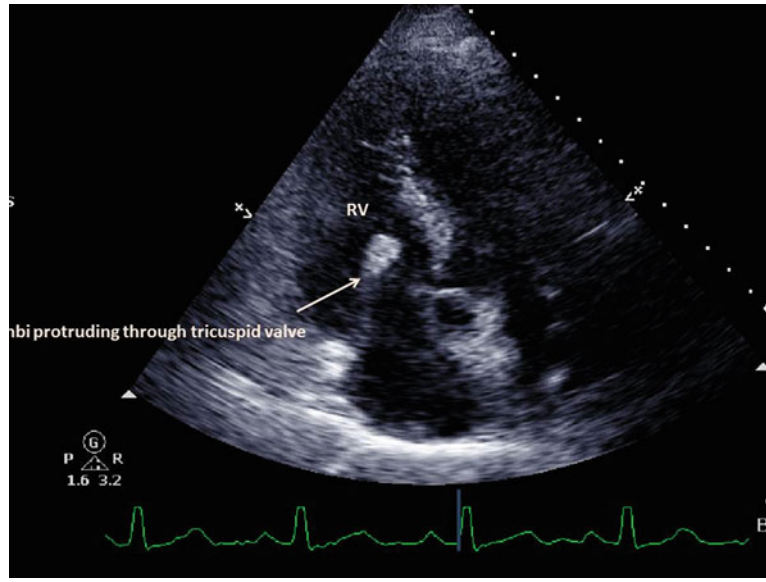

Fig. 1c Dilated right ventricle with large right atrial thrombi protruding through the tricuspid valve to the right ventricle

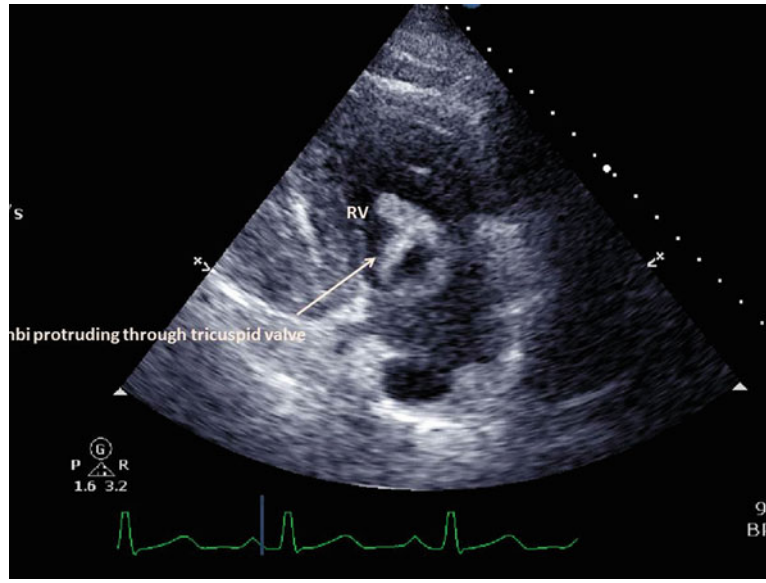

Fig. 1d Dilated right ventricle with large right atrial thrombi protruding through the tricuspid valve to the right ventricle

the PA), whereas distal thrombus generally is not amenable to surgery (e.g., intrapulmonary branches of the PA).

It is important to remember that no large trials prospectively and/or randomly analyzed the effectiveness and outcome of surgical pulmonary embolectomy versus fibrinolysis.

Furthermore, common practice in most large centers focuses on the hemodynamic stability of the patients in order to stratify them to the best treatment of choice. We propose a clinically directed approach which first divides the patients into hemodynamically stable versus hemodynamically unstable patients (Kasper et al. 1997).

Hemodynamically stable patients—a heterogeneous group, which may include either submassive PE (moderate/intermediate risk),

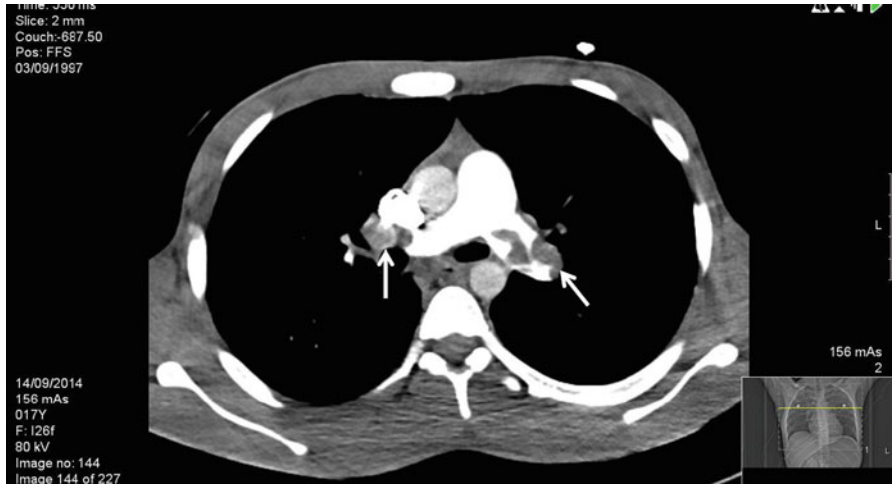

Fig. 2 Axial CT scan demonstrating a left main proximal pulmonary artery thrombus and a more distal right main thrombus (See *arrows*)

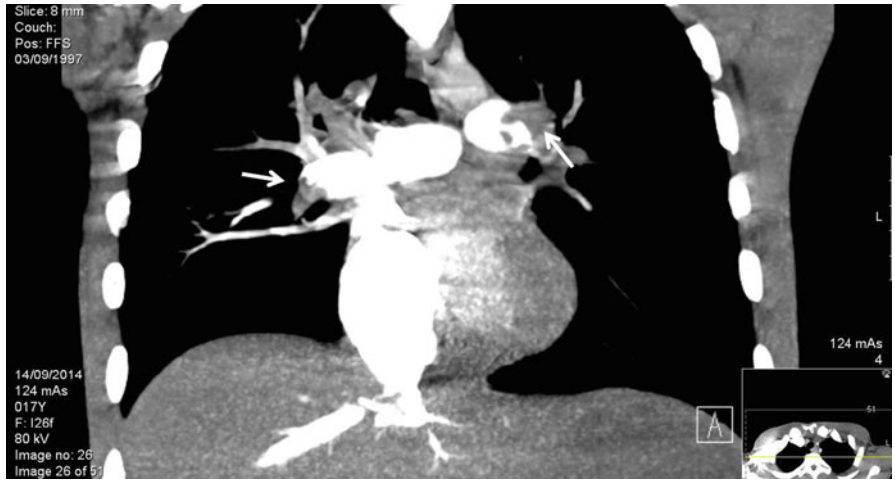

Fig. 3 Reconstructed CT image of Figure 1a. demonstrating a Left main proximal pulmonary artery thrombus and a more distal Right main pulmonary artery (See *arrows*)

and minor PE (low risk) patients. Those with minor/low-risk PE can be treated with anticoagulation. For those with intermediate-risk/submassive PE, therapy should be individualized: thrombolysis and/or catheter-based therapies may be considered on a case-by-case basis when the benefits are assessed by the clinician to outweigh the risk of hemorrhage.

Hemodynamically unstable patients—thrombolytic therapy is indicated in most patients, provided there is no contraindication. Embolectomy is appropriate for those in whom thrombolysis is either contraindicated or unsuccessful (surgical or catheter-based).

9 Embolectomy

Embolectomy can be performed surgically or using a catheter-based technique. The choice

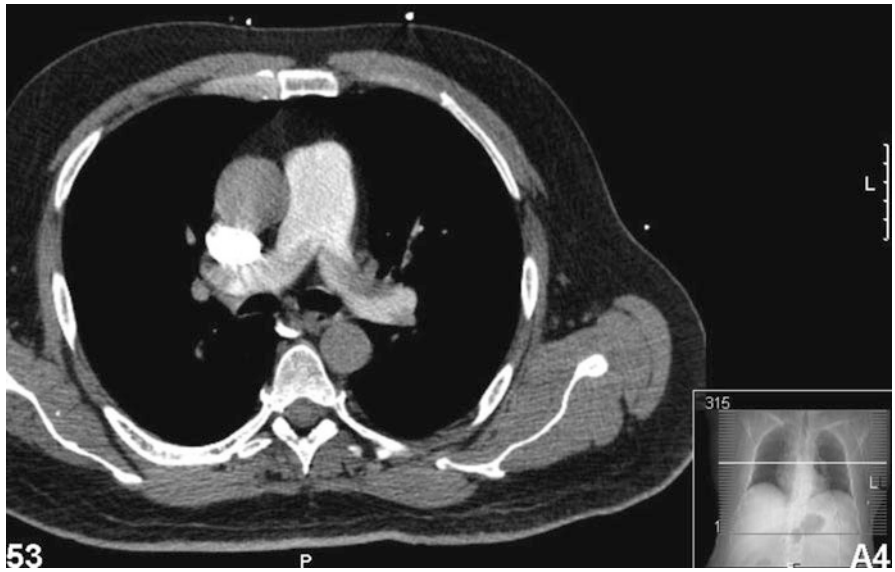

Fig. 4 Axial CT scan demonstrating thrombi in the right and left main pulmonary arteries

between these options depends mainly on available expertise.

Catheter-based modalities—several techniques are available, none has demonstrated superiority over the other. The studies comparing the different techniques are very limited for various reasons, mainly due to different inclusion criteria. Catheter-directed techniques are most commonly utilized in patients with moderate/intermediate risk PE.

The modalities rely on either ultrasound, suction, rotational, or rheolytic technology. Their review is beyond the scope of this chapter, but is should be known that common to all catheter-assisted embolectomy techniques is the risk of pulmonary artery perforation; although rare, it can lead to pericardial tamponade and life-threatening hemoptysis, and is frequently catastrophic. Additional complications include hemorrhage and infection of venipuncture sites, cardiac arrest, and death, as well as device-specific adverse effects.

Surgical embolectomy is discussed further below.

10 Technique of Operation

10.1 Preoperative Management

The preoperative management of patients with massive pulmonary embolism is probably the most critical part, reflecting on the success of the entire procedure. Patient management depends on their clinical status and the level of hemodynamic stability.

In general, this group of patients can be separated into three: Group 1, hemodynamically stable patients; Group 2, hemodynamically unstable patients; Group 3, patients under cardiopulmonary resuscitation (CPR).

Group 1 patients should receive high-dose unfractionated heparin (bolus of 5000 IU, followed by infusion of at least 1000 IU/h) once the diagnosis is made. Following that, maintaining adequate oxygenation and cardiac output before establishing CPB is essential. Endotracheal intubation should be established if hypoxemia is present. If adequate cardiac output cannot be maintained with vasopressors, phosphodiesterase inhibitors may be given. Otherwise, if the clinical situation permits, the usual

preparations for establishment of CPB should be made.

Most stable patients undergo chest CT for definite diagnosis. However, if diagnosis of pulmonary embolism has not been made with certainty before the patient is transported to the operating room, TEE should be performed to establish the diagnosis before the chest is opened (Kirklin/Barratt-Boyes Cardiac Surgery: Expert Consult).

In Groups 2 and 3 patients, maintaining adequate oxygenation and cardiac output is of paramount importance. This can be achieved either by endotracheal intubation and external (automatic) chest compression devices or, if available, emergent connection to an extracorporeal membrane oxygenator (ECMO) might be considered. ECMO has proven itself as an excellent tool for stabilizing such patients until their transfer to the operating room. In some instances, ECMO can stabilize patients before a definite diagnosis of massive pulmonary embolism is made, thus allow the performance of CT or echocardiography on ECMO before the final decision to perform surgical embolectomy is made.

Transesophageal echocardiogram is essential in all patients before median sternotomy is undertaken.

10.2 Surgery

A midline sternotomy is performed. If peripheral cannulation has not been established, central cannulation is undertaken, either using a single two-stage venous cannula or by bi-caval cannulation and an aortic cannula. CPB is established and mild hypothermia is instituted. Following, the surgery itself may be performed either on a beating heart or with aortic cross-clamping and cardioplegic infusion or fibrillatory arrest. Some authors advocate avoidance of aortic cross-clamping and cardioplegic arrest. (Leacche et al. 2005) Nevertheless, the literature is equivocal on the matter.

The left atrium and left ventricle may be decompressed with a venting catheter inserted into the right superior pulmonary vein.

The pulmonary trunk is incised longitudinally several centimeters distal to the pulmonary valve. If necessary, the incision can be extended into the left pulmonary artery, and a separate incision can be made in the right pulmonary artery between the superior vena cava and ascending aorta. (Fig. 5) Because of the size and fragile nature of a fresh clot in the main pulmonary arteries, it is extremely important to be able to extract the clot as much as possible

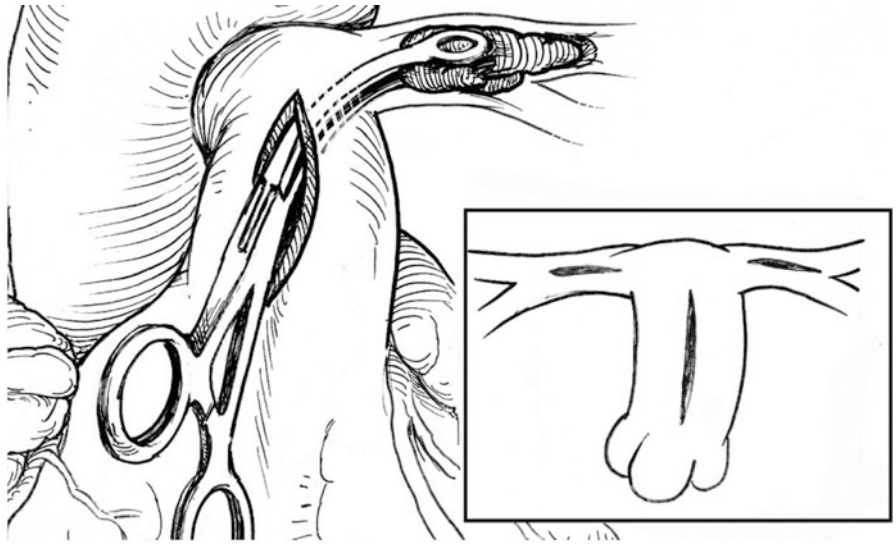

Fig. 5 Typical incisions and retrieval of pulmonary embolus from the left main pulmonary artery

without disrupting it. Therefore, in our experience, performing the operation with aortic cross-clamping, ensuring a blood-less surgical field, is the most efficient and safe way for effectively removing the clots. Additionally, various techniques and tools have been utilized for manual extraction of the pulmonary clots. It is essential to use an instrument that allows a wide and gentle grip on the clot. A sponge holder (Fig. 5, 6) or any other surgical tool that provides a wide, firm but gentle grip will assist in pulling the fresh clot without disrupting it (Fig. 7).

After the main clots are removed, further attempts are made for the removal of the smaller and more distal clots. These can be extracted using Fogarty catheters, forceps and suction tube.

If a sterile pediatric bronchoscope is available, the surgeon can use this instrument to locate and remove thrombi in tertiary and quaternary pulmonary vessels. Alternatively, the pleural spaces are entered, and each lung is gently compressed to dislodge small clots into larger vessels and suctioned out.

Depending on preoperative information with regard to thrombi in the right-heart chambers, the right atrial and RV cavities are explored through a right atriotomy to search for and remove residual thrombi.

After removing the thrombus, incisions in the pulmonary arteries are closed with continuous 4–0 polypropylene suture. After completion of rewarming and evacuation of air from the cardiac chambers, CPB is discontinued. Weaning from bypass may be long, depending on the extent and how long the right ventricular was compromised before the operation. Patients after CPR and patients with a modest amount of clot removal are prone to have difficulties in weaning from the heart-lung machine (Kronik et al. 1989).

Typical retrieved surgical specimens: (Fig. 8, 9 and 10).

10.3 Postoperative Management

Postoperative circulatory support is often required, depending on the status of the right ventricle and whether or not it suffered any ischemia. Circulatory support can be achieved with an RV assist device and intra-aortic balloon counter-pulsation or extracorporeal life support, as indicated for patients with persisting severe RV failure at the end of surgical embolectomy.

Fig. 6 Curved sponge holder

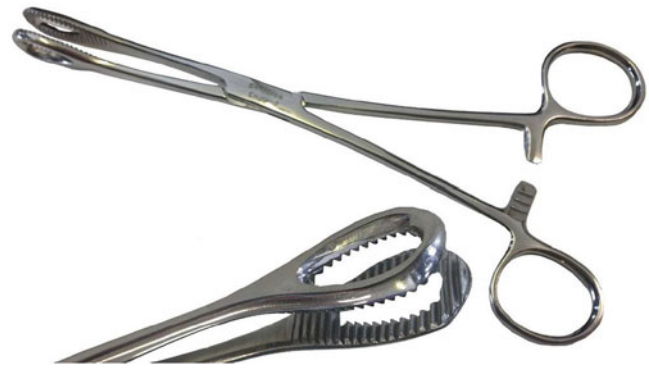

Fig. 7 Straight sponge holder

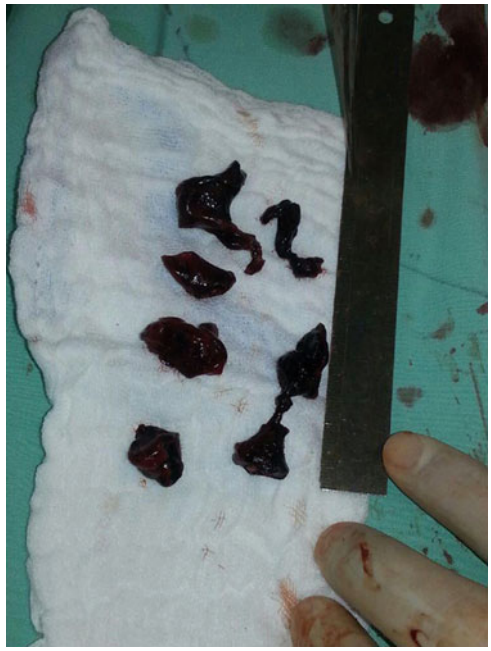

Fig. 8 Extracted thrombi

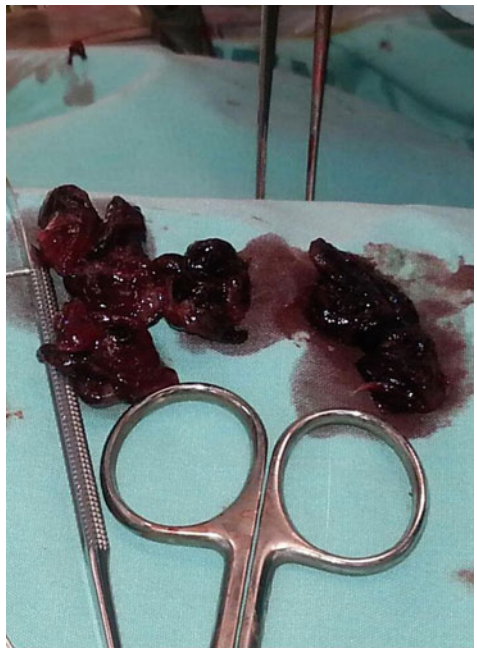

Fig. 9 Extracted thrombi

(Lango et al. 2008; Maggio et al. 2007) For patients with substantial distal blood clots in the peripheral pulmonary arteries and persistent hypoxia, ECMO may be the perfect bridge to recovery for a few days while the fresh clots undergo lysis.

Anticoagulation with warfarin is usually recommended for a minimum of 6 months if there is no contraindication. If not already in place, an inferior vena caval filter should be inserted into patients for whom anticoagulant therapy cannot be used, or those in whom the PE occurred while already on anticoagulant treatment.

10.4 Mechanical Circulatory Support in PE

There have been numerous reports of managing cases of severe acute RV failure using the Extracorporeal Membrane Oxygenator (ECMO). ECMO can provide the surgical team with sufficient time to perform embolectomy. ECMO can also be useful in severe cardiogenic shock (secondary to RV failure) and can even be initiated during resuscitation.

This approach is advantageous in cases with impaired hemodynamics due to massive PE by utilizing a venoarterial ECMO, thus essentially bypassing the lungs. (Bělohlávek et al. 2010)

ECMO can be implemented outside the operating room within 15–30 min by an equipped team of trained personnel. (Anderson et al. 1992; Wenger et al. 1988)

Several recent papers have been published on the topic, some represent reviews and others describe extreme case reports with various clinical scenarios focusing on the efficacy and advantages that the ECMO system provides.

One recent such review published in April 2015 summarized all case reports and case series published in the past 20 years, to evaluate the mortality rate and any poor prognostic factors (no RCT exist on the topic). They concluded that ECMO for selected patients with massive PE is associated with good outcomes. Patients presenting in cardiac arrest have worse outcomes, but better survival rates and good neurological recovery compared with other causes of cardiac arrest. The authors found ECMO to be a lifesaving therapeutic option, either as an adjunct to definitive management strategies (surgical

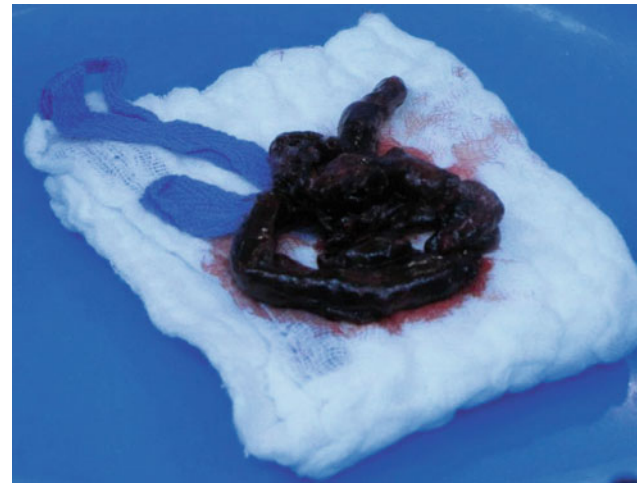

Fig. 10 Extracted thrombi

embolectomy, thrombolysis, catheter embolectomy) or on its own. In their review, the relationship between definitive treatment and mortality was not statistically significant. ECMO use in the context of massive PE should be considered, balancing benefits and the likelihood of recovery without significant neurological squeal and potential risks (Yusuff et al. 2015).

In our experience, we have found ECMO to provide lifesaving hemodynamic and respiratory support in patients with massive pulmonary embolism who are too unstable to tolerate other interventions. It may assist in stabilizing the patient pre and postoperatively. In some extreme cases, it might even provide a bridge-to-diagnosis and definitive treatment.

10.5 Inferior Vena Cava Filters

The primary indication for inferior vena cava (IVC) filter placement is when anticoagulation is contraindicated and when recurrent PE occurs despite therapeutic anticoagulation. However, it may be appropriate as an adjunct to anticoagulation in patients in whom another embolic event would be poorly tolerated (e.g., poor cardiopulmonary reserve, or severe hemodynamic or respiratory compromise), although clinical data are lacking.

The adjunctive use of filters should be individualized and take into consideration the risk of recurrence and bleeding, patient preferences, institutional expertise, medical morbidities, and surgical complications.

11 Results

With a rapid multidisciplinary approach and individualized indications for embolectomy before hemodynamic collapse, perioperative mortality rates of 6 % or less have been reported. (Leacche et al. 2005; Malekan et al. 2012; Aymard et al. 2013; Fukuda et al. 2011) Preoperative thrombolysis increases the risk of bleeding, but it is not an absolute contraindication to surgical embolectomy (Aklog et al. 2002).

The prognosis is poor in cases in which the procedure is undertaken when multi-organ dysfunction syndrome is fully developed (Table 1).

Series presenting high mortality rates (up to around 50 %) are mainly due to the fact that most patients who undergo surgical embolectomy are hemodynamically compromised and arrive at the operating room in cardiac arrest with cardiopulmonary resuscitation (CPR) in progress, or else they have had CPR performed beforehand.

Cardiac arrest upon presentation predicts mortality from surgical embolectomy (Aklog et al. 2002; Yalamanchili et al. 2004; Clarke

Table 1 In-hospital mortality according to the degree of hemodynamic compromise in 1001 patients with acute pulmonary embolism (Adapted from (Jaff et al. 2011))

Variable	*n*	Mortality(%)
RV dysfunction, no arterial hypotension	407	8.1
Arterial hypotension[a]	316	15.2
Cardiogenic shock[b]	102	24.5
Cardiopulmonary resuscitation	176	64.8

RV right ventricular

[a]Arterial hypotension—systolic arterial pressure <90 mmHg or drop in systolic pressure of at least 40 mmHg for >15 min but no need for catecholamines except for dobutamine ≤5 mg/kg/min

[b]Cardiogenic shock—arterial hypotension plus clinical signs of tissue hypoperfusion and hypoxia, including an altered level of consciousness, a urine output of <30 ml/h, or cold and clammy extremities

and Abrams 1986; Dauphine and Omari 2005). In one study of 36 patients with shock due to acute PE but without cardiac arrest, the operative mortality associated with surgical embolectomy was 3 % (Clarke and Abrams 1986). In contrast, operative mortality was 75 % among patients with acute PE who were resuscitated from a cardiac arrest and then underwent surgical embolectomy (Clarke and Abrams 1986; Dauphine and Omari 2005).

Data suggest that preoperative hemodynamic status is the most important prognostic indicator of postoperative outcome after surgical pulmonary embolectomy, and cardiac arrest and CPR are independent factors predictive of postoperative death (Ullmann et al. 1999). However, for patient undergoing CPR due to massive PE, surgical pulmonary embolectomy with or without ECMO may be the only chance for survival. Surgical embolectomy in hemodynamically stable patients as the primary treatment shows excellent long-term results (Digonnet et al. 2007).

Right atrial thrombus occurs in 4–8 % of patients with acute PE.

The optimal management of patients with right atrial thrombus is unclear. The 2-week mortality in 42 patients treated with heparin, thrombolysis or surgical embolectomy was equally poor (20–25 %), (Rose et al. 2002). A systematic review of 177 cases observed lower mortality in patients receiving thrombolysis (11 %) compared with anticoagulation (29 %) and surgery (24 %) (Ferrari et al. 2005). In a series of 16 consecutively thrombolyzed patients, right atrial thrombus disappeared in all patients within 24 h with a 30-day survival rate of 100 % (Ferrari et al. 2005). In a minority of patients, thrombus may straddle a patent foramen ovale (PFO) leading to an additional risk of systemic embolization. A literature review of 88 such patients demonstrated similar mortality (14 %), but a higher incidence of stroke in patients treated with anticoagulation rather than surgical embolectomy. (Fauveau et al. 2008) Patients treated with thrombolysis had a much higher mortality (36 %), although they had more hemodynamic compromise (Torbicki et al. 2003). AHA guidelines therefore recommend surgical embolectomy as the optimal treatment in this group.

12 Summary

It is our belief that there should be renewed enthusiasm for acute pulmonary embolectomy on the basis of the observed improved survival rates. Both identification and selection of appropriate candidates for acute pulmonary embolectomy have become easier because TEE and CT can detect early right ventricular dysfunction. Surgical embolectomy for stable patients demonstrates good short- and long-term results and is often the last resort for extremely unstable patients. We believe that surgical treatment for patient suffering from massive PE is underused. A randomized trial for short- and long-term results comparing surgical embolectomy to

thrombolysis for these high-risk patients may be of importance.

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The Optimal Duration of Anticoagulation in Patients with Unprovoked Venous Thromboembolism

Paolo Prandoni

Abstract

Once anticoagulation is stopped, the risk of recurrent venous thromboembolism (VTE) over years after a first episode is consistently around 30 %. This risk is higher in patients with unprovoked than in those with (transient) provoked VTE, and among the latter in patients with medical than in those with surgical risk factors. Baseline parameters that have been found to be related to the risk of recurrent VTE are the proximal location of deep vein thrombosis, obesity, old age, male sex and non-0 blood group, whereas the role of inherited thrombophilia is controversial. The persistence of residual vein thrombosis at ultrasound assessment has consistently been shown to increase the risk, as do persistently high values of D-dimer and the early development of the post-thrombotic syndrome. Strategies that incorporate the assessment of residual vein thrombosis and D-dimer have the potential to identify subjects in whom anticoagulation can be safely discontinued. Moreover, new opportunities are offered by a few anti-Xa and anti-IIa oral compounds, which are likely to induce fewer haemorrhagic complications than vitamin K antagonists while preserving the same effectiveness.

Keywords

Venous thromboembolism • Deep venous thrombosis • Pulmonary embolism • Anticoagulation • Thrombophilia • Residual thrombosis • Ultrasonography

1 Baseline Risk Factors for VTE Recurrence

Once anticoagulation is stopped, recurrent venous thromboembolism (VTE) is expected to develop in at least 30 % of patients who

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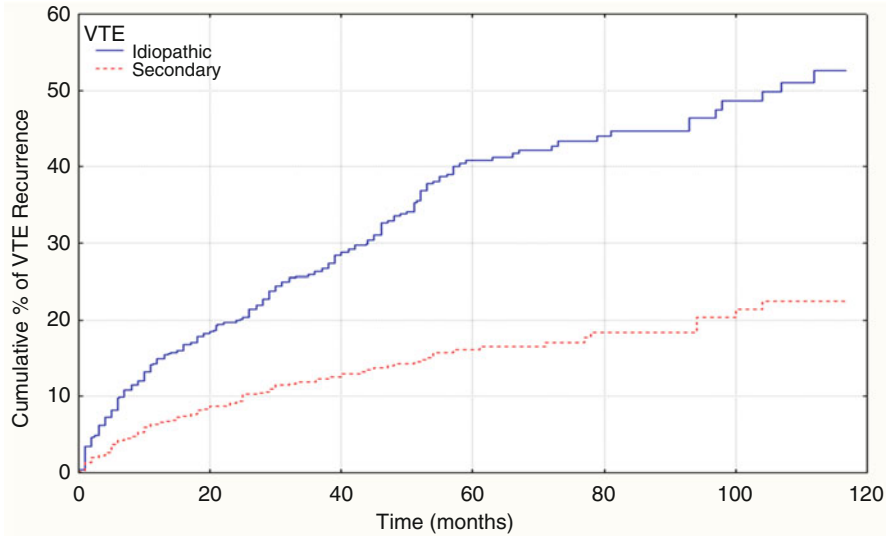

Fig. 1 Cumulative incidence of recurrent VTE after the first episode of DVT and/or PE. The incidence of recurrent VTE after discontinuing anticoagulation is twice as high in patients with idiopathic than in those with secondary VTE

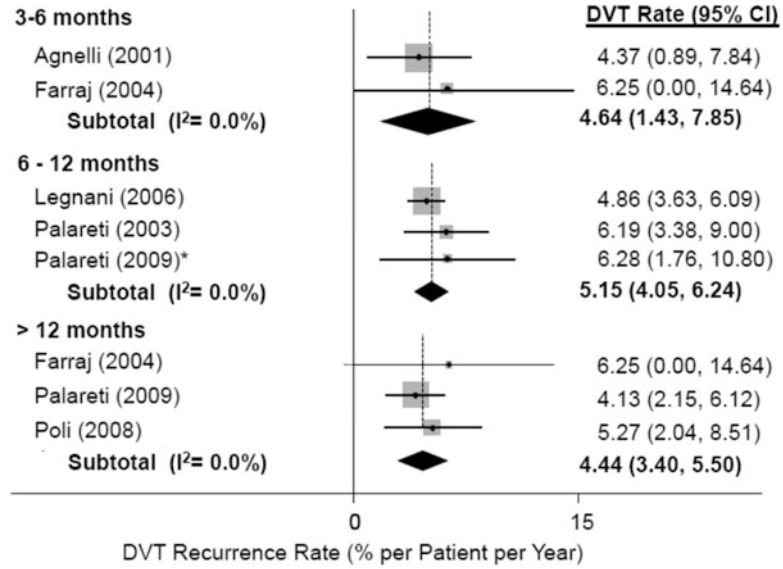

Fig. 2 DVT recurrence rates after treatment cessation. Whichever the duration of anticoagulation (up to 6 months, up to 12 months, longer than 12 months), the incidence of recurrent DVT remains unchanged

receive 3–6 months of anticoagulation after their first episode (Prandoni et al. 1996, 2007; Schulman et al. 1995; Hansson et al. 2000; Baglin et al. 2003) (Fig. 1). This rate will not change after extending anticoagulation up to 24 months (Holley et al. 2010; Boutitie et al. 2011) (Fig. 2).

1.1 Provoked Versus Unprovoked VTE

The risk of VTE recurrence is negligibly low after major surgery or trauma (annual rate, lower than 1.0 %), whereas it remains substantial if the thrombotic episode is triggered by "minor"

transient factors such as hormonal treatment, minor injury, pregnancy, puerperium or long trips (annual rate, around 4.0 %) (Baglin et al. 2003). Patients with permanent risk factors (active cancer, longstanding immobilization, antiphospholipid syndrome) and those without apparent explanations for their thrombotic episode have a remarkable higher risk (annual rate, higher than 7.0 %) (Prandoni et al. 1996, 2007; Schulman et al. 1995; Hansson et al. 2000; Baglin et al. 2003).

1.2 Clinical Characteristics

Single studies and meta-analyses have consistently shown that the risk of recurrent VTE is approximately 1.5 times as high in men than in women (Kyrle et al. 2004; McRae et al. 2006; Douketis et al. 2011). The discrepancy with the gender-specific risk of the first VTE episode is apparent, and most probably explained by sex-specific risk factors at time of first venous thrombosis that are removed later on (Lijfering et al. 2009; Le Gal et al. 2010). Indeed, when female reproductive risk factors are taken into account, the risk of a first venous thrombosis is twice as high in men as in women as well (Roach et al. 2014).

Old age, which is a well-known risk factor of venous thrombosis, has recently been identified – although not consistently (Eischer et al. 2009) – as a predictive factor of recurrent VTE (Prandoni et al. 2007). Accordingly, the common practice of giving old patients lower doses or shorter periods of anticoagulation should be reconsidered (López-Jiménez et al. 2006).

Overweight was recently found to be a powerful and independent risk factor of recurrent VTE (Eichinger et al. 2008). Obese patients should, therefore, be carefully educated, as weight-loss is likely to play a key role in reducing the risk of relapses.

Finally, in a recent cohort study non-0 blood type has been found to be an independent predictor of recurrent VTE (Gándara et al. 2013). This information, which can be easily obtained, has the potential to be incorporated in stratification models addressing the risk of recurrent VTE.

1.3 Modality of VTE Presentation

Patients with a first symptomatic unprovoked deep vein thrombosis (DVT) are at higher risk of recurrent VTE than those with a first unprovoked pulmonary embolism (PE) (Kovacs et al. 2010). In addition, patients with symptomatic PE have a risk of recurrent PE that is 2–3-fold higher than those with DVT alone. These findings, which have recently been confirmed by a patient-level meta-analysis (Baglin et al. 2010), should be taken into account when deciding the optimal duration of anticoagulation. Indeed, a PE episode is potentially more dangerous than an event confined to the leg veins.

2 Inherited Thrombophilia and Family History

Inherited thrombophilia does not increase the risk of recurrent thromboembolism while on anticoagulation (Kearon et al. 2008), while its role in recurrent VTE once anticoagulation is stopped is controversial. It is generally accepted, although not conclusively demonstrated, that carriers of (even mild) antithrombin, protein C and S defects (De Stefano et al. 2006; Di Minno et al. 2014), carriers of hyperhomocysteinemia (Eichinger et al. 1998) and carriers of increased levels of factor VIII or IX (Kyrle et al. 2000; Eischer et al. 2008; Weltermann et al. 2003) have a recurrence risk that is higher than that of control subjects. It is, instead, matter of debate if carriers of factor V Leiden or prothrombin G20210A variant have a higher risk of recurrence as well, as there are data in favour and against this association (Segal et al. 2009; Lijfering et al. 2010). As a consequence, whether detection of these abnormalities, which are highly prevalent in western countries, has the potential to identify subgroups of patients who might benefit from individually adjusted prevention strategies, is uncertain.

Two studies have consistently shown that the family history of VTE – a well known risk factor of VTE (Zöller et al. 2013) – does not increase

the risk of recurrent VTE (Hron et al. 2006; Gauthier et al. 2013).

3 Post-Baseline Factors

3.1 D-Dimer

Several studies consistently suggested that positivity of D-dimer at the time of warfarin discontinuation or soon after its interruption helps identify patients at a higher risk of developing recurrent VTE (Palareti et al. 2002, 2003; Eichinger et al. 2003; Verhovsek et al. 2008). These findings have recently been confirmed by a meta-analysis of available investigations (Bruinstroop et al. 2009) (Fig. 3).

3.2 Post-Thrombotic Syndrome

Another post-baseline factor potentially associated with an increased risk of recurrent VTE is the early development of post-thrombotic manifestations (Stain et al. 2005).

3.3 Residual Vein Thrombosis

In a few cohort studies, the ultrasound persistence of residual thrombosis after an episode of proximal DVT was found to be an independent risk factor for recurrent VTE (Prandoni et al. 2002; Piovella et al. 2002) (Fig. 4). Two recent meta-analyses of available investigations suggest that, whichever the method used for measuring the thrombotic mass, residual vein thrombosis is a powerful and independent predictor of recurrent VTE (Tan et al. 2011; Donadini et al. 2014). Of interest, residual vein thrombosis predicts not only the development of recurrent ipsilateral DVT, but also that of contralateral DVT and even of PE apparently not associated with DVT, suggesting that residual vein thrombosis is a marker of hypercoagulability (Prandoni et al. 2002; Piovella et al. 2002; Tan et al. 2011; Donadini et al. 2014).

In a recent prospective cohort study, residual vein thrombosis at 3 months after DVT (defined as the ultrasound incompressibility of at least 4 mm in the transverse section either in the popliteal or in the common femoral vein) was found to double the risk for subsequent recurrent VTE, post-thrombotic syndrome, arterial thrombotic events and cancer (Prandoni et al. 2015). The likelihood of residual vein thrombosis was higher in males, in patients with previous VTE and in those with extensive thrombosis. These findings suggest that a single assessment of residual thrombosis at 3 months can help risk stratify patients with proximal DVT and guide treatment decisions.

Whether the persistence of residual emboli after an episode of PE may predict the risk of recurrent PE as well is uncertain (Golpe et al. 2012). A recent prospective cohort study showed an unexpectedly high rate (85 %) of pulmonary artery recanalization in patients with PE treated with anticoagulants alone for 6 months, while in the remaining 15 % the

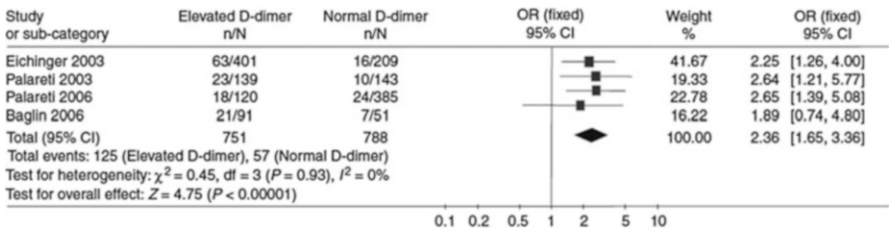

Fig. 3 D-dimer and the incidence of recurrent VTE. The positivity of D-dimer after discontinuing anticoagulation consistently predicts the development of recurrent VTE

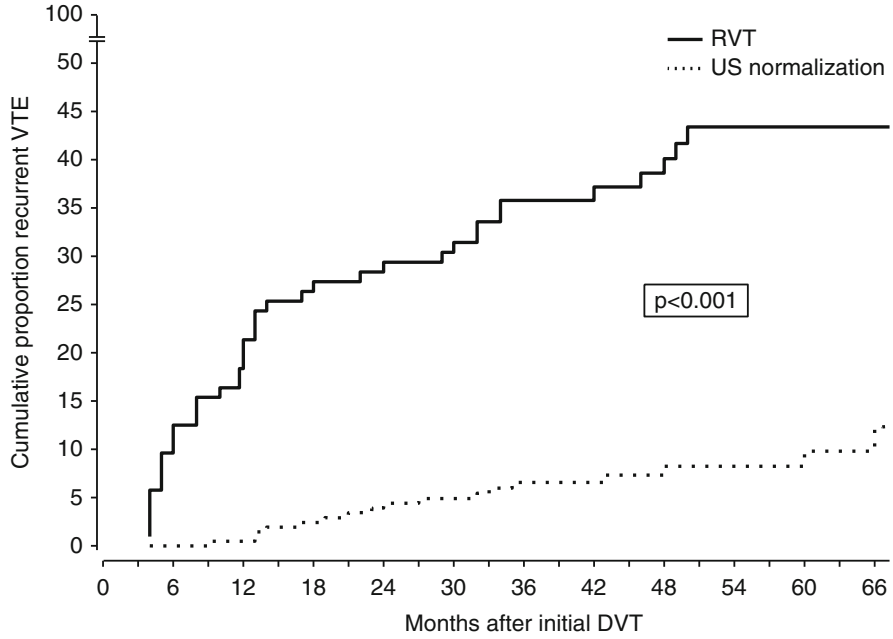

Fig. 4 Cumulative incidence of recurrent VTE according to the persistence of residual vein thrombosis (RVT) or ultrasonography normalization. The incidence of recurrent VTE after discontinuing anticoagulation is remarkably higher in patients with RVT than in those with earlier recanalization

Table 1 Models to predict recurrent VTE

	Men continue and HER D002 (Pesavento et al. 2014)	Vienna prediction model (Rodger et al. 2008)	DASH-score (Eichinger et al. 2010)
Study design	Prospective cohort	Prospective cohort	Patient level meta-analysis
Patients	646	929	1818
Predictive variables	Men: none		
	Women:		
	age $\geq$ 60 years	Sex	Abnormal D-dimer after anticoagulation
	signs of PTS	Location of first VTE	Age $<$ 50 years
	BMI $\geq$ 30 kg/m^2	D-Dimer after anticoagulation	Male sex
	D-dimer $>$ 250 µg/l during anticoagulation		Hormonal therapy
Increased risk of recurrent VTE	$>$1 point	$>$180 points (according to a nomogram)	$>$1 point
Recurrence rate in patients at low risk	1.6 % (95 % CI, 0.3–4.6)	4.4 % (95 % CI, 2.7–6.2)	3.1 % (95 % CI, 2.3–3.9)

thrombotic burden decreased by more than 80 % (Pesavento et al. 2014). These findings add to the current perception that residual thrombotic obstruction following PE is rare and unlikely to predict recurrent PE.

4 Risk Stratification Models

A novel approach for assessing risk of recurrent VTE consists of linking clinical patient characteristics with laboratory testing (Table 1).

In a Canadian model, women with idiopathic VTE and none or one of several parameters (age older than 65, obesity, D-dimer positivity at time of discontinuing anticoagulation and post-thrombotic manifestations) exhibited a considerably lower risk of recurrent VTE than the remaining patients (Rodger et al. 2008). Another prediction model enables identification of the recurrence risk based on the combination of two baseline factors (sex and type of clinical presentation) and one post-baseline factor (D-dimer) (Eichinger et al. 2010). In the third model, based on a patient-level meta-analysis (the DASH score), D-dimer after stopping anticoagulation, age $<$ 50 years, male sex and VTE not associated with hormonal therapy (in women) were found to be the main predictors of recurrence and were used to derive a prognostic recurrence score (Tosetto et al. 2012). All these scoring models require prospective validation before they can be applied in daily routine care (Kyrle and Eichinger 2012).

5 Duration of Treatment in Patients with Unprovoked VTE: Old and New Scenarios

Patients presenting with a first episode of unprovoked VTE should be offered at least 3 months of vitamin K antagonists, targeting an INR between 2.0 and 3.0 (Kearon et al. 2012), which is the duration that is commonly recommended for patients whose thrombotic episode is triggered by transient risk factors (Kearon et al. 2004). The decision as to go on or discontinue anticoagulation after the first 3 months should be individually tailored and balanced against the haemorrhagic risk, taking into account also patients' preferences. An indefinite anticoagulation can be considered in selected patients at low bleeding risk (Kyrle and Eichinger 2012), while in all other patients this decision requires caution. Indeed, the annual incidence of major bleeding from long-term anticoagulation is 1.5–2.0 %, and the 'case-fatality rate' of major bleeding is considerably higher than that of recurrent VTE (Carrier et al. 2010; Lecumberri et al. 2013). Of interest, major bleeding increases the risk of recurrent VTE and decreases life expectancy (Spencer et al. 2008; Prandoni et al. 2010).

Following the demonstration that D-dimer can help stratify the individual risk of recurrent VTE (Palareti et al. 2002, 2003; Eichinger et al. 2003; Verhovsek et al. 2008; Bruinstroop et al. 2009), a randomized clinical trial showed that in patients in whom anticoagulation was withdrawn the annual rate of recurrent events was much lower in patients with negative (4.4 %) than in those with positive D-dimer (10.9 %), as assessed 1 month after warfarin discontinuation; however, it was higher than that (2.0 %) observed in patients in whom anticoagulation was not discontinued (Palareti et al. 2006). Of interest, in a recent prospective cohort study the annual rate of patients with unprovoked VTE who experienced recurrent events in the 2 years following the discontinuation of therapy owing to a negative D-dimer – as assessed 1 month after stopping warfarin – was found to be as high as 6.7 % (Kearon et al. 2015). Repeating D-dimer more times testing after anticoagulation suspension has the potential to identify individuals requiring resuming anticoagulation in order to prevent VTE recurrences (Cosmi et al. 2010).

In a few randomized clinical trials it has been shown that adjusting the duration of anticoagulation according to the persistence of residual thrombosis reduces the risk of recurrent VTE by approximately 40 % [(Prandoni et al. 2009; Siragusa et al. 2008)].

Of the two multicenter Italian studies, designed to evaluate the value of combining residual vein thrombosis with the serial D-dimer determination in adjusting the duration of anticoagulation, the DULCIS study has recently been published (Palareti et al. 2014). In this study, involving almost 1000 outpatients, D-dimer tests persistently below age and gender specific cut-offs were obtained in more than 50 % of patients, and discontinuation of vitamin K antagonists resulted in a subsequent annual recurrence rate lower than 3.0 %. The second – the Morgagni study – is still ongoing.

6 New Opportunities

6.1 New Oral Anticoagulants

New categories of oral antithrombotic drugs are emerging. These drugs have the potential to simplify the treatment of patients with VTE by obviating the need for periodic laboratory monitoring and are associated with a favourable benefit-to-risk ratio. They include compounds that selectively inhibit factor Xa, such as rivaroxaban, apixaban and edoxaban, and compounds that selectively inhibit thrombin, such as dabigatran etexilate. The results of several randomized clinical trials suggest that these drugs have a favourable benefit-to-risk profile in the first 6–12 months after an episode of VTE in comparison with conventional treatment (Schulman et al. 2009, 2014; The Einstein Investigators 2010, 2012; Agnelli et al. 2013a; The Hokusai-VTE Investigators 2013). The value of long-term administration in preventing recurrent VTE has been evaluated in four studies performed in patients who had completed a 6–18-month period of conventional anticoagulation.

Two clinical trials were designed to assess the efficacy and safety of dabigatran for the extended treatment of VTE. In the RE-SONATE study, 1343 patients with unprovoked VTE who had completed 6–18 months of anticoagulant therapy were randomized to dabigatran (150 mg bid) or placebo for an additional period of 6 months (Schulman et al. 2013). A 92 % relative reduction in the relative risk for recurrent VTE was shown in favor of dabigatran, with a low risk for major bleeding (0.3 % vs 0). In the RE-MEDY study, 2856 patients at a higher risk of recurrent VTE who had been treated for 6 months with vitamin K antagonists for a first VTE were randomized to dabigatran (150 mg bid) or warfarin (INR 2–3) for the long-term prevention of recurrent VTE (Schulman et al. 2013). Dabigatran was shown to be non-inferior to vitamin K antagonists (1.8 % primary outcome events in dabigatran patients versus 1.3 % in warfarin patients). Major bleeding complications occurred in 0.9 % and 1.8 % of patients, respectively (reduction in the relative risk, 48 %).

The EINSTEIN Extension trial randomized 1197 patients with unprovoked VTE who had completed 6–12 months of anticoagulant therapy for an acute index VTE event to an additional 6–12 months of therapy with either rivaroxaban, 20 mg once daily, or placebo (The Einstein Investigators 2010). Recurrent symptomatic VTE events were recorded in 1.3 % of patients in the rivaroxaban group and 7.1 % of patients in the placebo group (relative risk reduction, 82 %). Major bleeding occurred in 4 (0.7 %) rivaroxaban-treated patients as compared to none in the placebo group.

The AMPLIFY-Extension was a 12-month randomized clinical trial where apixaban 2.5 mg and 5 mg bid were compared with placebo for extended treatment to prevent recurrent VTE in approximately 2500 patients with unprovoked VTE who had completed 6–12 months of treatment for DVT or PE (Agnelli et al. 2013b). Apixaban demonstrated superiority versus placebo in the reduction of the composite endpoint of symptomatic, recurrent VTE and death from any cause ($p < 0.001$). Apixaban was superior to placebo for the predefined secondary efficacy outcome of recurrent VTE and VTE-related death (8.8 % in the placebo group, compared with 1.7 % in both the apixaban 2.5 mg and 5 mg groups; $p < 0.001$). The rates of major bleeding were comparable for 2.5 mg (0.2 %), 5 mg (0.1 %), and placebo (0.5 %) treatment groups. The rate of the composite of major bleeding and clinically relevant non-major bleeding for the 5 mg treatment group (4.3 %) was higher than in the placebo group (2.7 %), while 2.5 mg treatment group (3.2 %) demonstrated similar rates to placebo.

Because of the potential to induce fewer bleeding complications, the new drugs may open new scenarios for decisions on the optimal duration of anticoagulation in patients with unprovoked VTE. However, these findings should be interpreted with caution for a number of reasons. Only selected patients were included in the clinical trials, thus no information is available for different patients categories, including carriers of major thrombophilias, patients with severe renal or hepatic failure, patients requiring

anticoagulation for reasons other than VTE and so on. In only one study (the REMEDY) was the new anticoagulant (dabigatran) compared with warfarin in patients at a higher recurrence risk (Schulman et al. 2013), whereas in all the remaining the comparator was placebo, and the extent by which recurrent VTE was reduced over placebo did not exceed that achieved by vitamin K antagonists in studies adopting a similar study design (Boutitie et al. 2011). In only one study (the AMPLIFY-Extension) was there a head-to-head comparison between the conventional and a lower dose of the index compound (apixaban), whereas in all the remaining the initial dose was tested unchanged throughout the whole period of anticoagulation (Agnelli et al. 2013b). As the duration of these studies did not surpass 6–12 months, the persistence of a favourable benefit-to-risk ratio beyond this period cannot be anticipated. The results of the AMPLIFY-Extension study suggest that halving the initial dose after the first 6 months in patients with unprovoked VTE is likely to preserve protection against recurrent VTE while further reducing the haemorrhagic risk (Agnelli et al. 2013b).

6.2 Low-Dose Aspirin

Recent studies have shown the efficacy of low-dose aspirin in the prevention of recurrent VTE. In a multicenter, double-blind study (the WARFASA trial), more than 400 patients with unprovoked VTE who had completed 6–18 months of oral anticoagulant treatment were randomly assigned to aspirin, 100 mg daily, or placebo for at least 2 years (Becattini et al. 2012). VTE recurred in 28 of the 205 patients who received aspirin and in 43 of the 197 patients who received placebo (6.6 % vs. 11.2 % per year; HR, 0.58; 95 % CI, 0.36–0.93). One patient in each treatment group had a major bleeding episode.

The ASPIRE trial, which involved 822 patients, showed a non-significant decrease in the rate of recurrent VTE with aspirin (100 mg per day) as compared with placebo (rate of recurrence, 4.8 % vs. 6.5 % per year; hazard ratio, 0.74; 95 % CI, 0.52–1.05; P = 0.09) (Brighton et al. 2012). However, since arterial thrombotic events occurred only about half as often in the aspirin-treated group as in the placebo group (10 events vs. 19 events), aspirin was associated with a significant reduction in the rate of major vascular events (hazard ratio, 0.66; 95 % CI, 0.48–0.92; P = 0.01).

When data from these two trials are pooled, there is a 32 % reduction in the rate of recurrence of VTE (hazard ratio, 0.68; 95 % CI, 0.51–0.90; P = 0.007), and a 34 % reduction in the rate of major vascular events (hazard ratio, 0.66; 95 % CI, 0.51–0.86; P = 0.002) (Fig. 5). Moreover, these benefits are achieved with a low risk of bleeding (Warkentin 2012).

Hence, based on available evidence, aspirin in low doses may offer a safe and highly

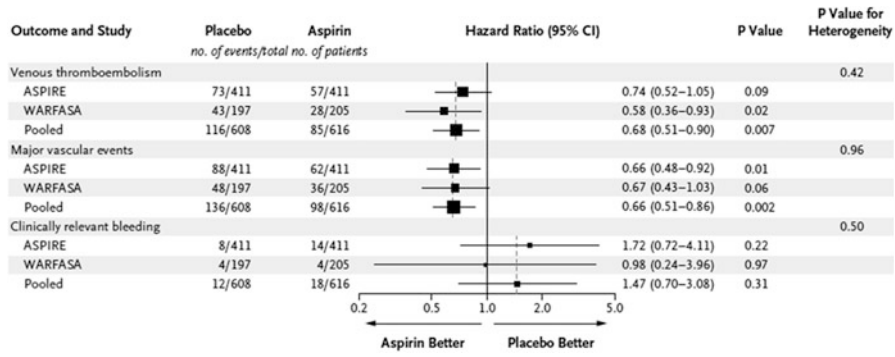

Fig. 5 Meta-analysis of the WARFASA and ASPIRE studies. The use of 100 mg of aspirin after completing 3–12 months of conventional anticoagulation in patients with unprovoked VTE reduces both the incidence of recurrent VTE and that of major vascular events (including arterial cardiovascular events) without increasing the bleeding risk

cost-effective option for the long-term prevention of recurrent VTE. However, the degree by which aspirin reduces the rate of recurrent VTE is remarkably lower than that achieved by old and new anticoagulants. In addition, in real practice, the bleeding risk related to the use of even low doses of aspirin may not be as low as that observed in the WARFASA and in the ASPIRE studies (Warkentin et al. 2012). Finally, aspirin does not seem to confer any appreciable protection against recurrent VTE in patients with symptomatic atherosclerosis (Milan et al. 2012; Sørensen et al. 2009). An appealing perspective (to be tested in future investigations) may be replacing warfarin with aspirin in patients with unprovoked VTE at low risk of recurrent VTE, such as those with early veins recanalization and/or persistent D-dimer negativity and in those with VTE associated with "minor" risk factors.

6.3 Statins

Finally, the recent studies suggest a potential role for statins, whose value has already been shown in the primary prevention of VTE (Agarwal et al. 2010), in reducing the risk of recurrent VTE (Biere-Rafi et al. 2013; Nguyen et al. 2013; Schmidt et al. 2014). Whenever there is the need for lowering the lipids level or controlling the development of atherosclerotic lesions in patients with VTE, the use of statins is, therefore, likely to improve the outcome of the venous thrombotic disorder as well.

7 Conclusions

Identifying the optimal duration of anticoagulation in patients who experience an episode of unprovoked VTE is a challenging task. After completing the first 6 months of anticoagulation with either a VKA or a novel anticoagulant, continuing indefinitely anticoagulation is associated with a high degree of protection against recurrent VTE, but exposes to the risk of unpredictable bleeding complications. Indeed, there is currently no score that can help reliably identify the bleeding risk from anticoagulant drugs in patients with VTE. Continuing indefinitely anticoagulation is certainly the best option for patients with personal or familial history of VTE, in those with major thrombophilias (such as deficiencies of the natural anticoagulants, homozygosity for the factor V Leiden or the prothrombin variant or the antiphospholipid syndrome) and in those in whom an extensive work-up for cancer has led to the detection of an underlying malignancy. What to do in the remaining patients? Repeating leg vein ultrasonography and assessing D-dimer (before the drug interruption and then at least once monthly for the first 3 months) have the potential to identify a reasonable high proportion of patients in whom anticoagulation can be safely discontinued. In all remaining patients, the currently best option is offered by the indefinite use of low-dose apixaban (2.5 mg twice daily), which has been shown to possess the best benefit-to-risk profile.

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Anticoagulation Therapy in Patients with Chronic Kidney Disease

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Abstract

Patients with chronic kidney disease (CKD) are at increased risk for both thrombotic events and bleeding. The early stages of CKD are mainly associated with prothrombotic tendency, whereas in its more advanced stages, beside the prothrombotic state, platelets can become dysfunctional due to uremic-related toxin exposure leading to an increased bleeding tendency. Patients with CKD usually require anticoagulation therapy for treatment or prevention of thromboembolic diseases. However, this benefit could easily be offset by the risk of anticoagulant-induced bleeding. Treatment of patients with CKD should be based on evidence from randomized clinical trials, but usually CKD patients are excluded from these trials. In the past, unfractionated heparins were the anticoagulant of choice for patients with CKD because of its independence of kidney elimination. However, currently low-molecular-weight heparins have largely replaced the use of unfractionated heparins owing to fewer incidences of heparin-induced thrombocytopenia and bleeding. We undertook this review in order to explain the practical considerations for the management of anticoagulation in these high risk population.

Keywords

Chronic kidney disease • Anticoagulation • Thrombosis • Bleeding • Platelets • Heparin • Enoxaparin • Oral anticoagulants

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1 Introduction

Chronic kidney disease (CKD) is a global public health problem, with more than 500 million people worldwide estimated to have some form of kidney problem [1]. Risk factors affecting the increased prevalence of CKD include the

elderly and patients with diabetes mellitus [2]. In the United State more than half of people aged 70 years or above have CKD [1]. The prevalence of moderate to severe CKD has been reported to be 38 % for adults older than 70 years compared to 1 % in adults aged 20–30 years [3]. Diabetes mellitus is often associated with CKD, with moderate to severe CKD found in 15–27 % of patients with diabetes [4]. Additionally, diabetes is the main cause of kidney failure in 50 % of patients who receive dialysis therapy [5].

Patients with CKD display a wide range of abnormalities in the hemostatic pathway that may result in their increased risk for both thrombotic events and bleeding [6]. The early stages of CKD are mainly associated with prothrombotic tendency [6]. There is a suggestion that the risk of venous thromboembolism (VTE) is more associated with albuminuria than to declined glomerular filtration rate (GFR) [7]. Moreover, beside the prothrombotic state, CKD can lead to platelets becoming dysfunctional due to uremia-related toxin exposure leading to an increased bleeding tendency in its more advanced stages [6].

The increased risk of thrombosis requires anticoagulation for prophylaxis or treatment of thromboembolic events [8]. Decisions for therapy, including the choice of anticoagulant, duration of therapy, dosage, and approaches to drug monitoring, should balance the risks of bleeding-to-benefit ratio with anticoagulation therapy in CKD. Patients with CKD have been underrepresented in randomized pharmacotherapy trials [9], with the current anticoagulant dosing suggestions for CKD patients mostly influenced by postmarketing experiences.

The purpose of this chapter is to explore selected anticoagulant agents and provide an overview of the available evidence with their use in patients with CKD. A discussion of anticoagulation therapy in patients with acute kidney injury and maintaining the dialysis circuit in end stage renal disease is beyond the scope of this chapter.

2 Definition and Stages of CKD

The Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation (NKF) defines CKD as either structural or functional kidney damage with or without a decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for 3 or more months [10]. Structural or functional kidney damage can be revealed by pathological markers, abnormalities in blood or urine, or imaging tests [10].

In practice, kidney function in adults is mostly reported on the basis of estimated glomerular filtration rate (eGFR) normalized to a body surface area of 1.73 m^2 and derived from the Modification of Diet in Renal Disease (MDRD) equation [11]. The equation was developed in 1999 based on demographic data from 1628 patients with CKD. The MDRD equation includes variables for age, gender, race, and body-surface area [11]. eGFR is expressed as mL/min/1.73 m^2. Based on eGFR, the NKF guidelines categorize CKD into 5 stages [10]. Patients with moderate CKD are at stage 3 with eGFR of 30–59 mL/min/1.73 m^2, those with severe CKD are at stage 4 with eGFR of 15–29 mL/min/1.73 m^2, and those with kidney failure are at stage 5 with eGFR of less than 15 mL/min/1.73 m^2 and require initiation of kidney replacement therapy (dialysis or transplantation) [10].

Another method to assess kidney function in adults is estimating creatinine clearance (CrCl) using the Cockcroft and Gault equation. It is important to consider that CrCl and GFR are two different measures of kidney function and are not interchangeable in practice. CrCl is a surrogate for GFR, but CrCl slightly overestimates GFR [12]. In the kidney, creatinine undergo glomerular filtration but are also actively secreted by the renal tubules.

In the past, CrCl estimation was used for dosing drugs in relation to kidney function but nowadays the eGFR estimated using the MDRD is considered the standard test for assessing

kidney function. In the British National Formulary (BNF) [13], for most drugs, the information on dose adjustment is reported in terms of eGFR, rather than CrCl; however, they state that for potential toxic drugs with a narrow therapeutic index, CrCl calculated from the Cockcroft and Gault equation should be used to adjust drug doses.

3 Heparin-Induced Thrombocytopenia in CKD

Heparin-induced thrombocytopenia (HIT) can be classified into HIT I and HIT II. HIT I is a pharmacological condition that occurs when platelet counts fall in the 24–48 h after the start of therapy with unfractionated heparin (UFH) or to a lesser extent with low-molecular-weight heparin (LMWH). Thromboembolic events never occur in this condition, and does not require stopping heparin [14]. HIT II is the most common drug-induced immune thrombocytopenia. The mechanism causing HIT II in patients with administrated heparins is the synthesis of the heparin-platelet-factor-4-(PF4) that induces antibodies. Antibody-heparin-PF4 complexes then bind to the cell membrane of thrombocytes and endothelial cells, leading to the activation of thrombocytes and, in turn, to their aggregation [15].

Recognition of HIT II in patients with CKD can be difficult due to their lower baseline platelet counts [16]. The diagnosis depends on the occurrence of thromboembolic events with current or recent therapy with UFH or LMWH and a significant drop of platelets (approximately 50 % drop in platelet counts) which typically lies within 7–14 days after the start of anticoagulation [14]. In hemodialysis patients, if unexpected clotting of the dialysis apparatus occurs, which can occur even before the 50 % fall in platelets, HIT II has to be considered [16].

In the setting of HIT II, therapy with heparin or LMWH must be stopped immediately and an appropriate alternative anticoagulant must be started. In patients with CKD, the latest clinical practice guidelines suggest the use of argatroban over other nonheparin anticoagulants [15].

In hemodialysis condition, all the exposure of dialysis apparatus to heparin including heparin flushes and bathing the dialysis filter with heparin should be eliminated [16].

4 Indirect Thrombin Inhibitors

4.1 Unfractionated Heparin

Less than a century ago, the anticoagulant effect of unfractionated heparin (UFH) was discovered by McLean [17]. Brinkhous and colleagues [18] then showed that UFH requires a plasma cofactor to exhibit its anticoagulant effect. Later, in 1968, this cofactor was identified as antithrombin III [19] which is now known as antithrombin (AT) cofactor [20].

4.1.1 Structure and Mechanism of Action

UFH is a sulfated polysaccharide with a mean molecular weight (MW) of 15,000 Da, which correspond to approximately 45 saccharide units. UFH binds to AT through its active pentasaccharide unit, resulting in the inhibition of thrombin (IIa) and factor Xa in an equal ratio (1:1) (Fig. 1) [21].

Only one-third of UFH molecule contain the high-affinity pentasaccharide required for anticoagulant effect [22]. The UFH fraction with low-affinity for AT have more effect on platelet function [23]. In vitro, UFH binds to platelets and, based on experiments, can either induce or inhibit platelet aggregation [24]. In vivo, UFH can prolong the bleeding time in humans [25] and can increase vessel wall permeability in rabbits [26]. The interaction of UFH with platelets can lead to heparin-induced bleeding through mechanisms independent of its anticoagulant effect [27].

Besides its hemorrhagic adverse effects, UFH inhibits the proliferation of vascular smooth muscle cells [28], and promotes osteoporosis through inhibiting osteoblast formation and activation of osteoclast [29]. Heparin-induced

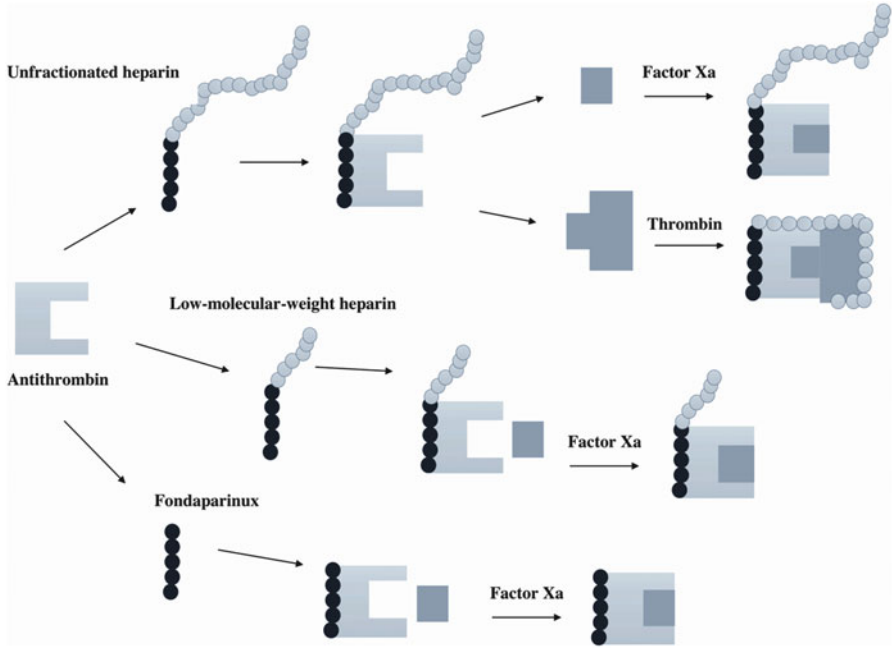

Fig. 1 Mechanism of action of unfractionated heparin, low-molecular-weight heparin, and fondaparinux

thrombocytopenia (HIT) is the most common non-hemorrhagic adverse effect of UFH [15].

4.1.2 Pharmacokinetics

UFH has marginal intestinal absorption and for that reason must be administered parenterally [20]. UFH is given by an initial bolus dose, followed by continuous infusion. If patient intravenous line is not readily accessible, weight adjusted subcutaneous UFH may be a suitable choice.

There is inter-patient variability to the anticoagulation response to UFH because after entering the circulation, UFH binds to plasma proteins different from AT, which can reduce its bioavailability [20].

Heparin is eliminated by a combination of a rapid saturable, dose-dependent mechanism and a slower, nonsaturable, dose-independent mechanism. At therapeutic doses, a large proportion of UFH is eliminated rapidly from plasma by binding to endothelial cells and macrophages [8]. No clear recommendations is available for reducing the maintenance dose in CKD patients. However, high doses of UFH are eliminated predominantly by the slower nonsaturable mechanism of renal clearance once saturation of cellular mechanism occurs. Therefore, over anticoagulation can occur in patients with severe CKD (GFR <30 mL/min/1.73 m^2), and the dose may need reduction to avoid the risk of bleeding [13].

4.1.3 Dosing

In acute thromboembolic events, an intravenous bolus of up to 80 units/kg and a continuous infusion of 18 units/kg/h may be administered to rapidly reduce the activity of clotting factors [13]. In the setting of acute coronary syndromes (ACSs), a lower intravenous bolus dose of 60 units/kg and 12 units/kg/h is commonly used [30].

In the absence of acute need for anticoagulation or in the case of high bleeding risk, the bolus dose may be avoided and only a continuous infusion may be initiated. This has the benefit of establishing more steady anticoagulation therapy, reducing the risk of bleeding and removing the need for early monitoring of activated partial thromboplastin time (aPTT) used in the case of bolus dose. The target aPTT

ranges used in the initial continuous infusion of UFH should be selected based on the indication for anticoagulation therapy and do not require special dose adjustment because of CKD alone [31].

4.1.4 Monitoring

Since the anticoagulation response to UFH varies between patients, it is common practice to monitor UFH and to adjust the dose based on the results of a coagulation test. A retrospective study done among VTE patients in the 1970s reported that an aPTT range between 1.5 and 2.5 was associated with a reduced risk of recurrent VTE [32]. According to this study, a therapeutic range of 1.5–2.5 times baseline gained acceptance [20]. In the setting of ACSs, a lower target aPTT range of 1.5–2 times baseline is desired [30].

4.1.5 Clinical Practice

UFH has been extensively used clinically since 1937, and there are limited randomized clinical trials comparing bleeding complication rates in patients with CKD and those without CKD.

A post-hoc subgroup analysis of the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) and Thrombolysis in Myocardial Infarction (TIMI IIB) trials investigated the safety of enoxaparin, a low-molecular-weight heparin (LMWHs), and UFH anticoagulation therapy of ACSs in patients with CKD stages 4–5. Patients were randomized to receive either enoxaparin (unadjusted dose to account for kidney function; 1 mg/kg actual body weight subcutaneously twice daily) and UFH (full-therapeutic dose; intravenous infusion UFH adjusted to maintain an aPTT level of 55–85 s in the ESSENCE and 1.5–2 times control in the TIMI 11B). Although CKD was an exclusion criteria in ESSENCE and TIMI IIB trials, about 2 % of both study population had CKD stage 4 or 5 with no patient on renal replacement therapy. This study showed that the rate of major bleeding in patients with CKD was 6.6 % and in those with no CKD was 1.1 % ($P < 0.0001$), regardless of whether UFH or enoxaparin was used. However, the number of patients with CKD were small with a total of 143 patients randomized to UFH ($n = 74$) or enoxaparin ($n = 69$) compared with those with no CKD ($n = 6{,}969$), as was the number of major bleeds among CKD patients (UFH, 4 patients; enoxaparin, 5 patients) [33].

A retrospective medical record review of 620 hospitalized patients with an estimated GFR of less than 60 ml/min/1.73 m^2 compared the rates of bleeding in patients who received anticoagulation therapy with full-therapeutic dose of UFH, or with unadjusted enoxaparin (1 mg/kg twice daily). Authors reported that the major bleeding rates were 26.3 per 1,000 person-days for UFH and 20.7 per 1,000 person-days for enoxaparin (nonsignificant), and that the bleeding complications increased for both UFH and enoxaparin therapy at each stage as CKD progressed, suggesting that factors other than drug clearance is responsible for anticoagulant bleeding complications [34].

More recently, a 1 year prospective observational study was conducted in 488 patients with CKD stages 3–5 (estimated GFR, 10–59 ml/min/1.73 m^2), who were admitted to the renal ward of a government hospital in Dubai. The study identified the incidence of major bleeding events from therapy with full-therapeutic doses of UFH, or with adjusted enoxaparin (1 mg/kg once daily), and compared the rates of major bleeding between the UFH and enoxaparin users. In this study, major bleeding occurred in 1 in 3 patients who received anticoagulation during hospital stay (hazard ratio [HR], 4.61 [95 % confidence interval [CI], 2.05–10.35]). Compared with enoxaparin users, patients who received anticoagulation with UFH had a higher risk of major bleeding (HR, 4.79 [95 % CI, 1.85–12.36]); with 51 % patients bleeds with UFH versus 22 % patients bleeds with enoxaparin therapy, and had a lower mean [SD] level of platelet counts (139.95 [113] $\times$ 10^3/mL vs 205.56 [123] $\times$ 10^3/mL; $P < 0.001$) [35].

In the above mentioned studies, the risk of bleeding complication was higher with full-therapeutic doses of UFH compared to enoxaparin. Despite the fact that enoxaparin is dependent on the kidney for its elimination and that it can bioaccumulate with reduced kidney

function, this might not result in higher bleeding rates. The increased rate of bleeding observed with UFH may be attributed to the inhibition of platelet function and increase in vascular permeability; properties that are independent to anticoagulant effects [36]. Unlike UFH, enoxaparin binds less to platelets because of its smaller molecular size and so has fewer incidences of heparin-induced thrombocytopenia and bleeding events [36]. This is beneficial because patients with advanced CKD are already more susceptible to bleeding from uremia-related platelet dysfunction [37].

In practice, UFH is used for anticoagulation in patients with high bleeding risks such as patients with CKD, as the anticoagulant effects of UFH can rapidly and completely be reversed by protamine sulphate. The drug formulary recommends that the dose be reduced in patients with severe CKD and patients to be observed carefully for signs and symptoms of bleeding but does not provide any guidance regarding dose adjustment or laboratory monitoring [13].

4.2 Low-Molecular-Weight Heparin

LMWHs are produced from UFH by enzymatic depolymerization. Compared to UFH, LMWHs, when used to treat thromboembolic events, have better pharmacokinetics properties with more favorable efficacy-to-safety ratio [8].

4.2.1 Structure and Mechanism of Action

The molecular weight of a LMWH is about one-third of an UFH, with a mean MW of 5,000 Da, which corresponds to about 15 saccharide units. Each LMWH is produced using different depolymerization methods so there is some variation in their pharmacokinetics properties, anticoagulant effects, and in their dosing strategies [36].

Similar to UFH, LMWHs produce their anticoagulant effect through the AT-mediated inhibition of coagulation factors. UFH chains of at least 18 saccharide units are of enough length to bridge AT to thrombin (IIa), whereas LMWH chains are too short and cannot bind to AT and thrombin (IIa) at the same time although these chains are able to inhibit Xa through AT because the reaction does not need bridging. Compared to UFH, LMWHs specifically inhibit the activity of Xa with lower affinity for thrombin (IIa) (Fig. 1). Depending on molecular size, LMWHs have anti-Xa to anti-IIa ratios from between 2:1 or 4:1. Currently, there is no clinical evidence that the variations in anti-Xa to anti-IIa ratio between different LMWHs affect clinical outcomes such as recurrent thrombosis or bleeding risk [8].

4.2.2 Pharmacokinetics

The pharmacokinetic advantage of LMWH over UFH is that after entering the circulation, LMWH binds less to plasma proteins other than AT, and that it has a bioavailability of around 90 % which leads to more predictable anticoagulant effect than UFH. Also, unlike UFH, LMWH binds less to platelets and PF4 and has a lower incidence of HIT. A disadvantage of LMWH is its dependence on kidney function for excretion and thus accumulation of its anticoagulant effect in patients with decreased kidney function [38]; therefore dosage adjustment is required as kidney function declines.

4.2.3 Dosing

The rates of bleeding with LMWHs differ, with higher rates observed in patients with kidney failure, especially when the dose was not adjusted for kidney dysfunction [39]. For tinzaparin and dalteparin, dosing adjustments are not required when the estimated GFR is more than 20 mL/min/1.73 m^2 [16]; However, enoxaparin, because of its smaller molecular size (mean MW 4,400 Da) compared to tinzaparin (mean MW 6,500 Da) and dalteparin (mean MW 5,700 Da), is more depended on kidney clearance requiring a dosing adjustment when the GFR drops below 30 mL/min/1.73 m^2 [16].

LMWHs are administered in weight-adjusted doses for both thrombophylaxis or for therapeutic purposes. Numerous studies have helped define dosing adjustment for enoxaparin therapy; these individualized dosing strategies based on weight and kidney function reduce bleeding risk

while preserving therapeutic benefits [40]. For example, a pharmacokinetic study in patients enrolled in the TIMI IIA trial [41] suggested that enoxaparin kidney clearance was decreased by 22 % in patients with a CrCl less than 40 mL/min compared with those with greater creatinine clearance (mean, 88 mL/min), which led the authors to extrapolate that enoxaparin clearance would be reduced by approximately 50 % in patients with a CrCl less than 20 mL/min. Authors concluded that patients with a creatinine clearance of less than 40 mL/min had higher trough and peak anti-Xa activity compared with those with no CKD and were more likely to have major bleeding events. Of note in this trial [41], enoxaparin doses were not reduced to account for kidney function that resulted in bleeding events while in a few recent studies [42] it was administrated in adjusted therapeutic doses to CKD patients who were associated with lower bleeding events. The results of these studies [42] highlight the safety of enoxaparin if administered in therapeutic doses with dose adjustment to patients with advanced CKD.

Another theory of reducing the adverse effects of LMWHs in clinical practice is to split their total daily dose into two equal doses, which will reduce trough and peak anti-Xa activity of LMWHs and in accordance minimize bleeding risk associated with these peak in treated patients. Based on a Cochrane review of 22 randomized controlled trials [43] in patients presenting with acute VTE found that the rate of bleeding were similar between the two dosing regimens with the convenience of a once daily dose of anticoagulants outweighing the potential for a lower efficacy. However, the above review was based on the initial treatment of VTE in patients with normal kidney function therefore, due to concerns of over-anticoagulation and subsequent risk of bleeding in patients with decreased kidney function, an initial bolus dose adjustment is needed with monitoring of anti-Xa activity for further individualized dosing strategies.

4.2.4 Monitoring

In clinical practice, it is difficult to measure LMWH concentrations directly therefore, pharmacokinetic studies use surrogate effect markers such as anti-Xa activity, which has been shown to be correlated with the amount of LMWH present, rather than the degree of anticoagulation effect. Some studies have reported that high anti-Xa levels were associated with increased bleeding complications [20]. Thus, routine monitoring of anti-Xa activity is not commonly required during anticoagulation therapy with LMWHs, but may be necessary in patients at increased risk of bleeding such as those suffering from CKD and those who are underweight or overweight [13].

4.2.5 Clinical Practice

LMWHs are used routinely in clinical practice for anticoagulation and have largely replaced the use of UFH. The ease of use, and the predictable anticoagulant effect of LMWHs eliminates the need for routine laboratory monitoring. Many randomized trials have demonstrated the greater safety and clinical efficacy of LMWHs (enoxaparin) compared to UFH in non CKD patients [44]. These large trials excluded CKD patients and the kidney function of randomized subjects was not reported. In general, due to lack of safety and efficacy data from randomized controlled trials, caution is required when administering LMWHs in patients with severe CKD. Prospective studies must be conducted to define the anticoagulant therapeutic activity and dosage adjustments in these patients.

Enoxaparin is the most commonly used LMWHs in patients with CKD. Mostly due to its well studied reduced dose of 1 mg/kg once daily for patients with an eGFR of less than 30 mL/min/1.73 m^2. However, this reduced dose of enoxaparin should not lead to sub-therapeutic anticoagulation therapy in CKD. An investigation conducted among patients with an estimated GFR of less than 30 mL/min/1.73 m^2, who received a dose adjusted enoxaparin therapy of 0.61 $\pm$ 0.03 mg/kg twice daily showed that under-anticoagulation, defined as peak anti-Xa levels of below 0.5 IU/mL occurred in about 1 in 4 patients; anticoagulation within the therapeutic range, defined as anti-Xa levels from between 0.5 and 1.2 IU/mL which occurred in 1 in 9 patients; and

over-anticoagulation, defined as an anti-Xa levels of more than 1.2 IU/mL occurred in 1 in 20 patients [45].

The bleeding risk should be minimized with LMWHs for both the prevention and treatment of VTE in patients with CKD. For example, in a retrospective observational study of 7721 dialysis patients who received thrombophylaxis therapy with either UFH or enoxaparin, reported that enoxaparin was not associated with higher bleeding risk in comparison with UFH (risk ratio, 0.98; 95 % CI 0.78–1.23), concluding that thrombophylaxis doses of enoxaparin appeared to be safe and could be used as an alternative to UFH in dialysis patients [42]. More recently, in a prospective study for the treatment of thromboembolic events in hospitalized patients with CKD from stages 3–5, enoxaparin administrated in adjusted therapeutic doses was associated with lower bleeding events compared to UFH [35]. The results of the study highlighted the safety of enoxaparin when administered in therapeutic doses with dose adjustment for patients with severe CKD.

4.3 Fondaparinux

4.3.1 Structure and Mechanism of Action

Fondaparinux is a synthetic pentasaccharide that is an anti-Xa-specific anticoagulant. It binds to AT and produces a conformational change at the reactive site of AT that increases its affinity for factor Xa. AT then forms covalent bond with factor Xa (Fig. 1). Fondaparinux specific anti-Xa activity is higher than that of LMWHs. Since its molecule is too short to bridge AT to thrombin, fondaparinux does not inhibit thrombin (IIa) through AT [36].

4.3.2 Pharmacokinetics

The pharmacokinetic advantages of fondaparinux over UFH or LMWHs are that it has almost complete bioavailability after subcutaneous injection, has predictable anticoagulant effect, and that it has a long elimination half-life that can be administered subcutaneously one dose daily without routine coagulation monitoring. The disadvantage of its use is that fondaparinux is eliminated by the kidney, therefore it should be avoided in patients with eGFR level of below 20 mL/min/1.73 m^2 [13].

4.3.3 Dosing

The appropriate fondaparinux dosage and intervals could range from one dose daily in patients with mild CKD to every other day in more severe CKD settings. For treatment of ACSs or VTE, fondaparinux must be used with caution in eGFR levels of between 30 and 50 mL/min/1.73 m^2. For thrombophylaxis, the dose of fondaparinux should be reduced by 50 %, or 1.5 mg once daily if eGFR 20–50 mL/min/1.73 m^2 [13]. Numerous studies in patients with moderate CKD (CrCl of 20–50 mL/min) reported that 1.5 mg of fondaparinux given once daily was effective and safe for preventing VTE [46].

4.3.4 Monitoring

Fondaparinux can be monitored by measuring its anti-Xa activity in a way similar to the one used for monitoring LMWHs. Fondaparinux rarely needs monitoring due to its predictable anticoagulant activity, however its dose must be monitored in patients with CKD [20]. In a study that was conducted among patients with moderate CKD (CrCl of 20–50 mL/min) undergoing major orthopedic surgery, the relationship between kidney function and fondaparinux pharmacokinetics profiles was assessed [47]. Authors reported that fondaparinux trough and peak anti-Xa activity was lower in patients with CKD treated with 1.5 mg daily compared to patients with normal kidney treated with 2.5 mg daily ($p < 0.01$).

4.3.5 Clinical Practice

In the setting of CKD, UFH or potentially LMWHs are preferred over fondaparinux for anticoagulation therapy. However, because of its small molecule size, it does not have the same potential to cause heparin-induced thrombocytopenia (HIT) as UFH or LMWHs, and may be considered in patients with CKD when direct thrombin inhibitors (DTIs) or warfarin therapy

are not feasible choices [36]. A case study in a dialysis patient with HIT showed that a fondaparinux dose of 2.5 mg every other day was a safe alternative anticoagulant [14].

5 Parenteral Direct Thrombin Inhibitors

In the settings of HIT or AT deficiency the choice of an optimal anticoagulant can be complicated and DITs can be a proper option for anticoagulation [36]. The most commonly DTIs used are argatroban, bivalirudin, and lepirudin. Unfortunately, pharmacotherapy trials for the DTIs did not consider the effect of kidney dysfunction, with the current dosing suggestions mostly influenced by postmarketing experiences [16].

Argatroban is hepatically excreted, and it has been proposed that no dose adjustment is necessary for CKD or hemodialysis. In trials, the average dose used in HIT therapy was 1.6 μg/kg/min, targeting aPTT values 1.5–3 times the baseline value [48]. Postmarketing studies of patients with moderate to severe CKD recommended a lower dosing strategy, with a dose reduction of approximately 0.1–0.6 μg/kg/min for each 30 mL/min decrease in the CrCl. In another study, the average argatroban dose to achieve target ranges was 0.8 μg/kg/min with a CrCl of below 30 mL/min, 1.2 μg/kg/min if CrCl was between 31 and 60 mL/min, and 2.2 μg/kg/min if CrCl was above 60 mL/min [48].

Bivalirudin is primarily excreted independent of kidney function, with 80 % eliminated enzymatically, but 20 % of unchanged drug is excreted via the kidney [49]. It has a short elimination half-life with rapid off set of activity; therefore, bivalirudin is commonly being used in the setting of ACSs in patients where urgent and early anticoagulation treatment is required. For percutaneous coronary intervention (PCI) procedure in patients with an eGFR range of 30–60 mL/min/1.73 m^2, the dose is 1.4 mg/kg/h, and for those with an eGFR below 30 mL/min/1.73 m^2, bivalirudin should be avoided for the treatment of ACSs and for PCI procedure [13]. In a hemodialysis setting, since bivalirudin has the high affinity for enzymatic degradation through thrombin, it may not be an ideal anticoagulant to flush lines. Instead, citrate, saline, or lepirudine can be used to maintain catheters [16]. The target aPTT ranges for bivalirudin is 1.5–2.5 times the baseline value [16].

Lepirudin is the anticoagulant most dependent on kidney excretion in comparison with argatroban and bivalirudin, and it requires substantial dosing reduction as kidney function declines. The target aPTT ranges for lepirudin is 1.5–2.5 times the baseline value [16]. In patients with an eGFR below 60–15 mL/min/1.73 m^2, the bolus dose should be reduced to 200 μg/kg and subsequent maintenance doses to be reduced by 50–80 %, and lepirudin should be avoided in patients with an eGFR below 15 mL/min/1.73 m^2 [13].

6 Oral Anticoagulants

6.1 Warfarin

Vitamin K antagonist, warfarin, is the clinical oral anticoagulant of choice, and is typically used for long-term therapy. However, the effect takes 2–3 days to develop completely, hence for an immediate anticoagulation, parenteral anticoagulants must be given together with the warfarin.

6.1.1 Structure and Mechanism of Action

Warfarin produces its anticoagulant effect by interfering with the vitamin K cycle. Mainly, it interacts with the vitamin K epoxide reductase enzyme so that vitamin K epoxide cannot be recycled back to vitamin K. This leads to a depletion of vitamin K, thereby limiting the carboxylation of vitamin K dependent coagulation factors in the liver, which include factors II (prothrombin), VII, IX and X. The carboxylation is essential for the proper functioning of the coagulating factors [50].

6.1.2 Pharmacokinetics

The anticoagulant response to warfarin is influenced by pharmacokinetic factors, including multiple drug–drug and drug–food interactions that affect its absorption or metabolic clearance, and by pharmacodynamic factors, which alter the anticoagulant response to given concentrations of warfarin [51]. For example, the anticoagulant effect of warfarin is reduced by cholestyramine, a bile acid sequestrant, which impairs its gastrointestinal absorption, and is potentiated by amiodarone that inhibit warfarin hepatic clearance [52].

Warfarin pharmacodynamics are subject to genetic and environmental factors. Patients with genetic warfarin resistance need doses higher than average to achieve the therapeutic index required for anticoagulant effect. This disorder is related to reduced affinity of warfarin for its hepatic receptor [51]. Also, increased dietary vitamin K intake reduces the anticoagulant effect of warfarin in patients consuming green vegetables or vitamin K–containing supplements, whereas reduced dietary vitamin K intake potentiates its effect in sick patients treated with antibiotics and IV fluids without vitamin K supplementation [52].

6.1.3 Clinical Practice

In the general population, warfarin therapy is complicated by a narrow therapeutic index, making warfarin therapy cumbersome [50]. In addition, patients with reduced kidney function have unstable and fluctuating international normalized ratios (INRs), which makes them spend a longer time outside of the target therapeutic INR and they are at the highest risk of both sub-therapeutic INR with an increased risk of thromboembolism, or supra-therapeutic INR with an increased risk of bleeding [53].

For example, Chan et al. [53], in a retrospective cohort analysis using the INR data of 1671 hemodialysis patients who received warfarin therapy for their preexisting atrial fibrillation, reported that there is a dose–response relationship between the degree of warfarin anticoagulation and a new stroke event (HR 1.35 per unit of INR; 95 % CI 0.91–2.00; $P = 0.02$ for trend), and that those warfarin users who received no in-facility INR monitoring in the first 3-months of hemodialysis had the highest risk for stroke compared with non-warfarin users (hazard ratio 2.79; 95 % confidence interval 1.65–4.70). Therefore, clinicians should be reminded of the possible risks associated with warfarin therapy for atrial fibrillation in patients with CKD, with careful evaluation of the risk-to-benefit ratio for each individual patient. Also, monitoring the degree of anticoagulation (INR) in each patient who are on warfarin would also be rational to reduce the risk for bleeding complications.

Patients with CKD appear to require somewhat lower doses of warfarin than those with no CKD. According to warfarin's package insert [54] "no dosage adjustment is necessary for patients with renal impairment." However, a recent study by Limdi et al [55], who analyzed data on 980 patients whose warfarin therapy was monitored in two anticoagulation clinics in the United States, found that in analyses adjusted for different clinical, demographic, and genetic factors that could affect warfarin dosing, the average warfarin dose required to maintain a therapeutic INR differs depending on the level of eGFR. Compared with patients whose eGFRs were $\geq$60 mL/min/1.73 m^2, the average warfarin dose for those with an eGFR of 30–59 mL/min/1.73 m^2 and those with an eGFR of $<$30 mL/min/1.73 m^2 were lower by 10 % and 19 %, respectively. Authors suggested that a possible mechanism could be the down-regulation of hepatic cytochrome P450 in CKD patients.

Despite the lack of existing proper warfarin dosing algorithms that incorporate kidney dysfunction which make it easier to maintain INRs in the therapeutic range for patients with CKD, warfarin is still recommended for VTE and atrial fibrillation treatment. Therefore, prior to initiating warfarin therapy, the risks of bleeding associated with warfarin therapy must be weighed against the benefit of prevention or treatment of thromboembolic events.

7 Novel Oral Anticoagulants

In recent years, novel oral anticoagulants (NOAs) have been suggested as alternatives to warfarin anticoagulation for the prevention and treatment of VTE, and stroke prevention in AF patients. Several NOAs are in research and development, with the focus on direct thrombin inhibitors and factor-Xa inhibitors. Each of this NOAs has varying pharmacokinetic and pharmacodynamic properties. In contrast to warfarin, the NOAs are target specific and directly inhibit a specific factor in the coagulation cascade [56].

Dabigatran etexilate, is an oral direct thrombin inhibitor that binds directly to the active site of thrombin (IIa), which is the last step in blood coagulation. Dabigatran etexilate, is a prodrug that is rapidly converted to its active form, dabigatran. It has a small molecular size and minimally binds to plasma proteins, and thus, produces a predictable anticoagulant effect requiring no monitoring [56]. Eighty percent of the dabigatran is eliminated unchanged by the kidney [56], and requires 30 % dose reduction in bolus and in maintenance dose in patients with an eGFR of 30–50 mL/min/1.73 m^2 [13]. In clinical practice, dabigatran etexilate is indicated for the prevention of VTE in adults after major orthopedic surgery. For patients with an eGFR of 30–50 mL/min/1.73 m2, reduction of bolus dose to 75 mg and subsequent maintenance doses to 110 mg once daily is required. Dabigatran should be avoided in patients with an eGFR of below 30 mL/min/1.73 m^2 [13].

Rivaroxaban and **apixaban** are oral factor-Xa inhibitors that bind directly, and reversibly, to the active site of factor-Xa, thereby blocking the reaction with its substrate [56]. Rivaroxaban has dual elimination pathways; it is partially eliminated by the kidney and partially metabolized through the CYP450 system leading to several major drug interactions. Apixaban is also eliminated through various pathways, with only 25 % through renal elimination, and is metabolized through CYP450 3A4 to several metabolites; however, it is not thought to directly inhibit or induce CYP450 and therefore has a low affinity for major drug interactions through that pathway [56, 57].

In practice, rivaroxaban and apixaban produce a predictable anticoagulant effect and do not need routine monitoring [57]. Currently, Rivaroxaban is the most extensively studied medication of this class. It is indicated for the prevention of VTE in adults after major orthopedic surgery, and should be used with caution in patients with eGFR 15–50 mL/min/1.73 m^2, and concurrent use of drugs that increase its plasma concentration. It should be avoided in patients with an eGFR below 15 mL/min/1.73 m^2 [13]. An analysis of data from the Apixaban For Reduction In Stroke And Other Thromboembolic Events In Atrial Fibrillation (ARISTOTLE) trial [58], showed that in patients with atrial fibrillation, apixaban provides effective anticoagulation with a reduced risk of bleeding compared with warfarin. However, only 15 % of participants had an eGFR of $\leq$50 mL/min/m^2 and 1.5 % of participants had an eGFR $<$30 ml/min/min/m^2. This trial showed that apixaban anticoagulation was safe in patients with atrial fibrillation and mild-to-moderate CKD. However, further evidence that NOAs could be a safe anticoagulant option for patients with advanced CKD who have a greater need for anticoagulantion therapy and are at greater risk of bleeding than are patients with mild-to-moderate CKD, is therefore required.

8 Summary and Recomendations

The increased risk of thromboembolic diseases among CKD patients commonly requires anticoagulation therapy. Historically, UFH was the anticoagulant of choice for patients with CKD because of its independence of kidney elimination.

The increased rate of bleeding observed with UFH may be attributed to the inhibition of platelet function. Unlike UFH, LMWHs bind less to platelets because of their smaller molecular size and hence have fewer incidences of HIT and bleeding events. This is beneficial because

patients with advanced CKD are already more susceptible to bleeding from uremia-related platelet dysfunction.

Currently LMWHs are used day-to-day in clinical practice for anticoagulation and have largely replaced the use of UFH. Doses of LMWHs should be reduced to account for kidney function. Warfarin provides a safe oral alternative to UFH and does not require any significant dosing adjustment because of CKD alone.

However, it is hoped that new clinical trials will provide us with further information on the anticoagulant's role and dosage adjustments in CKD patients. Until then, the following practical points might be considered with the use of anticoagulants in CKD patients.

(i) Before prescribing an anticoagulant to a patient with CKD, a risk–benefit analysis should be made concerning anticoagulation therapy and the choice of the specific agent on the basis of approved indications.
(ii) Concerning the choice of a given anticoagulant, it is also important to consider the clinical profile of the patient and co-medications, some of which may be nephrotoxic and pose unfavourable adverse effect.
(iii) Patient baseline kidney function must be assessed before initiating an anticoagulant agent.
(iv) Because sensitivity to anticoagulant increases in patients with advanced CKD, prescribing should be kept to the minimum in these high risk population.
(v) To avoid the risk of bleeding from over-anticoagulation therapy, preventive measures such as laboratory monitoring and/or dose adjustment are warranted.

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Cancer-Associated Thrombosis: Regulatory Mechanisms and Emerging Directions

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Abstract

Venous thrombosis is a common complication in cancer patients, and some cancer chemotherapies are associated with an increased risk of venous thromboembolism. The regulatory mechanisms that control thrombus formation and subsequent resolution in patients with cancer, however, are incompletely understood, and novel treatments for cancer-associated thrombosis may arise from a better understanding of such mechanisms. In this chapter, pathways that regulate cancer-associated thrombus formation are outlined, and the effects of anti-angiogenic cancer chemotherapies on venous thrombus resolution are highlighted. Potentially pro-thrombotic effects of anti-angiogenic agents are important considerations when managing the complications of venous thrombosis in cancer patients.

Keywords

Anti-angiogenic • Cancer • Chemotherapy • Hypoxia • Resolution • Thrombosis

1 Introduction

Venous thrombi are composed of fibrin, platelets, and leukocytes, which form a mesh that entraps the main erythrocyte mass. These thrombi form in regions of low blood flow, often in the deep veins of the calf, or in veins exposed to trauma. Conversely, arterial thrombi form under high flow conditions, often following atherosclerotic plaque rupture. Arterial thrombi also have a higher proportion of platelets and a lighter appearance. Notably, the layered structure of both types of thrombi distinguishes them from blood clots, which are amorphous fibrin deposits that passively trap erythrocytes and leukocytes, and form upon cessation of blood flow. Deep vein thrombosis (DVT) has an incidence of

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approximately 1 in 1000/year of the general population [1–3], and can lead to venous thromboembolism, a major cause of mortality and morbidity [4]. Approximately 1 in 3 DVT patients develop post-thrombotic syndrome, which is a chronic and debilitating condition characterised by leg pain, swelling, and ulceration [5, 6].

Venous thrombosis and thromboembolism are common complications in cancer patients [7–9], and the incidence of venous thromboembolic events is increased in cancer patients receiving certain chemotherapeutic (including anti-angiogenic) agents [10, 11]. The mechanisms that regulate cancer-associated thrombosis, however, are not fully understood. A better understanding of such mechanisms could lead to the development of novel treatments for Trousseau's syndrome (i.e. cancer-induced hypercoagulability), while investigation of the effect of anti-cancer therapies on thrombus propagation could influence treatment strategies. The aim of this chapter is to outline the mechanisms that mediate cancer-induced thrombus formation and to highlight the potentially pro-thrombotic effects of anti-angiogenic cancer chemotherapies.

2 Cancer-Associated Thrombus Formation

Thrombi form when at least two of Virchow's triad of factors are present (i.e. reduced blood flow, increased blood coagulability, and endothelial disturbance). Risk factors for DVT include age, immobility, trauma, obesity, surgery, and pregnancy. Malignancy is also an independent risk factor for venous thrombosis, the incidence of which is influenced by clinical interventions that cancer patients receive (e.g. surgery, chemotherapy, and radiotherapy) [12]. Cancer patients are ~7 times more likely to develop venous thrombosis than the general population, with the greatest increase in thrombotic risk occurring in the 3 months following cancer diagnosis (Fig. 1) [8, 9]. The risk of thrombosis is also increased in metastatic compared with non-metastatic cancer patients [8, 9].

Mechanisms that regulate cancer-induced thrombogenesis are multiple and interacting, and have been described in detail by others (Table 1) [11, 15, 24–30]. Aberrantly glycosylated mucins, for example, are pro-coagulant glycoproteins secreted into the blood by tumour epithelial cells, which act as selectin ligands, and mediate the interaction between platelets, white cells, and endothelial cells [16]. Distinct selectin binding sites are present on these mucins, and regulate adhesion between circulating tumour cells and other vascular cells known to contribute to thombosis (e.g. platelets) [16].

Other potent pro-coagulant factors are also upregulated in the circulation of cancer patients compared with healthy individuals. Tissue factor (TF) and plasminogen activator

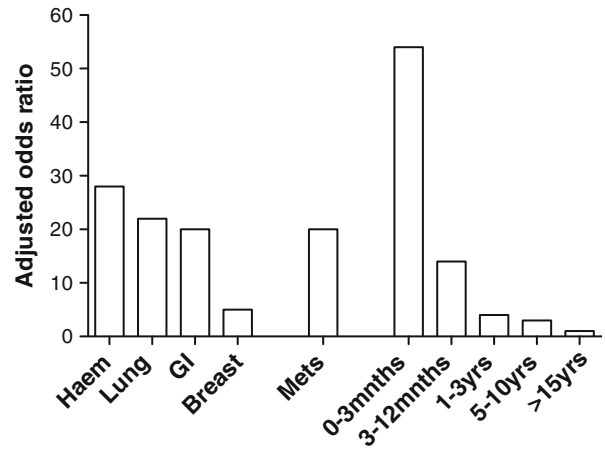

Fig. 1 Impact of cancer on risk of venous thrombosis. Adjusted odds ratios for venous thrombosis in patients with different cancer types, with distant metastasis (mets), and at different times post-cancer diagnosis (versus non-cancer sufferers). Abbreviations: *GI* gastrointestinal, *Haem* haematological

Table 1 Mechanisms that regulate cancer-induced thrombus formation

	Mechanism	Effect	Refs.
Acute	Malignancy leads to increases in the expression and activation of inflammatory molecules in cancer and endothelial cells	Inflammatory molecules such as TNF activate the coagulation pathway via increased TF expression or suppression of the anti-coagulant protein C pathway	[11, 13, 14]
Systemic	Cancer cells release glycosylated mucins and TF-expressing microvesicles	Mucins act as ligands for adhesive selectin molecules; TF triggers the coagulation cascade resulting in formation of cross-linked fibrin	[15–18]
Local	Tumour hypoxia increases the expression of pro-coagulant factors such as TF and PAI1 and supresses anti-coagulant factors such as thrombomodulin	Increased expression of coagulant factors or suppression of anti-coagulant factors stimulate thrombus formation and impair thrombolysis	[19–21]
Genetic	Coagulants such as TF and PAI1, and the thrombin receptor PAR1, are induced following activation of oncogenes or inactivation of tumour suppressor genes	Binding of thrombin to PAR1 stimulates the formation of cross-linked fibrin from fibrinogen	[15, 22, 23]

Abbreviations: *PAI1* plasminogen activator inhibitor 1, *PAR1* protease-activated receptor 1, *TF* tissue factor, *TNF* tumour necrosis factor

inhibitor 1 (PAI1), for example, are increased by reductions in oxygenation (hypoxia) that commonly occur in propagating tumours [19, 20, 31]. Hypoxia has been shown to activate the early growth response 1 transcription factor, which leads to increased tissue factor expression in macrophages and smooth muscle cells, and subsequent fibrin deposition [20]. It has also been shown that cancer cells release TF-expressing microvesicles, and that these cellular fragments are activated under hypoxia [17, 18]. In one such study, for example, hypoxia led to increased expression of protease-activated receptor 2, which regulates coagulation-dependent signalling in endothelial cells, and in turn, an increase in heparin-binding EGF-like growth factor expression [18]. Furthermore, endothelial coagulant function is stimulated by hypoxia, e.g. via suppression of the anti-coagulant factor, thrombomodulin [21]. In this study, reduced oxygen levels resulted in increases in Factor X activation and endothelial cell size, as well as reductions in endothelial intracellular gaps [21].

Activation of oncogenes (such as K-ras and MET), or inactivation of tumour suppressor genes (such as p53 or PTEN) can also increase the expression of pro-coagulants PAI1, and the expression and activity of TF [15, 22, 23]. The elevated inflammatory status in cancer patients also potentiates thrombus formation [11]. Pro-thrombotic cytokines such as tumour necrosis factor are highly expressed by cancer cells and acutely elevated in activated endothelial cells. The roles of this and other cancer-induced and pro-coagulant inflammatory mediators in thrombus formation, however, warrant further investigation [11].

2.1 Clinical and Future Perspectives

Most DVT patients are currently treated with low molecular weight heparin and warfarin, with few receiving additional treatment to remove the thrombus by thrombolysis or thrombectomy. Anticoagulation allows slow natural resolution of the thrombus, but does not reduce the incidence of post-thrombotic syndrome or accelerate resolution, and may result in excessive bleeding [32–34]. Thrombolytic agents are contraindicated in some cases, and this treatment also increases the risk of bleeding [35]. Recent advances in catheter-directed thrombolysis with or without pharmacomechanical adjuncts may increase the efficacy of

lysis, reduce the amount of lytic agent used, and with it, the risk of bleeding. Catheter-directed or pharmacomechanical thrombolysis has been used in selected patients with symptomatic iliofemoral DVT [36]. There is, however, a paucity of data regarding their effectiveness in patients without cancer, and currently no study examining their effect in this group of patients.

Although therapies under development for the treatment of DVT often aim to target specific molecular pathways, it may be that complex pathologies (such as Trousseau's syndrome) would be better combatted using treatments with multiple actions [15]. Heparin, for example, is the preferred treatment for patients with Trousseau's syndrome, while vitamin K antagonists, or thrombin inhibitors, appear insufficient in many cases [15]. The primary actions of heparin are to irreversibly inactivate coagulant factor Xa and thrombin, which impairs platelet activation and thrombus formation. Heparin may also reduce cancer-induced thrombus formation by: (i) activating heparin cofactor II and protein C [37, 38]; (ii) inhibiting the adhesion molecules L- and P-selectin [39, 40]; and (iii) stimulating the release of TF pathway inhibitor [41]. Low molecular weight heparin, which can be administered in a single dose, is another treatment option for Trousseau's syndrome patients; the CLOT trial, for instance, showed that low molecular weight heparin (versus warfarin) reduced the risk of recurrent thromboembolism in cancer patients, without increasing the risk of bleeding [42]. Novel oral anti-coagulants are under active investigation in clinical trials [43]. Such agents may ultimately prove effective in the prevention and treatment of venous thrombosis in cancer patients, but the effects of such agents should first be thoroughly investigated in large-scale randomised clinical trials, and compared with established treatments [44]. Combination therapies may also eventually come to fruition, although these may carry an increased incidence of side effects [15]. Future studies could investigate therapeutic targeting of the multiple pathways that regulate cancer-induced thrombus formation.

3 Cancer-Associated Thrombus Resolution

Venous thrombi resolve naturally with time, but this is a slow process that takes more than 6 months in man [45]. Veins that recanalise rapidly have preserved valve integrity and a lower incidence of venous reflux [46, 47]. Rapid recanalisation times are consequently associated with favourable clinical outcome [48]. Thrombus resolution is a complex process of intravascular remodelling, similar to the formation of granulation tissue that is crucial for wound healing [49]. Natural resolution involves recruitment of white cells (initially neutrophils then monocytes), endothelial cells and their progenitors, and myofibroblasts [49]. Vein recanalisation is achieved through a combination of new blood vessel formation in the thrombus and thrombus contraction from the vein wall [49]. The endothelial-lined channels that form within and around the thrombus coalesce and form larger vascular channels, which together with thrombus contraction help to restore blood flow [49]. Vein recanalisation and thrombus resolution are accelerated when the angiogenic response to thrombus formation is stimulated in the thrombus and surrounding vein [50–52].

3.1 Clinical and Future Perspectives

Chemotherapy increases the risk of venous thrombosis in cancer patients, but the mechanisms responsible for this observation are unclear [11]. Different types of chemotherapy carry varying thrombotic risks. For example, the addition of cyclophosphamide, methotrexate, and fluoracil to tamoxifen treatment is associated with an increased the incidence of venous thromboembolism in breast cancer patients, compared with tamoxifen alone [53]. Similarly, addition of a dexamethasone and a multi-agent chemotherapy cocktail to thalidomide treatment alone increases venous thromboembolism rate in myeloma patients [54].

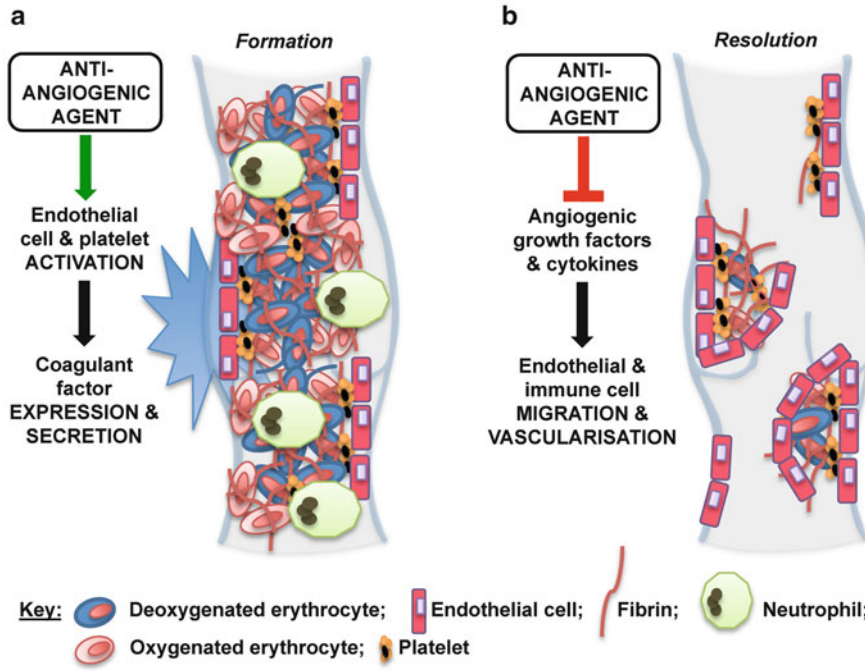

Fig. 2 Potential effects of anti-angiogenic agents on cancer-associated thrombosis. Anti-angiogenic cancer agents may increase the incidence of thrombosis in cancer patients through: (**a**) activation of endothelial cells and platelets, which stimulates thrombus formation (e.g. via increased expression of coagulant factors including E-selectin and the thrombin/antithrombin complex); and (**b**) inhibition of the angiogenic response to thrombogenesis, which impairs subsequent resolution (e.g. via reduced growth factor expression in cells within and surrounding the thrombus)

Anti-angiogenic drugs have also been implicated in both thrombus formation and resolution (Fig. 2) [10, 11, 55, 56]. Treatment with bevacizumab, an antibody against vascular endothelial growth factor (VEGF) is associated with increased risk of venous thromboembolism [57–59]. Treatment with sorafenib in conjunction with another VEGF pathway inhibitor, axitinib, also increases the incidence of venous thromboembolism in patients with metastatic renal cell carcinoma compared with sorafenib treatment alone [60]. Such anti-angiogenic agents could activate endothelial cells and platelets, and thereby increase thrombus formation [11, 61]. The anti-angiogenic SU5416, for example, increases the expression of endothelial TAT complexes, F1 and 2, and E-selectin [61]. It has subsequently been suggested that VEGF-depleted endothelial cells are susceptible to chemotherapy-induced activation of the coagulation [11, 61]. Anti-angiogenic therapies also prevent thrombus resolution [55, 56]. Treatment with axitinib or 2-methoxyestradiol inhibits venous thrombus resolution in a mouse model of vena cava thrombosis [55, 56]. Both agents impair thrombus organisation, and neovascularisation, reducing vein recanalisation [55]. The ingrowth of blood vessels from the vein wall is an important part of the angiogenic response following thrombus formation [49]. Anti-angiogenic agents also inhibit the expression of angiogenic factors such as VEGF (known to accelerate resolution) [52, 62] in the surrounding vein wall, suggesting that the deleterious effect of such treatments on resolution could occur partly through suppression of angiogenic drive in the local vein [56].

Both the prothrombotic and anti-resolution side effects of anti-angiogenic treatments that could contribute to the increased thrombotic

complications seen in cancer patients treated with these agents should be carefully considered when managing venous thrombosis (and subsequent complications) in cancer patients. Large-scale clinical studies of the effect of approved cancer chemotherapies on thrombus propagation are warranted. Future studies should continue to investigate pro-thrombotic mechanisms by which cancer chemotherapies (including anti-angiogenics) could enhance venous thrombosis. These studies could ultimately lead to the development of novel cancer treatments that are not associated with increased thrombotic risk.

4 Conclusions

Mechanisms that regulate cancer-associated thrombus formation are complex and multifaceted. Cancer chemotherapies can increase the incidence of venous thrombosis, but the mechanisms responsible for this effect are not fully characterised. Although priority should be given to prevention of disease progression and increased survival in cancer patients, potentially pro-thrombotic effects of cancer treatments should be carefully considered in the clinic. A better understanding of the mechanisms that regulate cancer-induced thrombus formation and resolution may lead to the development of novel treatments for patients such as those with Trousseau's syndrome.

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The Treatment of Venous Thromboembolism in Patients with Cancer

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Abstract

Venous thromboembolism (VTE) is a frequent complication in cancer patients and represents an important cause of morbidity and mortality. The treatment of VTE complications in cancer patients remains a difficult clinical task. Low-molecular-weight heparins (LMWH) are the cornerstone of VTE treatment in cancer patients, including the treatment of catheter-related thrombosis. LMWH dose adjustment is effective in treating recurrent thrombosis and in patients with bleeding or thrombocytopenia. The duration of treatment is dependent on several factors that need to be individually evaluated. The novel anticoagulants should be investigated more carefully before being routinely implemented in the treatment of cancer-associated VTE. Incidentally detected isolated sub-segmental pulmonary embolism is unlikely to require systematic full-dose anticoagulation. Whether the long-term use of LMWHs has the potential to prolong survival in subgroups of cancer patients requires further investigations.

Keywords

Venous thromboembolism • Pulmonary embolism • Cancer • Anticoagulation • Low-molecular-weight heparin • Vitamin K antagonists • New oral anticoagulants

1 Introduction

The association between cancer and venous thromboembolism (VTE) was first suggested by Dr Armand Trousseau, nearly 150 years ago. Since this initial observation, a considerable number of studies have been conducted to assess the association between cancer and VTE. VTE

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may be in some cases the first clinical presentation of cancer, as approximately 10 % of patients presenting with unprovoked VTE develop cancer within the next 1–2 years. Moreover, there is a substantial amount of evidence demonstrating that cancer patients experience a significantly higher risk of VTE than patients without malignancies (Prandoni et al. 2005a).

According to a recent systematical review, the annual average total cost for cancer patients with VTE is almost 50 % higher than that of cancer patients without VTE. Inpatient care costs accounts for more than 60 % of total cost. The existing evidence demonstrates the significant health and economic consequences of cancer-related VTE, which make a strong case for the importance of its proper and efficient prevention and management (Kourlaba et al. 2015).

The treatment of VTE complications in cancer patients remains a difficult clinical challenge. Cancer patients often require invasive surgical procedures, have an increased risk of infection and may have therapy-related platelets drop that increase their bleeding risk. Chemotherapy, hormonal agents, invasive procedures and the presence of long-term venous catheters not only increase the risk of thrombosis but also create complex clinical situations that make anticoagulation particularly problematic. Temporary cessation of anticoagulant therapy may be needed to accommodate chemotherapy-induced thrombocytopenia and invasive procedures, while poor nutrition, infection, concomitant medication and impaired liver function can cause unpredictable changes in the dose-response of anticoagulants.

2 Initial Treatment

Patients with cancer who develop a VTE episode should be managed according to guidelines that are currently followed for patients free from malignancy (Kearon et al. 2012). Particularly in those cancer patients who have a poor life expectancy, preventing death from pulmonary embolism (PE) is the mainstay of treatment. Indeed, most patients with advanced cancer do not survive long enough to develop late post-thrombotic sequelae or chronic pulmonary hypertension.

2.1 Intracaval Filters

On average, patients with cancer present with major – often permanent – contraindications to anticoagulant treatment much more frequently than patients free from malignancy (Kearon et al. 2012; Lyman et al. 2015; Farge et al. 2013). In these patients, the only therapeutic option is the insertion of a (retrievable) vena caval filter (Kearon et al. 2012; Lyman et al. 2015; Farge et al. 2013), which should be done without hesitation. Indeed, prolonging life and/or improving its quality are invaluable goals to be achieved even in patients in poor condition. Our view is supported by the findings from a Spanish registry. In a large number of patients with acute VTE who were managed without the insertion of a vena caval filter after a recent episode of major bleeding, the incidence of fatal bleeding and that of fatal PE in patients with cancer was ten times as high as that observed in those without malignancy (Nieto et al. 2005). As soon as the bleeding resolves, anticoagulation should be resumed; accordingly, the filter should be removed (Carrier et al. 2013).

2.2 Thrombolytic Treatment

Those patients who present with severe hypotension or other clinical manifestations suggestive of critical PE and who do not have contraindications to thrombolysis should promptly be administered drugs that have the potential to rapidly restore the patency of obstructed pulmonary arteries (Kearon et al. 2012; Lyman et al. 2015; Farge et al. 2013). Among the drugs that have been shown to achieve a rapid and substantial lysis of fresh pulmonary emboli are urokinase, streptokinase and t-PA. We favor the last, because the administration of a loading dose of 10 mg followed by the intravenous infusion of 90 mg produces in only 2 h the result that can be

obtained by 12–24 h of infusion of urokinase or streptokinase (Goldhaber et al. 1988; Meyer et al. 1992). As compared to heparin alone, the administration of t-PA relieves patients' symptoms and improves prognosis to a greater extent (Dalla Volta et al. 1992; Goldhaber et al. 1993; Konstantinides et al. 2002). During the administration of t-PA or soon after its discontinuation, heparin treatment should be implemented (Kearon et al. 2012).

As far as the role of local or systemic thrombolytic agents and pharmacomechanical thrombolysis for acute DVT in cancer patients is concerned, they can be considered in patients with good prognosis who present with massive iliofemoral DVT available evidence is against their use except for very selected patients with massive iliofemoral thrombosis (Kearon et al. 2012; Lyman et al. 2015; Farge et al. 2013). In patients with contraindications to pharmacological thrombolysis, (percutaneous) mechanical thrombectomy can be considered (Kearon et al. 2012; Lyman et al. 2015; Farge et al. 2013).

2.3 Anticoagulant Therapy

Except for selected patients requiring aggressive treatments, the large majority of cancer patients should be treated with therapeutic doses of low-molecular-weight heparin (LMWH), unfractionated heparin (UFH) or fondaparinux (Kearon et al. 2012; Lyman et al. 2015; Farge et al. 2013). Except for patients with severe renal failure, in whom UFH still represents the treatment of choice, in all other patients the VTE episode should be managed with LMWHs, as they represent the standard of long-term treatment (Table 1) (Kearon et al. 2012; Lyman et al. 2015; Farge et al. 2013). In the absence of contraindications, LMWHs should be administered as soon as there is a reasonable possibility that venous thrombosis exists, even before the diagnostic algorithm is completed. LMWHs present a number of potential advantages over UFH, including a longer plasma half-life, an improved subcutaneous bioavailability and less variability in response to fixed doses (Kearon et al. 2012). As a result of these pharmacokinetic properties, a stable and sustained anticoagulant effect is achieved when these drugs are administered subcutaneously in doses adjusted to body weight, once or twice daily, without laboratory monitoring (Kearon et al. 2012). These compounds have the potential to greatly simplify the initial treatment of deep-vein thrombosis (DVT) and of selected low-risk patients with PE (Hirsh and Raschke 2004), making the treatment of suitable patients feasible in an outpatient setting (Aujesky et al. 2011; Zondag et al. 2012; Wells et al. 1998). Treatment on home basis appears feasible and safe, which is particularly attractive for cancer patients, in whom prevention or reduction of hospital stay has the potential to improve the quality of life (Ageno et al. 2005; Siragusa et al. 2005). According to the results of worldwide surveys, LMWHs are by far the most commonly used drugs for the initial treatment of VTE in cancer patients (Kakkar et al. 2003; Kleinjan et al. 2012). Based on the results of many comparative trials between UFH and LMWH for the initial treatment of patients with DVT that were conducted in the '90s, LMWHs appear to be at least as effective and safe as UFH both in patients with and in those without cancer (Gould et al. 1999; Dolovich et al. 2000). It should be noted, however, that in these clinical trials cancer patients represented only 10–15 % of the total population, as the majority of them were excluded because of their poor performance status. Of interest, the use of LMWH was associated with a significantly lower mortality, which was essentially dependent on the reduction of cancer-related mortality (Gould et al. 1999; Dolovich

Table 1 LMWHs for the initial treatment of VTE in cancer patients

Compound	Dosage
Bemiparin	115 IU/Kg/od
Dalteparin	200 IU/Kg/od
Enoxaparin	100 IU/kg/bid or 150 IU/kg/od
Nadroparina	90 IU/Kg/bid or 180 IU/kg/od
Reviparin	100 IU/Kg/bid
Tinzaparin	175 IU/Kg/od

Table 2 Nomogram for the intravenous administration of UFH in the initial treatment of cancer patients with VTE

Loading dose of 5000 IU, followed by 1280 IU/h. First APTT assessment after 6 h, then proceed as follows				
APTT sec (6 h)	Bolus	Interruption (min)	Variation (U/h)	Repeat APTT
<50	5000	0	+120	6 h
50–59	0	0	+120	6 h
60–85	0	0	0	The morning after
89–95	0	0	−80	6 h
96–120	0	30	−80	6 h
>120	0	60	−160	6 h

et al. 2000). It should not be forgotten that patients undergoing LMWH treatment require close monitoring of platelet count, as the risk of heparin-induced thrombocytopenia in medical patients treated with LMWH may not be different from that observed during UFH administration (Prandoni et al. 2005b).

Although in clinical practice UFH has virtually been replaced by LMWHs, we think that several indications still remain for UFH, especially in cancer patients. The short half-life of intravenous UFH indeed allows for rapid reversal of anticoagulation in patients who begin to bleed or will require an invasive procedure. Also the presence of (severe) renal insufficiency makes it attractive to use a short-acting drug that in addition can be timely monitored and possesses a specific antidote (the protamine sulphate). UFH is generally administered intravenously, while the use of nomograms assures that most patients will achieve the therapeutic range for the activated partial thromboplastin time (APTT), the most commonly recommended test for its monitoring (Table 2) (Cruickshank et al. 1991). Subcutaneous heparin treatment has been suggested as an alternative to intravenous standard heparin provided that the APTT is performed in order to achieve a full therapeutic effect (Hommes et al. 1992). This modality of heparin administration, particularly desirable in those cancer patients who have difficult vein access, has been shown to be as effective and safe as LMWH for treatment of patients with acute VTE, including more than 20 % of cancer patients (Prandoni et al. 2004).

Fondaparinux is the first drug of a new class of synthetic antithrombotic agents designed specifically for a single physiologic target in the coagulation cascade and acts by indirect inhibition of factor Xa. This compound does not bind to platelet factor-4, which makes the development of immune thrombocytopenia extremely unlikely. In two large phase III multicentre clinical trials, involving the treatment of almost 4500 patients with clinically symptomatic DVT or PE (approximately 10 % with cancer), the once daily subcutaneous administration of 7.5 mg of fondaparinux (5 mg in individuals weighing less than 50 Kg, 10 mg in those weighing more than 100 Kg) overlapped with and followed by vitamin K antagonists (VKA) was found to be at least as effective and safe as UFH or LMWH for the treatment of DVT or PE (Buller et al. 2004; The Matisse Investigators 2003). However, when the analysis is confined to the only cancer patients randomized to the Matisse DVT study, recurrent VTE was significantly more frequent in patients who had received an initial treatment with fondaparinux than in those allocated to enoxaparin (van Doormaal et al. 2009). In any case, fondaparinux is rarely employed for the initial treatment of VTE in cancer patients, because unlike LMWHs it is not (yet) registered for the long-term treatment of thromboembolic disorders, nor can it be followed by VKAs, whose efficacy is definitely lower than that of LMWHs (Lee et al. 2003).

3 Long-Term Anticoagulation

Cancer patients are often resistant to oral anticoagulant therapy while at the same time exhibiting a higher hemorrhagic risk. The best evidence of a higher risk of recurrence and clinically relevant hemorrhages while patients are receiving anticoagulation comes from a retrospective analysis of data from two large randomized clinical trials (Hutten et al. 2000) and two prospective

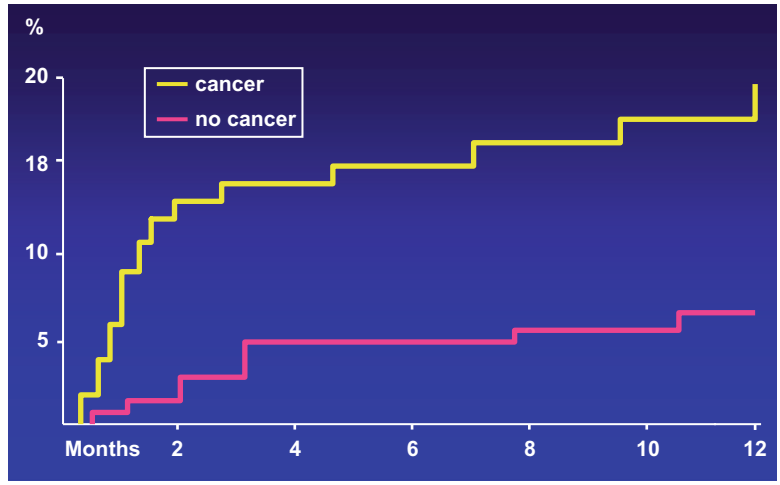

Fig. 1 Cumulative proportion of recurrent thromboembolism during VKA treatment. Patients with cancer have a risk of recurrent symptomatic VTE that is more than three times as high as that observed in patients without cancer

cohort studies (Palareti et al. 2000; Prandoni et al. 2002). Hutten et al. extracted the rates of recurrent VTE and major bleedings in more than 1300 patients receiving at least 3 months of oral anticoagulant therapy for an acute episode of DVT (Hutten et al. 2000). The overall incidence of recurrent thrombosis in patients with cancer was 27.1 per 100 patient-years, versus 9.0 per 100 patient-years in those without cancer. The risk of major bleeding was 13.3 per 100 patient-years and 2.1 per 100 patients-years, respectively. Palareti et al. compared the outcome of anticoagulation courses in 95 cancer patients and 733 patients without malignancy (Palareti et al. 2000). Based on 744 patient-years of treatment and follow-up, there was a trend towards a higher rate of thrombotic complications in cancer patients (6.8 % vs 2.5 %; relative risk = 2.5). The rate of major bleeding was significantly higher in cancer patients (5.4 %) than in those without malignancy (0.9 %; relative risk = 6.0). We conducted a prospective cohort study in 842 consecutive patients with DVT who were administered conventional anticoagulation, of whom 181 were carriers of cancer (Prandoni et al. 2002). The 12 month cumulative incidence of recurrent thromboembolism in cancer patients was 20.7 % versus 6.8 % in patients without cancer, for an age-adjusted hazard ratio of 3.2 (95 % CI, 1.9–5.4) (Fig. 1). The 12 month cumulative incidence of major bleeding was 12.4 % in patients with cancer and 4.9 % in patients without cancer, for an age-adjusted hazard ratio of 2.2 (95 % CI, 1.2–4.1) (Fig. 2). In summary, cancer patients have a three to fourfold higher risk of recurrent VTE during anticoagulant therapy than cancer-free patients, very likely as a consequence of the release of cancer procoagulants that are not inhibited by conventional anticoagulation. This risk correlates with the extent of cancer (Prandoni et al. 2002). Recently, a stratification score has been developed and validated that has the potential to help clinicians predict the VTE recurrence risk and thus tailor treatment, improving clinical outcomes while minimizing costs (Table 3) (Louzada et al. 2012).

According to the results of three randomized clinical trials, LMWHs in full doses for the first month followed by a dose ranging from 50 to 100 % of the initial regimen have the potential to provide a more effective antithrombotic regimen in cancer patients with venous thrombosis than the conventional treatment and are not associated with an increased hemorrhagic risk (Lee et al. 2003; Meyer et al. 2002; Hull et al. 2006) (Fig. 3), even in patients with disseminated cancer such as those with liver or brain metastases (Monreal et al. 2004). In addition, LMWHs provide an anticoagulation that is easier to administer, more convenient and flexible, and not influenced by nutrition problems or liver impairment (Kearon et al. 2012). Thus, the

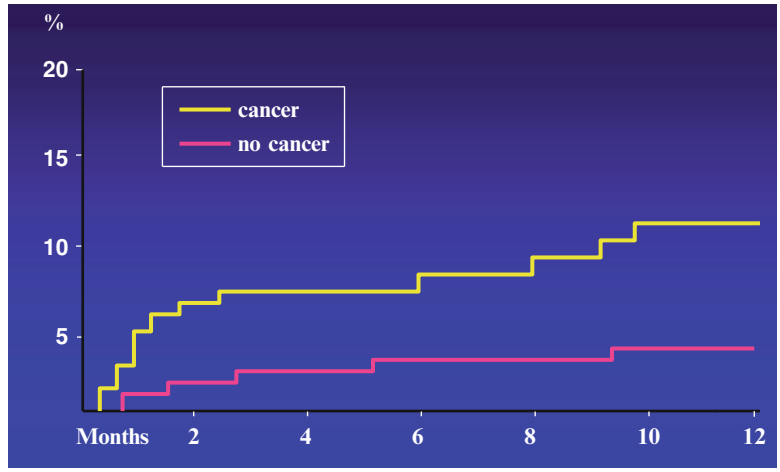

Fig. 2 Cumulative proportion of major bleeding during VKA treatment. Patients with cancer have a risk of major bleeding that is more than two times as high as that observed in patients without cancer

Table 3 Ottawa score for recurrent VTE risk in cancer-associated thrombosis

Variable	Regression coefficient	Points
Female	0.59	1
Lung cancer	0.94	1
Breast cancer	−0.76	−1
TNM[a] stage	−1.74	−2
Previous VTE	0.40	1
Clinical probability		
- low (≤0)		−3 to 0
- high (≥1)		1 to 3

[a]TNM (tumor-nodes-metastasis staging system) for solid tumors only

long-term administration of LMWH should now be considered the treatment of choice in patients with metastatic disease and in those with conditions limiting the use of oral anticoagulants (Kearon et al. 2012; Lyman et al. 2015; Farge et al. 2013).

After discontinuation of antithrombotic treatment, cancer patients with venous thrombosis present a risk for recurrences that is almost twice as high as that observed in patients free from malignancies (Prandoni et al. 1996; Hansson et al. 2000; Heit et al. 2000). Among the factors associated with an increased risk of recurrent VTE after anticoagulation withdrawal are residual vein thrombosis, as determined by compression ultrasound 3 months after the index event (Donadini et al. 2014), and abnormal D-dimer values, measured on the day of drug suspension and 1 month later (Cosmi et al. 2005). In view of the persistently high risk of recurrent thrombotic events, prolongation of anticoagulation should be considered for as long as the malignant disorder is active provided that it is not contraindicated. For most patients, this translates into life-long anticoagulation. This decision should be frequently reassessed during patients' follow-up.

4 Treatment of Challenging Situations

The treatment of challenging situations has recently been addressed by the Subcommittee of the International Society of Thrombosis and Haemostasis (Carrier et al. 2013).

4.1 Management of Recurrent VTE Despite Anticoagulation

Recurrent VTE despite appropriate anticoagulation is common among cancer patients (Carrier et al. 2009; Luk et al. 2001). Cancer patients with symptomatic recurrent VTE despite therapeutic anticoagulation with VKA should be switched to therapeutic weight-adjusted doses of LMWH. Cancer patients with symptomatic recurrent VTE despite anticoagulation with LMWH should continue with LMWH at a higher dose, starting at an increase of approximately 25 % of

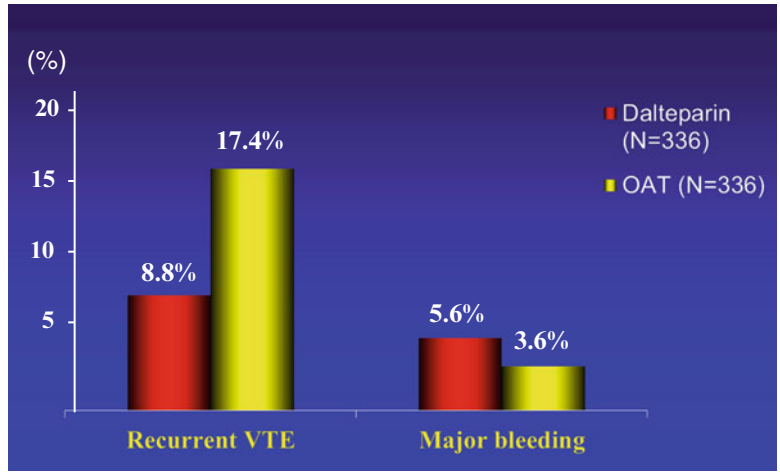

Fig. 3 Main results of the CLOT study. The initial and long-term treatment with LMWH in patients with cancer-associated thrombosis reduces by approximately 50 % the risk of recurrent VTE in comparison with VKAs and is not associated with an increased bleeding risk

the current dose or increasing it back up to the therapeutic weight-adjusted dose if they have been receiving non-therapeutic dosing. All cancer patients with recurrent VTE despite anticoagulation should be reassessed 5–7 days after a dose escalation of their anticoagulant therapy. Patients with symptomatic improvement should continue the same dose of LMWH and resume their usual follow-up. In patients without symptomatic improvement, the peak anti-Xa level can be used to estimate the dose of further escalation (Carrier et al. 2013).

4.2 Management of Cancer-Associated VTE in Patients with Thrombocytopenia

Thrombosis is commonly diagnosed in patients with malignancy and thrombocytopenia. Full therapeutic doses of anticoagulation without platelet transfusion should be given in patients with platelet count $\geq 50 \times 10^9$/L. In patients with platelet count $< 50 \times 10^9$/L, the recommended strategy diverges in patients with acute (less than 1 month) from those with sub-acute (1–3 months) or chronic (more than 3 months) VTE. In the former group, full therapeutic doses of anticoagulation with platelet transfusion should be given to maintain a platelet count $\geq 50 \times 10^9$/L.

If platelet transfusion is not possible or contraindicated, the insertion of a retrievable filter is suggested, as well as its removal when platelet count recovers and anticoagulation can be resumed. In the remaining groups, subtherapeutic or prophylactic doses of LMWH should be used in patients with platelet count of 25–50 $\times 10^9$/L, whereas anticoagulation should be discontinued in patients with platelet count $< 25 \times 10^9$/L (Carrier et al. 2013).

4.3 Management of Cancer-Associated VTE in Patients Who Are Bleeding

A careful and thorough assessment of each bleeding episode, including identification of the source, its severity or impact, and reversibility should be done, as well as the usual supportive care with transfusion and surgical intervention to correct the bleeding source, whenever indicated and possible. Withholding anticoagulation in patients having a major or life-threatening bleeding episode is mandatory. The insertion of a caval filter is suggested for patients with acute or sub-acute VTE who are having a major or life-threatening bleeding episode, while it is discouraged in patients with chronic VTE. Once the bleeding resolves, anticoagulation should be initiated or resumed, and the retrievable caval

filter (if inserted) should be removed (Carrier et al. 2013).

5 The Potential of the New Oral Anticoagulants

As new categories of drugs have emerged that have the potential to replace conventional treatment for the initial and long-term treatment VTE, major improvements are expected for the management of cancer patients with venous thrombosis. They include direct inhibitors of factor Xa (such as rivaroxaban, apixaban and edoxaban) and direct inhibitors of factor IIa (such as dabigatran etexilate). They possess several advantages over conventional drugs, including the inhibition of fibrin-bound Xa or thrombin, respectively, a dose response that is more predictable because there is no binding to plasma proteins, and a lack of potential to produce immune thrombocytopenia. As a consequence of their pharmacokinetic and pharmacodynamic properties, they can be administered orally, in fixed doses, without laboratory monitoring. Based on available information coming from well designed and conducted phase-3 randomized clinical trials, they possess a more favourable benefit-to-risk profile than the old compounds, make it possible to implement the treatment from the beginning, and cover the whole spectrum of clinical presentations, including severe pulmonary embolism (Schulman et al. 2009, 2013; The Einstein Investigators 2010, 2012; Agnelli et al. 2013a, b; The Hokusai-VTE Investigators 2013).

However, for the time being their use in patients with cancer requires caution. Indeed, only a small minority of patients with cancer (consistently around 5 %) were included in the abovementioned studies. Although based on the results of recent subgroups analyses (Prins et al. 2014) and meta-analyses of available studies (Vedovati et al. 2015; van der Hulle et al. 2014; van Es et al. 2014), the benefit-to-risk ratio of these new drugs for the treatment of cancer patients with VTE is encouraging, there is the need for a direct comparison with the LMWHs, which represent the standard of treatment in cancer-associated thrombosis (Kearon et al. 2012). Severe liver and renal dysfunctions, which contraindicate the use of all new oral compounds, are quite common in patients with cancer. There is uncertainty about the proper management of patients requiring emergency procedures and in those with thrombocytopenia. In conclusion, we believe that the novel anticoagulants need further investigations before routine usage in cancer patients.

6 Management of Incidentally Detected Isolated PE

Asymptomatic PE is a common finding in medical oncology due to the routine use of modern computed tomography scanners for cancer staging (Fig. 4). Although the clinical relevance of these incidental findings is unknown, based on the results of a few investigations conducted in recent years they are likely to impact on both the incidence of recurrent VTE and on the overall prognosis to the same degree as the symptomatic findings (Menapace et al. 2011; Sahut D'Izarn et al. 2012; Agnelli et al. 2014; Connolly et al. 2013; den Exter et al. 2011; Heidrich et al. 2009; O'Connell et al. 2010). Accordingly, the most recent international guidelines recommend the same initial and long-term anticoagulation as for comparable patients with symptomatic PE (Kearon et al. 2012).

However, there is still uncertainty about the optimal management of patients with the incidental detection of isolated subsegmental PE. Indeed, whether the outcome of these patients is comparable to that of patients with symptomatic involvement of subsegmental arterial vessels (den Exter et al. 2013) is unknown, as is the accuracy of detecting PE on CT-scans that were not specifically ordered to diagnose PE. Higher risk of false positive diagnosis compared to patients with suspected PE cannot be excluded. In a series of 70 patients diagnosed with subsegmental PE, this diagnosis was confirmed in only 51 % by a reviewing radiologist (Pena et al. 2012). PE may not be acute but

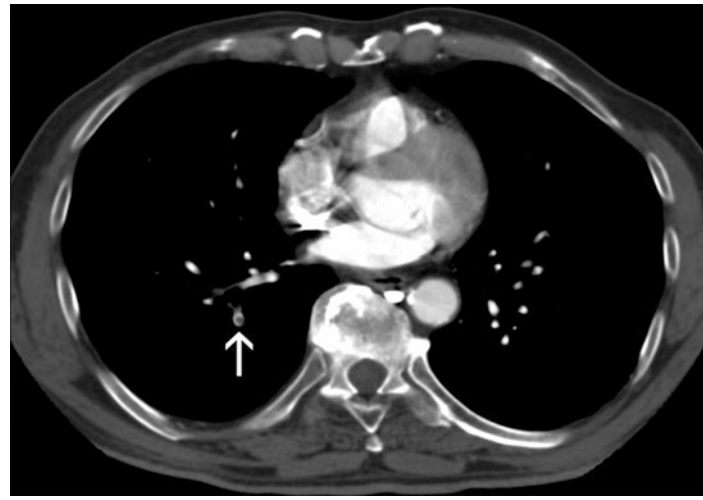

Fig. 4 CT-scanning. Isolated subsegmental pulmonary embolism (*arrow*)

chronic. In a series of 65 cases of untreated subsegmental PE reported so far, none of these patients developed recurrent VTE (Donato et al. 2010). Finally, there is uncertainty about the outcome of patients with incidental PE who receive anticoagulants. In a cohort study of 51 patients with incidental PE, 5 (9.8 %) patients developed major bleeding of which 2 cases were fatal (den Exter et al. 2011). Thus, a careful evaluation should be individually done rather than giving full-dose anticoagulation to all cancer patients with the occasional detection of isolated subsegmental PE.

7 Treatment of Catheter-Related Thrombosis

Published data and clinical experience suggest that catheter-related thrombosis is associated with a low risk for thrombosis recurrence and postthrombotic syndrome (Elman and Kahn 2006; Frank et al. 2000). Therefore, conservative treatment is recommended. A sensible approach is to remove the catheter only if central venous access is no longer required; the device is nonfunctional or defective; or line-related sepsis is suspected or documented. Unless contraindicated, therapeutic anticoagulation should be given using either LMWH alone or LMWH followed by warfarin therapy. A short period of anticoagulation (3–5 days of LMWH) may even salvage some thrombosed catheters and obviate the need to remove and replace the line. Anticoagulation is recommended for a minimum of 3 months and while the catheter remains in place.

8 Impact of Antithrombotic Drugs on Cancer Evolution

Anticoagulant treatment of cancer patients, particularly those with lung cancer, has been reported to improve survival (Zacharski et al. 1984). Since then, studies conducted in animal tumor models have demonstrated that both UFH and LMWH interfere with various processes involved in tumor growth and metastasis (Mousa 2002). These processes might include fibrin formation, binding of heparin to angiogenic growth factors such as basic fibroblast growth factor and vascular endothelial growth factor, modulation of tissue factor and other mechanisms (Mousa 2002).

The evidence of lowered cancer mortality in patients on LMWH in comparison with those treated with UFH (Gould et al. 1999; Dolovich et al. 2000) has stimulated renewed interest in these agents as antineoplastic drugs. Five randomized studies have compared the long-term survival of cancer patients receiving conventional treatment with that of patients

receiving a supplementary dose of LMWH in therapeutic or prophylactic doses (Klerk et al. 2005; Kakkar et al. 2004; Lee et al. 2005; Altinbas et al. 2004). Two of these studies showed a favorable impact of the tested heparin on patients' survival, this result being particularly evident in those with better prognosis (Lee et al. 2005; Altinbas et al. 2004). In the other two studies, a post-hoc analysis showed a better survival in subgroups of patients with less advanced disease (Klerk et al. 2005; Kakkar et al. 2004). The fifth virtually excluded any appreciable advantages (van Doormaal et al. 2011). In conclusion, we believe that further studies are needed before LMWH can be implemented in the routine treatment of patients with cancer.

9 Conclusions

The development of VTE in patients with cancer poses a number of therapeutic challenges. As, unfortunately, most patients with cancer do not survive long enough to develop long-term sequelae, the use of aggressive therapies is rarely indicated. Thrombolytic drugs should be confined to patients with life-threatening PE and the insertion of caval filters in patients with absolute contraindication to antithrombotic drugs provided the VTE episode is acute (<1 month). All other patients should receive conventional anticoagulation, favoring the use of intravenous or subcutaneous UFH followed by VKAs in those with severe renal impairment, and that of full-dose LMWH followed by subtherapeutic doses of the same compounds in patients with no or moderate renal insufficiency. Indeed, VKAs are often inconvenient and inadequate, and there is not (yet) enough evidence favoring the use of the novel oral anticoagulants. Needless to say, the strong advantage of LMWH over VKA adds to the still unresolved issue on the need for cancer detection in patients with otherwise unexplained VTE. Indeed, the detection of cancer gives indication for prolonging the initial LMWH treatment or shifting from VKA – whenever initiated – to LMWH therapy. LMWHs are also the drugs of choice for the treatment of catheter-related thrombosis.

As there is no evidence coming from clinical trials, the optimal duration of anticoagulation in cancer patients remains unanswered, as does the choice between LMWHs and VKAs once the first months of treatment have been completed. Most opinion leaders recommend at least 3–6 months of LMWH treatment, whereas further prolongation with either LMWH or VKAs essentially depends on the individual risk of recurrence versus risk of bleeding. Anticoagulation should be prolonged as long as cancer is active or chemotherapy is ongoing and discontinued if the risk of serious bleeding is high. Patients should be often reevaluated, and the duration of treatment tailored to potential benefits, risks and patients' preferences.

Whether the incidental detection of VTE poses indication for full-dose anticoagulation in all cancer patients is controversial. This is likely to be correct in patients with the involvement of segmental or more proximal pulmonary arteries, in those with the simultaneous involvement of multiple subsegmental vessels, and in those with proximal DVT, provided they are not at high risk of bleeding. Conversely, patients with below-knee DVT and those with splanchnic thrombosis are unlikely to benefit from full-dose anticoagulation, and those with the involvement of one or two subsegmental pulmonary arteries should be managed carefully. Ideally, there is the need for additional investigations. Instead of instant initiation of anticoagulation, we suggest a careful evaluation of patients (Are patients really asymptomatic?) and a careful reevaluation of their imaging studies (Is the diagnosis accurate? Is there the involvement of at least one segmental vessel? Compared with recent CT scans, are the findings new?). Whenever the final decision is against the use of full-dose anticoagulation, physicians should not forget that subsegmental PE, below-knee DVT and splanchnic thrombosis should be regarded as markers of systemic hypercoagulability, which is quite common in patients with cancer, and therefore are likely to require at least long-term prophylaxis with low-dose anticoagulants.

Finally, for the time being, the long-term use of LMWH in cancer patients without thrombosis should be discouraged, as evidence favoring an impact on survival is weak.

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The Role of New Oral Anticoagulants (NOACs) in Cancer Patients

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Abstract

New oral anticoagulants (NOACs) are likely to have a major impact in the next few years, changing clinical practice of anticoagulation therapy. Evidence on its efficacy and superiority to vitamin K antagonists (VKAs) in treating non-cancer patients have been reported in a few clinical trials. However, patients with cancer are complicated by the prothrombotic nature of the disease, need for potentially invasive surgery and interventions, and altered drug handling. This chapter examines the available evidence and guidelines on the use of NOAC in patients with cancer.

Keywords

New oral anticoagulants • Direct oral anticoagulants • Cancer • Venous thromboembolism • Deep venous thrombosis • Pulmonary embolism

1 Introduction

The association between malignancy and venous thromboembolism (VTE) was been established by Trousseau in the 1860 s (Trousseau 1865). Since then, the risk of VTE, which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE) in cancer patients has been quantified as 13 per 1000 person years, and up to 58 per 1000 person years in high risk groups (Horsted et al. 2012). Patients with malignancy have a seven fold increase in the risk of VTE (Blom et al. 2005). Paradoxically, up to 10 % of patients who present with idiopathic VTE are diagnosed with cancer within one year (Carrier et al. 2008). Clinically detectable VTE are found 15 % of all cancer patients and the incidence is higher in subclinical or asymptomatic patients (Caine et al. 2002). VTE is the second leading cause of death in oncology

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patients (Khorana et al. 2007) and a poor prognostic index of disease progression (Sorensen et al. 2000).

New oral anticoagulants (NOAC) have been trialled against conventional therapy in several multicentre randomised controlled trials (RCTs) recruiting patients with VTE. However, information is lacking on the safety and efficacy of these new drugs, specifically in patients with cancer. This chapter reviews the challenges associated with anticoagulation in cancer patients, the current anticoagulation guidelines and evidence for the role of NOAC in managing patients with cancer.

2 Cancer Related VTE Risk Factors

Patients with cancer are at a higher risk than the general population of developing VTE due to a complex interplay of patient, tumour, treatment-related factors and certain biomarkers of disease (Elyamany et al. 2014; Kyriazi and Theodoulou 2013). Patient related factors include female gender, age, inherited thrombophilia and medical comorbidities such as diabetes mellitus, obesity, previous VTE and inflammation. Tumour related factors such as tumour site, histology, stage and time since diagnosis have been implicated. Haematological malignancies carry the highest risk of VTE, followed by lung and gastrointestinal tumours (Kyriazi and Theodoulou 2013). Treatment related factors include hospitalisation, cancer therapy, erythropoiesis-stimulation agents and presence of indwelling venous catheters. Antiangiogenic agents such as bevacizumab, thalidomide and lenalidomide also contribute to risk of thrombosis through endothelial cell and platelet activation and damage to the vascular endothelium (Mandala et al. 2011). High tissue factor expression by tumour cells, pre-chemotherapy platelet and leukocyte counts of $>$350,000/mm and $>$11,000/mm respectively are biomarkers of high risk VTE (Khorana et al. 2005).

3 Challenges of Anticoagulation in Patients with VTE

Treatment of VTE in patients with cancer is more challenging than its management in the general patient population. Balancing the risk of thrombosis to the risk of bleeding is complicated by a variety of drug and treatment related factors. Drug related factors include the altered pharmacokinetics of the drug due to interaction with chemotherapeutic or other medication, altered renal and liver function, decreased nutrition, gastrointestinal side effects such as nausea and vomiting, and altered haematological parameters such as platelet count. Cancer patients undergoing chemotherapy also often have indwelling catheters, which carries a risk of central venous catheter (CVC) related VTE due to a combination of endothelial injury, venous stasis and hypercoagulability. The incidence of symptomatic CVC related VTE ranges from 0.3 to 28.3 % (Verso and Agnelli 2003). These patients may undergo several invasive interventions or surgery during the course of treatment, which interrupts the course of anticoagulation therapy (Prandoni et al. 2005), leaving periods of subtherapeutic anticoagulation.

4 Current Management of VTE

Current guidelines on the management of VTE is broadly categorised into acute and long-term treatment (Mandala et al. 2011; Lyman et al. 2013a; Farge et al. 2013; Kearon et al. 2012; NCCN 2014). Initial treatment consists of a bridging period of anticoagulation with unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux (Factor Xa inhibitor). Long-term therapy involves LMWH, fondaparinux or vitamin K antagonists (VKAs).

In patients with cancer, LMWH is the preferred anticoagulant in VTE prophylaxis and treatment due to the longer plasma half-life, improved subcutaneous bioavailability and

predictable dose-response effect (Prandoni et al. 2014). UFH is indicated in patients with renal insufficiency (creatinine clearance <30 ml/min), at high risk of bleeding or undergoing invasive procedures due to its shorter half-life and the availability of an antidote (protamine sulphate). However, it requires regular venepuncture for the monitoring of activated partial thromboplastin time (APTT) to achieve a therapeutic effect. In addition, UFH carries a higher risk of heparin-induced thrombocytopenia (HIT) compared to LMWH. Fondaparinux is a synthetic indirect Factor Xa inhibitor, which is found to be as effective and safe as UFH and LMWH in the treatment of DVT and PE (Prandoni et al. 2004).

5 New Oral Anticoagulants (NOACs)

In recent years, new oral anticoagulants (NOACs) have been developed, which act either as a direct thrombin inhibitor (dabigatran) or reversible Factor Xa inhibitor (rivaroxaban, apixaban, edoxaban). The oral route of administration of these drugs offers an attractive alternative to conventional parenteral anti-coagulants (e.g. UFH, LMWH, fondaparinux). In addition, they overcome several of the disadvantages of traditional oral anticoagulants (e.g. VKA) including inter-patient variability, the need for therapeutic level monitoring (hence, requiring regular venepuncture) and the non-linear dose-response as there is no binding to plasma proteins.

Direct thrombin (Factor IIa) inhibitors competitively bind to the active site on thrombin, inhibiting both free and clot bound thrombin (Fig. 1). Thrombin plays central roles in converting fibrinogen to fibrin, activating several other clotting factors (Factors V, VIII, XI and XIII), and activating platelet protease-activated receptors, which mediate platelet aggregation. Therefore, developing a pharmacological agent that directly inhibits thrombin appears to be an effective strategy, producing a predictable anti-coagulant response (Eriksson et al. 2009; Cabral 2013).

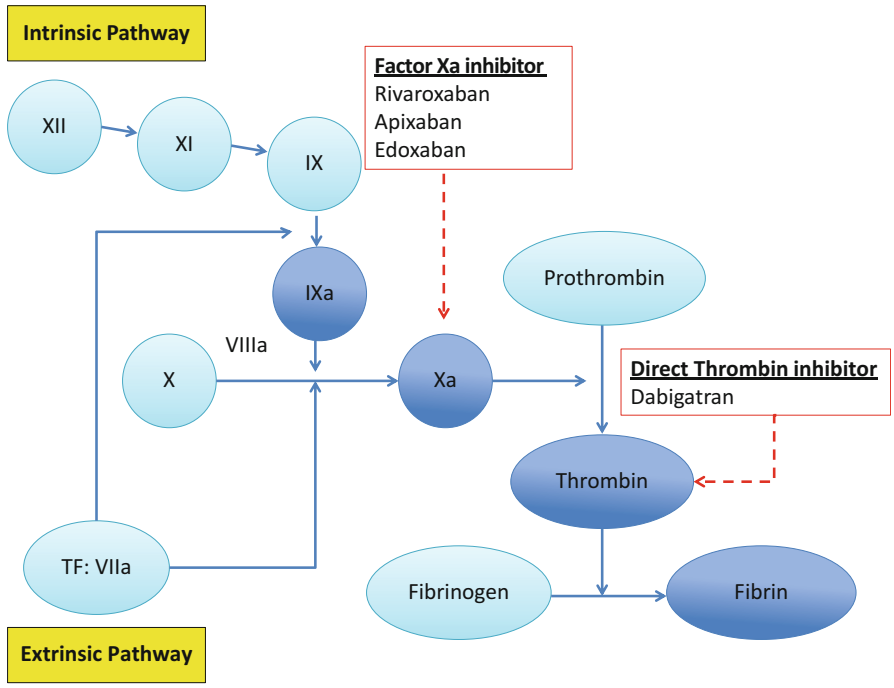

Fig. 1 Schematic diagram demonstrating mode of action of new oral anticoagulants (NOAC) on the coagulation pathway

Table 1 Pharmacokinetics and pharmacodynamics of new oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Prodrug	Yes	No	No	No
Tmax (h)	1.5–3	2–4	1–3	1–2
Half life (h)	12–17	5–9	9–14	9–11
Bioavailability	6.5 %, pH sensitive	>80 %	>50 %	45 %
Protein binding	35 %	92–95%	87 %	40–59%
Metabolism	Conjugation	CYP3A4, CYP2J2	CYP3A4	CYP3A4
Elimination	80 % renal	66 % renal (33 % as active metabolites)	25 % renal	35 % renal
Effects of food	T_{max} delayed; C_{max} & AUC unchanged	T_{max} delayed; C_{max} & AUC increased	T_{max} delayed; C_{max} & AUC unchanged	T_{max} delayed; C_{max} &AUC unchanged
Drug interactions	Potent P-gp inducers/inhibitors	Potent CYP3A4 inhibitors & P-gp inducers/inhibitors	Potent CYP3A4 inhibitors & P-gp inducers/inhibitors	CYP3A4 inhibitors; P-gp inducers/ inhibitors

AUC area under curve, C_{max} peak serum concentration, *h* hour, *P-gp* Glycoprotein P, T_{max} time of peak concentration

Meanwhile, Factor Xa inhibitors selectively and reversibly bind directly to the active site of Factor Xa (Fig. 1). In the coagulation cascade, Factor Xa binds to Factor Va on the surface of platelets to form the prothrombinase complex which converts prothrombin to thrombin (Eriksson et al. 2009; Cabral 2013). By blocking this interaction, Factor Xa inhibitors prevent the final effects of thrombin generation.

NOACs have predictable pharmacokinetic and pharmacodynamics (Table 1), permitting fixed dosing and eliminating the need for regular monitoring. Although NOACs have minimal food and drug interactions, they are affected by chemotherapeutic drugs that induce or inhibit the P-glycoprotein transport or CYP3A4 pathway (Table 2) (Cabral 2013).

However, NOACs are not without limitations themselves. In the presence of severe liver and renal dysfunctions, a relatively common feature of patients with cancer, the pharmacodynamics of NOACs may be unpredictable. Dabigatran is excreted by the kidney, and should be used with caution in patients with renal impairment (Cabral 2013). There are no assays to measure the anticoagulation level of NOACs if treatment failure or non-compliance is suspected. The lack of antidote has led to an uncertainty regarding the management protocol in the event of major bleeding or need for urgent reversal of anticoagulation (Prandoni et al. 2014). There is also very little reported about the efficacy or safety of these drugs in children or pregnant women.

6 Treatment of Acute VTE in Patients with Cancers

The aims of acute VTE treatment are to prevent the extension of DVT, prevent fatal PE, recurrent VTE and the subsequent long term complications of VTE such as post thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension. Cancer patients have an annual risk of recurrent VTE of 21–27 % (Hutten et al. 2000; Levitan et al. 1999) despite appropriate anticoagulation with VKA and are 3–4 times more likely to develop VTE than non-cancer patients. The annual risk of bleeding complications whilst on anticoagulation has been estimated to be 12–13 % or 2–6 folds higher than in non-cancer patients (Prandoni et al. 2002).

6.1 Acute Management of Cancer Related VTE

Current guidelines favour LMWH for long term anticoagulation management of acute VTE in cancer patients (Mandala et al. 2011; Farge

Table 2 Interactions between chemotherapeutic agents and immunosuppressants with NOACs based on known metabolic pathway activity

Interaction effect	Dabigatran	Rivaroxaban	Apixaban
	P-glycoprotein	P-glycoprotein	P-glycoprotein
		CYP3A4	CYP3A4
Increases NOAC plasma levels	Cyclosporine	Cyclosporine	Cyclosporine
	Tacrolimus	Tacrolimus	Tacrolimus
	Tamoxifen	Tamoxifen	Tamoxifen
	Lapatinib	Lapatinib	Lapatinib
	Nilotinib	Nilotinib	Nilotinib
	Sunitinib	Sunitinib	Sunitinib
		Imatinib	Imatinib
Reduces NOAC plasma levels	Dexamethasone	Dexamethasone	Dexamethasone
	Doxorubicin	Doxoribucin Vinblastine	Doxoribucin Vinblastine
	Vinblastine		

CYP3A4 cytochrome P450 3A4
Drugs that inhibit P-glycoprotein transport or CYP3A4 pathway can increase NOAC levels
Drugs that induce P-glycoprotein transport or CYP3A4 can lower NOAC levels

et al. 2013; Kearon et al. 2012; NCCN 2014; Lyman et al. 2013b). The evidence available to support the routine use of NOACs in the prevention and treatment of VTE remains limited. Six phase III RCTs have been conducted comparing NOACs to conventional anticoagulation therapy on the general VTE patient population (summarised in Table 3) (Schulman et al. 2009; 2014; Bauersachs et al. 2010; 2012; Agnelli et al. 2013a; Hokusai et al. 2013). Cancer patients encompassed 2.5–6 % of trial population. The cancer patients involved in these trials may also not truly reflect the complexity of anticoagulation management in cancer patients, as more complicated patients are more likely to have been excluded. Hence, the results should be interpreted with caution as these trials were not designed and powered specifically for patients with cancer.

The RECOVER I (Schulman et al. 2009) and RECOVER II (Schulman et al. 2014) were multicentre double-blinded, double-dummy trials involving patients with acute VTE who were randomised to receive either dabigatran or warfarin (target INR 2.0–3.0) following initial parenteral anticoagulation therapy. Pooled data of patients with active cancer in these two trials reported no significant difference in efficacy between dabigatran and warfarin for cancer at baseline (HR 0.75; 95 % CI, 0.20–2.8) or diagnosed during the study (HR 0.63; 95 % CI, 0.20–2.0) (Schulman et al. 2015). The risk of bleeding was not increased by dabigatran. Recurrent VTE occurred more often in patients with (HR 3.3; 95 % CI 2.1–5.3) than without cancer. The authors concluded that dabigatran had a similar efficacy and safety profile to warfarin, with the added benefit or fixed dosage and not requiring monitoring.

The EINSTEIN-DVT (Bauersachs et al. 2010) and EINSTEIN-PE (Buller et al. 2012) were open-label, randomised non-inferiority trials comparing oral rivaroxaban (15 mg twice daily, followed by 20 mg once daily) to standard therapy (subcutaneous enoxaparin followed by vitamin K antagonists) over a period of 3, 6 or 12 months in patients with DVT and PE, respectively.

In a pooled sub-group analysis of cancer patients in both trials, recurrent VTE occurred in 5.1 % of patients in the rivaroxaban arm, compared to 7.1 % of patients in the standard therapy arm (HR 0.69; 95 % CI 0.36–1.33). Corresponding rates of major bleeding occurred in 2.8 % and 5.0 % of patients (HR 0.53; 95 % CI 0.23–1.23). Rivaroxaban was found to have a significantly better net clinical benefit (HR 0.60; 95 % CI 0.36–0.99) in cancer patients.

The AMPLIFY (Agnelli et al. 2013a) and HOKUSAI trials (Hokusai et al. 2013) investigated the efficacy and safety of apixaban and edoxaban, respectively. However, sub-group

Table 3 Trials investigating the safety and efficacy of new oral anticoagulants compared to vitamin K antagonists

Trial acronym	Indication	Study phase	NOAC	Comparator	Total patients	Cancer patients	Treatment duration	Overall death (%) NOAC vs comparator	Recurrent VTE* (%) NOAC vs comparator	CRB (%) NOAC vs comparator
RE-COVER I 2009 (Schulman et al. 2009)	VTE acute treatment	III	Dabigatran 150 mg bd	VKA	2539	121 (4.8 %)	6 mo	1.6 vs 1.7	2.7 vs 2.5	5.6 vs 8.8
RE-COVER II 2013 (Schulman et al. 2009)	VTE acute treatment	III	Dabigatran 150 mg bd	VKA	2589	100 (3.9 %)	6 mo	2.0 vs 1.9	2.3 vs 2.2	5.0 vs 7.9
EINSTEIN-DVT 2010 (Bauersachs et al. 2010)	DVT acute treatment	III	Rivaroxaban 15 mg bd for 3wk followed by 20 mg od	VKA	3449	207 (6.0 %)	12mo	2.2 vs 2.9	2.1 vs 3.0	8.1 vs 8.1
EINSTEIN-PE 2012 (Buller et al. 2012)	PE acute treatment	III	Rivaroxaban 15 mg bd for 3wk followed by 20 mg od	VKA	4832	223 (4.6 %)	12mo	2.4 vs 2.1	2.1 vs 1.8	10.3 vs 11.4
AMPLIFY 2013 (Agnelli et al. 2013a)	VTE acute treatment	III	Apixaban 10 mg bd for 7d followed by 5 mg bd	VKA	5395	169 (3.1 %)	6 mo	1.5 vs 1.9	2.3 vs 2.7	4.3 vs 9.7
HOKUSAI 2013 (Hokusai et al. 2013)	VTE acute treatment	III	Edoxaban 60 mg od or 30 mg od	VKA	8240	208 (2.5 %)	12 mo	3.2 vs 3.1	3.2 vs 3.5	8.5 vs 10.3

bd twice daily, *CRB* major or clinically relevant non-major bleed *od* once daily *NOAC* new oral anticoagulant
*Recurrent VTE or VTE related death

analysis for patients with cancer was not provided by trial coordinators.

A recent meta-analysis performed subgroup analysis of cancer patients in 6 RCTs comparing the efficacy and safety of NOACs to VKAs for the initial treatment of VTE (Vedovati et al. 2015). The meta-analysis pooled a population of 1132 cancer patients from these 6 RCTs and reported the incidence of recurrent VTE in 3.9 % of patients on NOACs compared to 6.0 % of patients on conventional therapy (Odds Ratio [OR] 0.63; 95 % CI 0.37–1.10). Major bleeding occurred in 3.2 % and 4.2 % of patients receiving NOAC and conventional treatment, respectively (OR 0.77; 95 % CI 0.41–1.44).

Subgroup meta-analysis by Van Es et al. (van Es et al. 2014) reported a significantly lower risk of recurrent VTE with NOAC compared to VKA (relative risk (RR) 0.57; 95 % CI 0.36–0.91; P = 0.02), with no increased risk of major bleeding (RR 0.77, 95 % CI 0.44–1.33; P = 0.35).

Further RCTs that are specifically designed and powered for cancer patients are required. A review of guidelines should be undertaken in light of these findings to consider the cost-effectiveness of NOAC in the management of acute VTE in patients with cancer.

6.2 Extended Treatment of Cancer Related VTE

There is no consensus on the duration of anticoagulation following the diagnosis of VTE. The American College of Chest Physicians (ACCP) and National Comprehensive Cancer Network (NCCN) recommend that treatment of VTE should be continued for 3 months with annual reassessment of risk of thrombosis (Kearon et al. 2012; NCCN 2014). However, American Society of Clinical Oncology (ASCO) recommend at least 6 months of anticoagulation in patients with metastatic disease, receiving chemothreapy or recurrent thrombosis (Lyman et al. 2013a). Although LMWH has been found to significantly reduce the risk of VTE compared to VKA (Akl et al. 2011a), this is not a preferred method for patients due to daily injections. Four RCTs have been conducted comparing the safety and efficacy of extended treatment of VTE with NOACs to conventional therapy.

The RESONATE and RE-MEDY trials are multicentre, double-blinded trials comparing the efficacy and safety of extended treatment of VTE with dabigatran versus placebo and warfarin, respectively (Schulman et al. 2013). The AMPLIFY-EXT (Agnelli et al. 2013b) compared the safety and efficacy of two doses of apixaban (2.5 mg and 5 mg twice a day) to placebo in patients who had completed 6–12 months of anticoagulation. The EINSTEIN-EXT (Bauersachs et al. 2010), compared the efficacy and safety of rivaroxaban to placebo, after a 6 or 12 month treatment with either rivaroxaban on warfarin. However, the sub-group analysis of cancer patients was not performed on these trials.

6.3 Anticoagulant Therapy in Patients with Recurrence of VTE

Despite anticoagulation with LMWH, published studies suggest the rate of recurrent VTE may be as high as 6–9 % (Lee et al. 2003; Meyer et al. 2002). The ASCO recommend assessing compliance, risk of heparin induced thrombocytopenia and addition of mechanical compression prior to changing anticoagulant (Lyman et al. 2013a). The progression of malignancy should also be assessed (Mandala et al. 2011). Patients on VKA with the INR within therapeutic range should switch to weight adjusted LMWH, UFH or INR increased to a target of 3.5 (Mandala et al. 2011). The safety and efficacy of NOACs have not been studied for this indication.

7 Venous Thromboprophylaxis in Patients with Cancers

7.1 Ambulatory Cancer Patients Undergoing Chemotherapy

The risk of VTE in cancer patients receiving chemotherapy is increased by 2.2–6.5 folds

(Heit et al. 2000; Blom et al. 2006; Cronin-Fenton et al. 2010). Current guidelines from various bodies of medical experts including the ACCP (Kearon et al. 2012), European Society of Medical Oncology (ESMO) (Mandala et al. 2011), NCCN (NCCN 2014) and American ASCO (Lyman et al. 2013a) recommend against primary thromboprophylaxis for ambulatory cancer patients receiving chemotherapy, except in high risk groups. A recent Cochrane systematic review (Di Nisio et al. 2012) of 9 RCTs assessing the efficacy and safety of ambulatory cancer patients receiving chemotherapy reported a reduction in symptomatic VTE with LMWH (relative risk [RR] 0.62; 95 % CI 0.69–3.60) with no significant increase in major bleeding (RR 1.57; 95 % CI 0.69–3.60) compared with inactive control.

The ADVOCATE trial is a multi-centre, phase II double-blinded pilot RCT designed to evaluate the tolerability and acceptability of apixaban in ambulatory cancer patients receiving either first-line or second line chemotherapy (Levine et al. 2012). A total of 125 subjects with metastatic lung (n = 12), breast (n = 32), pancreatic (n = 15), gastric (n = 2), colorectal (n = 14), ovarian (n = 2) or prostate (n = 13) cancer, myeloma (n = 11) or lymphomas (n = 10) were randomised following stratification for the presence of liver metastases to one of four arms; apixaban 5 mg (n = 32), 10 mg (n = 30) or 20 mg (n = 33) daily or placebo (n = 30). Subjects were excluded if there was a prior history of VTE, severe renal impairment, liver dysfunction or coagulopathy. Subjects began the 12 week study within 4 weeks of chemotherapy. Follow up visits occurred at every 3 or 4 weeks, depending on their chemotherapy schedule.

Primary outcome measures of major bleeding and CRB occurred in one (3.1 %), one (3.4 %), 4 (12.5 %) and one (3.4 %) of the Apixaban 5 mg, 10 mg, 20 mg daily and placebo arms, respectively. There were no episodes of VTE in the apixaban arms, but three patients in the placebo group (10.3 %) developed VTE. Adverse events were reported in two patients in the apixaban 5 mg arm (rectal bleed and deranged liver function tests) and one patient in the apixaban 20 mg arm (lower gastrointestinal bleed). Three deaths occurred during the trial; one patient in the apixaban 5 mg arm died of heart failure, two patients in the placebo arm died of heart failure and progressive cancer.

The study concluded that apixaban was well tolerated and acceptable for the prevention of VTE in ambulatory subjects undergoing first-line and second-line chemotherapy for advanced metastatic cancer. Limitations include that the trial was not powered to detect a difference in incidence of VTE between the treatment arms and placebo group. In addition, the protocol selected patients with a low risk of bleeding and screening for asymptomatic patients was not performed.

7.2 Cancer Patients Undergoing Surgery

Cancer surgery is an established risk factor for VTE. Surgery for cancers carries a higher VTE and perioperative bleeding risk than surgery for benign disease (Siegal and Garcia 2012; Kakkar et al. 2005). The benefit of prophylactic heparin in cancer surgery has been established by Clagett and Reisch (Clagett and Reisch 1988), showing heparin significantly decreased perioperative VTE compared to no anticoagulation therapy (13 % vs 31 %). Current guidelines from the ACCP (Kearon et al. 2012), ESMO (Mandala et al. 2011), NCCN (NCCN 2014) and ASCO (Lyman et al. 2013a) recommend perioperative thromboprophylaxis with LMWH or UFH, starting preoperatively and to be continued for 7–10 days postoperatively.

There are no trials to date investigating the prophylactic role of NOAC during the perioperative period for cancer patients. Therefore, the authors do not recommend the regular use of NOACs for VTE prophylaxis in cancer patients undergoing surgery.

7.3 Extended Thromboprophylaxis in Cancer Patients Undergoing Surgery

Bergqvist et al. (Bergqvist et al. 2002) demonstrated that in patients with planned

curative open surgery for abdominal or pelvic cancer, an extended duration VTE prophylaxis with enoxaparin 40 mg daily (21 days vs 6–10 days) reduced the rate of VTE (4.8 % vs 12.0 %) with similar rate of bleeding. However, a systematic review concluded that there is low quality evidence that extended duration prophylaxis with LMWH reduced risk of asymptomatic DVT (RR 0.21, 95 % CI 0.05–0.94). The risk of major bleed four weeks post-operatively was also not significantly different (RR 2.94; 95 % CI 0.12–71.85) (Akl et al. 2008). There is no evidence available to support the regular use of NOACs in this patient group.

7.4 Hospitalised Non-Surgical Patients

Current major guidelines recommend the use of UFH, LMWH or fondaparinux in the management of all acute medical patients if this is not contraindicated by the risk of bleeding (Mandala et al. 2011; Lyman et al. 2013a; Farge et al. 2013; NCCN 2014).

The MAGELLAN trial (Cohen et al. 2011) was a multicentre double-blinded RCT involving patients aged ≥40 years, who were hospitalised for acute medical illness, with ≥3 risk factors of VTE and anticipated reduction in mobility. Patients were randomised to one of two arms; enoxaparin 40 mg od for 10 ± 4 days and oral (rivaroxaban) placebo for 35 ± 4 days, or oral rivaroxaban 10 mg od for 35 ± 4 days and (enoxaparin) placebo for 10 ± 4 days. In addition to detection of symptomatic DVT and PE, all patients underwent routine ultrasonography surveillance for DVT at day 10.

Of the 8101 patients randomised, 584 (7 %) had cancer. The primary outcome measures (a composite of asymptomatic proximal DVT, symptomatic DVT, symptomatic non-fatal PE or VTE related death) at day 1–10 were 2.7 % (RR with rivaroxaban 0.97; 95 % CI 0.81–1.31; P = 0.003 for non-inferiority) in both arms. In the 35 day analysis, the primary outcome measure occurred in 4.4 % in the extended duration rivaroxaban arm compared to 5.7 % in the group receiving enoxaparin followed by placebo (RR with rivaroxaban 0.77; 95 % CI 0.62–0.96; P = 0.02).

However, the incidence of CRB was greater in the rivaroxaban arm in both the short and extended phase of the trial. The net clinical benefit or harm in the rivaroxaban group was 6.6 %, compared to 4.6 % in the enoxaparin group (RR 1.44; 95 % CI 1.18–1.77; P < 0.001) at 10 days and 9.4 % compared to 7.8 % (RR 1.21; 95 % CI 1.03–1.43; P = 0.02) at 35 days.

The authors concluded that rivaroxaban was non-inferior to enoxaparin during the short duration of treatment, and was superior to short duration (10 ± 4days) enoxaparin followed by placebo. Limitations of this trial include inclusion of asymptomatic proximal DVT, which is not routinely performed and may alter the natural history of the disease. In addition, a substantial group of patients who underwent randomisation did not undergo ultrasonography, which may affect the findings of this trial.

The ADOPT trial (Goldhaber et al. 2011) was a multicentre, double-dummy, placebo-controlled trial on patients aged ≥40 years of age hospitalised with acutely ill medical conditions and an expected hospital stay of at least 3 days. Patients were randomised to two arms; apixaban 2.5 mg twice daily for 30 days or enoxaparin 40 mg daily for a minimum of 6 days. Follow up visits were scheduled on days 30 ± 2 and 90 ± 7. Of the 6528 patients who underwent randomisation, 632 (9.7 %) had a history of cancer.

The primary outcome measure, a composite of VTE related death, PE, symptomatic DVT or asymptomatic proximal leg DVT, occurred in 2.71 % and 3.06 % of the patients in the apixaban and enoxaparin groups, respectively (RR with apixaban 0.87; 95 % CI 0.62–1.23; P = 0.44). The primary safety outcome measure (major bleeding and CRB) occurred in 2.67 % and 2.08 % of the apixaban and enoxaparin groups, respectively (RR 1.28; 95 % CI 0.93–1.76; P = 0.12). There was no significant difference in death rates between both groups (4.1 % each). Subgroup analysis for cancer patients was not performed.

The authors summarised that an extended course of thromboprophylaxis with apixaban was not superior to a short course of enoxaparin, and was associated with a higher rate of major bleeding than enoxaparin. Limitations of this study include that patients receiving enoxaparin received extended thromboprophylaxis (up to 14 days despite discharge) compared to usual clinical practice.

7.5 Cancer Patients with Indwelling Central Venous Catheter

A Cochrane systematic review investigating the efficacy and safety of anticoagulant VTE prophylaxis in cancer patients with CVC (Akl et al. 2011b) reported that UFH, LMWH and low dose VKA (INR target of 1.5) was associated with a reduction trend of developing symptomatic DVT with no effect on mortality or bleeding. However, current major guidelines (Mandala et al. 2011; Lyman et al. 2013a; Kearon et al. 2012; NCCN 2014) do not recommend routine use of anticoagulation in cancer patients with central venous catheters. Therefore, the authors do not recommend the routine use of NOACs to prevent CVC related VTE in cancer patients.

8 Future Perspectives of NOACs in the Prevention and Treatment of VTE in Cancer Patients

NOACs have several favourable characteristics, which makes them an attractive treatment option. However, research is required to develop specific assays to monitor compliance and treatment efficacy. Protocols to manage severe bleeding and for reversal of anticoagulation in the event of an emergency are essential. Patients with cancer, in particular, would benefit from an antidote due to the higher risk of bleeding.

Patient with cancer are at a higher risk of VTE than the general population and this event has significant effects on the prognosis of patients. Evidence is scarce on the efficacy and safety of NOACs in this patient population. There is a need for more RCTs focusing on the efficacy of NOACs in preventing VTE, the side effects and interactions with chemotherapeutic drugs, patient compliance, quality of life outcome measures and cost effectiveness of treatment with NOACs. Trials should also stratify patients by their risk of VTE, cancer type and staging.

Current ongoing trials on cancer patients include the AVERT trial, a double blind RCT investigating the safety and efficacy of apixaban in preventing VTE in high risk ambulatory cancer patients (Clinicaltrias.gov identifier: NCT02048865). The Cancer Venous Thromboembolism trial is a RCT assessing the safety and efficacy of edoxaban at preventing recurrent VTE in patients with cancer (Clinicaltrials.gov identifier: NCT02073682). A cohort study in Asian patients with cancer-associated VTE (Clinicaltrials.gov identifier: NCT01989845) is currently investigating the risk of recurrent VTE. The Catheter-2 trial is an ongoing efficacy study investigating the safety and efficacy of rivaroxaban at preventing upper extremity catheter related venous thrombosis in patients with cancer. (Clinicaltrials.gov identifier: NCT01708850). An observational study is currently ongoing, investigating the efficacy and safety of NOACs to conventional anticoagulants in treating cancer related PE, with outcome measures including recurrence and bleeding risk (Clinicaltrials.gov identifier NCT01727427).

MARINER trial investigating the safety and efficacy of rivaroxaban compared to placebo at preventing VTE in medical patients following discharge (ClinicalTrials.gov identifier: NCT02111564). The FIRST trial is a prospective, observational study following up patients who have been treated with rivaroxaban 5 years following VTE, to assess the incidence of long term complications such as recurrent VTE, post thrombotic syndrome and chronic thromboembolic pulmonary hypertension (Clinicaltrials.gov identifier: NCT02248610).

Following the results of these trials, cost-effectiveness analysis on these drugs should be performed to provide evidence for the

incorporation of NOACs into anticoagulation guidelines.

9 Conclusion

At present, there is a paucity of trials investigating the efficacy and safety of NOAC in patients with cancer. Subgroup analyses from trials comparing VKA to NOAC have shown a benefit of NOACs over conventional therapy. However, the gold standard treatment for VTE recommended by the guidelines is LMWH and trials are required to investigate the safety and efficacy of NOAC in VTE prophylaxis as well as treatment.

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Venous Thromboembolic Disease in Children and Adolescents

Vlad C. Radulescu and John A. D'Orazio

Abstract

The VTE is mainly a disease of the older adult, though its incidence has increased significantly in the pediatric population over the past several years. This trend is likely due to enhanced awareness and recognition of VTE, as well as increased prevalence of thromboembolic associated risk factors, such as increases in the proportion of children with predisposing medical conditions. The evaluation and management of a child with VTE is similar to that of adults, however pediatric patients have their own distinct aspects of care, stemming from particularities of the hemostatic system, age-related risk factors and differences in response to anticoagulant and antithrombotic therapy. This review addresses the risk factors and the evaluation and management of children with VTE.

Keywords

Inherited thrombophilia • Thromboembolism • Clotting • Children • Anticoagulant therapy • Thrombolytic therapy

1 Venous Thrombosis

Rudolph Virchow, the famed German pathologist, hypothesized that clots formed because of three factors: stasis of blood flow, vascular damage and a propensity for the blood to clot [1]. More than a century later, "Virchow's triad" remains a relevant explanation of the mechanisms that underlie clotting of the blood (Fig. 1). Venous thrombosis can occur in any vein, however when clotting occurs in superficial veins this usually does not lead to major morbidity. Rather, the majority of clinical consequences

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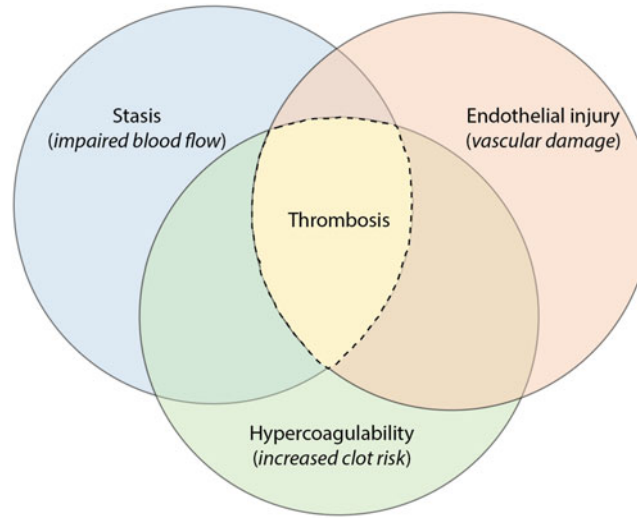

Fig. 1 Virchow's triad. Rudolph Virchow proposed three major factors that promote abnormal blood clotting

from inappropriate clotting occur when thrombi are located in the deep veins of the extremities, splahnic veins or the cerebral venous sinuses. Such clots, known as a "deep venous thrombosis" (DVT), are associated with immediate morbidities secondary to obstruction of venous blood flow (pain, edema, hyperemia), or embolism (pulmonary embolism) as well as long term sequelae such as venous insufficiency and post thrombotic syndrome [2].

2 Epidemiology

Currently, VTE incidence for patients under the age of 18 years is roughly 1–2 per 100,000 children year [3]. By comparison, VTE incidence in adults is up to 100–150 per 100,000 persons [4] making this disorder more common in adults by almost two orders of magnitude. Nonetheless the incidence of VTE in children has been increasing over the last several years [5, 6], making it very important that pediatricians understand VTE risk factors and presenting signs and symptoms to optimize recognition and timely management of children with VTEs [7, 8]. Many factors likely contribute to the increasing incidence of VTE in children, including better awareness and improved imaging modalities, complex therapies that increase the survival of VTE-prone children, increased use of central venous catheters and increasing prevalence of modifiable VTE risk factors (e.g. obesity, physical inactivity) [9–11]. The pediatric VTE incidence peaks in infancy, decreases in early to mid-childhood and increases again in adolescence.

3 Developmental Hemostasis

Hemostasis is a highly coordinated and regulated process aimed at stopping leaks when the continuity of the vessel wall has been compromised by injury (Fig. 2). The coagulation system is kept in balance through the activities of pro-coagulant factors on one side, anticoagulant and fibrinolytic factors on the other [12].

The hemostatic system undergoes constant changes over the lifespan of an individual; these changes are more pronounced during the first 6 months of life, but continue nonetheless in childhood, adolescence and adult life. Many studies have been focused on the age dependent quantitative differences of clotting and antithrombotic factors. At the time of birth the levels of most clotting and antithrombotic factors are low compared to the adult values. The vitamin K dependent factors II, VII, IX and X reach only 30–40 % of adult values [13]. This explains the physiologically prolonged activated

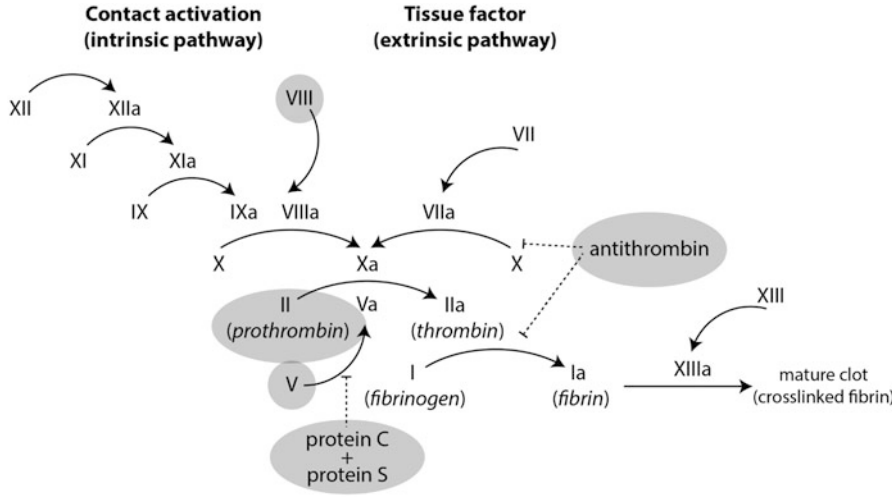

Fig. 2 The coagulation cascade and anticoagulation factors. The coagulation cascade consists of a series of carefully regulated sequential reactions in which serine proteases cleave pro-factors to activate the next factor's enzymatic activity. The central enzyme in the cascade is thrombin, which cleaves fibrinogen to form fibrin but also participates in the amplification loop of factors VIII and IX as well as the termination of coagulation cascade through the protein C protein S pathway. The coagulation cascade has many "built-in" regulators that serve to prevent inappropriate or excessive clot formation. Highlighted in gray are the anti-coagulation factors that when deficient or defective are known to play a role in VTE as well as the pro-coagulants that, when in excessive amounts predispose to thrombosis

thromboplastin time (aPTT) and prothrombin time (PT). The protein C, protein S, antithrombin, plasminogen and alpha 2 antiplasmin are lower at birth and only approach the adult values after 6 month to 1 year of age. Fibrinogen is moderately decreased at birth, reaching the adult levels after 1 month. Factors V, VIII and XIII do not change with age, while von Willebrand factor is typically elevated at birth, reaches a nadir around the age of 1 year and, thereafter, its activity increases through childhood and into adult life.

Acknowledging these variations is important in the interpretation of the hemostatic tests, in the choice and management of anticoagulant and thrombolytic therapy, especially during the first year of life

Another aspect of developmental hemostasis is the age related qualitative changes of the hemostatic proteins [14]. One example is the antithrombin, the serine protease that inhibits the thrombin and activated factor X (Xa). Antithrombin is secreted in several isoforms : native, pre-latent, cleaved and latent [15]. Latent antithrombin (LAT) has been associated with thrombosis in critically ill patients but it also has strong anti-angiogenic properties. Newborns have low levels of LAT compared to the adults; this may have to do more with the need to maintain active angiogenesis, but may be a contributing factor to the relatively low rate of thrombosis in childhood.

The overall physiologic implications of the developmental changes in the hemostatic system are not entirely understood. We do know that newborn and infants have a functional hemostatic system that offers relative protection against thrombotic events: individuals with congenital deficiencies of anti-coagulant factors (protein C, protein S, antithrombin) typically do not develop thrombotic events until the second or third decade of life, and thromboses secondary to acquired risk factors, like nephrotic syndrome or orthopedic surgeries, are much less common in young children compared to older adults.

Emerging data seems to suggest that the hemostatic proteins have more complex physiologic roles in angiogenesis and wound healing,

which may partially explain their age dependent variations.

4 Risk Factors

Deep venous thrombosis occurs when the hemostatic equilibrium is tilted toward clot formation. There is a variety of factors which may contribute to this disruption, some inherited, and others aquired (Table 1). The majority of pediatric patients with VTE have at least one identifiable risk factor; the truly idiopathic VTEs are uncommon in this age group. It is very important to identify the risk factors that led to the thrombotic event and determine whether they are transient or long lasting, modifiable or not modifiable through lifestyle changes, medical or surgical therapy.

Table 1 Risk factors for VTE in children

Acquired (Environmental) factors	Inherited (Genetic) factors
Anti-phospholipid antibody	Antithrombin deficiency
Autoimmune disorders (IBD)	Elevated homocysteine (MTHFR mutation)
Central venous catheters	Elevated VIII levels
Chemotherapy (e.g. L-asparaginase)	Factor V Leiden mutation
Dehydration	Family history of thromboembolism
Congenital Heart disease	Protein C deficiency
Hyperviscosity (polycythemia)	Protein S deficiency
Immobility	Prothrombin gene mutation (G20210A)
Infection (sepsis, cellulitis, osteomyelitis)	Vascular/anatomic abnormalities
Inflammation	
Lupus	
Malignancy	
Nephrotic syndrome	
Obesity	
Oral contraceptives (estrogen containing)	
Pregnancy	
Shock	
Smoking	
Surgery	
Total Parenteral Nutrition (TPN)	
Trauma (especially bone fractures)	
Ventriculo-atrial shunting	

The answer to those questions help tailor the duration and sometimes intensity of anticoagulation, as well as the lifestyle changes recommend in order to prevent a recurrence [16].

Inherited risk factors which may lead to a lifelong tendency toward hypercoagulability, are commonly referred to as inherited thrombophilias [17–19]. Inherited thrombophilias should be suspected when there is a positive family history of thrombosis (DVT, PE, myocardial infarction, stroke) or recurrent pregnancy loss, particularly if such events have occurred in multiple individuals in the family, in the same individual multiple times or at particularly young ages [20]. Inherited thrombophilias should also be suspected in a newborn or child when there is no obvious explanation for the thrombosis.

Fortunately the inherited thrombophilias with the severest phenotypes are quite rare. These include homozygous, protein C deficiency and protein S deficiency [17, 21, 22]. Each of these conditions typically presents in infancy with severe thrombosis, manifested as retinal arterial thrombosis, skin necrosis or VTE [23]. Heterozygous deficiency in these factors wherein affected individuals have low levels of antithrombin, protein C or protein S may predispose to clotting later in childhood or in adulthood [11] These deficiencies are found in less than 10 % of pediatric patients with VTE [18]. More common thrombophilic risk factors include the factor V Leiden mutation and the prothrombin gene G20210A mutation [24, 25]. Factor V Leiden mutation may affect up to 5 % of the population, and raises clotting risk by 3–7 times when only one allele is mutant. The prothrombin G20210A mutation, found in the regulatory (non-transcribed) region of the prothrombin gene, leads to elevated levels of serum prothrombin which in turn favors thrombus formation. In the heterozygous state this mutation increases the risk of a first thrombotic event by 2–3 times. Other predisposing conditions include increased

levels of serum homocysteine, which can result from inherited defects in the methylenetetrahydrofolate reductase (MTHFR) gene and which promotes endothelial cell injury [26, 27]. An additional inherited VTE risk factor is elevation of basal levels of circulating Factor VIII, which presumably results in excessive Xa formation to favor thrombosis [28].

Central venous catheterization represents a major risk factor for pediatric VTE, especially in newborns. These indwelling catheters, used more and more to provide supportive care for ill children, have a relatively high risk of associated clots in and around their venous location. Other "acquired" factors include either trauma or major surgery followed by bedrest, especially orthopedic involvement [29–32]. Prolonged immobilization, dehydration, infections (e.g. cellulitis, osteomyelitis, phlebitis), medications (especially L-asparaginase chemotherapy used for acute lymphoblastic leukemia), high estrogenic states (pregnancy, use of estrogen-containing hormonal contraceptives) and obesity are all important risk factors [33]. Medical conditions that predispose to VTE include congenital heart malformations and other anatomic anomalies that predispose to venous stasis such as May-Thurner syndrome wherein the left iliac vein is compressed when crossing between the right iliac artery and the lumbar vertebrae [34]. Presence of antiphospholipid (anti-cardiolipin antibodies, beta 2 glycoprotein 1 antibodies, lupus anticoagulant), as might occur as an isolated finding or in the context of a collagen vascular disorder, place patients at heightened risk [35, 36]. Nephrotic syndrome is a well-established medical predisposing risk factor, likely due to chronic renal loss of anticoagulant proteins such as antithrombin [37]. Inflammatory states such as Crohn's disease or rheumatoid arthritis also favor clot formation [38].

5 Clinical Presentation

Clinical signs and symptoms of VTE range from subtle to overt, therefore it is important to have a high index of suspicion and consider the diagnosis particularly in patients who carry risk factors for VTE. Most VTEs come to medical attention because of stasis, backflow and interrupted circulation caused by the clot (Table 2). Signs/symptoms of VTE in an extremity (e.g. leg) include pain, tenderness swelling and erythema. Function of the affected limb is often compromised by pain, weakness or fatigue [39]. More proximal VTEs such as might occur in the superior vena cava may result in SVC syndrome which is typified by swelling and erythema of the head and neck, prominence of jugular venous blood vessels and headache. Intracranial thrombosis (e.g. central venous sinus thrombosis) can present with acute neurologic dysfunction or headache. Signs and symptoms of pulmonary embolism include tachypnea, pleuritic chest pain, hypoxia, shortness of breath, diaphoresis and feeling of anxiety or doom [40].

Table 2 Clinical manifestations of venous thromboembolism

Deep venous thrombosis	Pulmonary embolism
Swelling/edema[a]	Shortness of breath
Pain or tenderness[a]	Anxiety
Erythema, hyperemia[a]	Chest pain
Visible surface veins[a]	Cough
Fatigue, weakness, loss of function[a]	Hemoptysis
Headache (sinus vein thrombosis)	Tachycardia

[a]Especially if unilateral and involving an extremity (especially leg)

6 Evaluation of Suspected Thrombosis

The most reliable and useful ways in which to test for venous thromboembolism are generally through imaging studies. The imaging modality of choice varies with the location of the suspected thrombus. For DVTs of the extremities color flow Doppler ultrasound is the preferred study because it is noninvasive, does not involve radiation, does not usually require sedation and offers reliable information about blood flow

through affected extremity vessels [41, 42]. Doppler ultrasounds may also be used for the evaluation of portal and renal veins, however, given their deeper location ultrasound is less reliable in these settings and may not be useful for the evaluation of the inferior vena cava or its tributaries. The right atrium and proximal portions of the superior vena cava and inferior vena cava can be visualized through echocardiography. Computerized tomography (CT) angiography and magnetic resonance venogram MRV can be used to visualize venous blood flow in the cerebral venous sinuses and deep veins in the thorax or abdomen. The contrast venogram may image central catheter -related thrombosis. Pulmonary embolism in children is best evaluated by CT angiography a test that for the most part has replaced the ventilation perfusion nuclear medicine imaging.

7 Diagnostic Laboratory Studies

There are no definitive serologic studies that are unequivocally diagnostic of VTE. Certainly, elevated D-dimers, which are produced as a consequence of fibrinolysis, can be observed in the presence of a clot. D-dimer testing has been used in adults in the diagnostic algorithms of PE, however in children with suspected PE, normal D-dimer levels lacks the same negative predictive value as in adults because at least 15 % of children with PE have a normal D-dimers [39]. In adult patients, persistent D-dimer elevation (and factor VIII elevation) for many months after diagnosis, may predict VTE recurrence. Similar data supporting this observation is available in the pediatric age group [28, 43].

8 Evaluation of Inherited Thrombophilia

There are no clear guidelines regarding which patients should be evaluated for thrombophilia. Testing of asymptomatic children is controversial and it is not supported by clinical evidence, however many hematologists agree that a thrombophilic work-up is probably indicated for the following patients:

- neonates with non-catheter related VTE
- adolescents with spontaneous, unprovoked VTE
- children with VTE who have a family history of thrombosis or inherited thrombophilia
- children with recurrent thrombosis

Levels of antithrombin, protein C and protein S must be put into context for proper interpretation. Thus, each is physiologically lower than adult levels for the first several months of life, and each may be consumed during acute thrombotic events. For this reason, it is important to determine basal antithrombin, protein C and protein S levels after infancy and several months after the VTE diagnosis. Various medications are also known to confound natural anticoagulant levels. Thus, antithrombin levels may be influenced by heparin therapy, and protein C and S levels will be lowered by warfarin or other vitamin K antagonists. Functionally, some clot-based assays for protein C and S activity may be influenced by the factor V Leiden mutation, factor VIII levels or the presence of the lupus anticoagulant [11, 44, 45].

With the exception of uncommon homozygous deficiency for protein C or protein S, the results of the thrombophilia evaluation may not influence the immediate management of the VTE. Homozygous protein C or protein S deficiency typically presents in the newborn period with extensive thrombosis and necrotic skin lesions of purpura fulminans and warrants prompt replacement therapy in addition to anticoagulant therapy [46]. However, such cases are quite rare, and for the usual pediatric VTE patient, the thrombophilia evaluation may provide information about the risk of recurrence and guide preventative interventions.

9 Therapy

Most of the clinical data used in the treatment algorithms for children with VTE has been

derived from adult clinical trials. While this approach has resulted in advances in the treatment and survival for pediatric VTE, some adult data cannot be immediately extrapolated to children because of age-related physiologic differences in the hemostatic system and differential responses to anticoagulant or thrombolytic medications [47, 48].

Goals of VTE therapy are to inhibit clot extension, prevent embolism, restore venous patency, limit long term sequelae and reduce risk of VTE recurrence [49]. These are achieved by recognizing and modifying risk factors and by pharmacologically restoring hemostatic balance with anticoagulant or thrombolytic therapies.

Anticoagulant or thrombolytic therapies carry a real risk of bleeding, therefore risks and benefits must be carefully taken into account in order to determine how aggressive to be. Several factors should be taken into account when choosing initial therapy for a newly-diagnosed VTE:

- Urgency of the clinical situation. Medically severe clots such as large PEs causing hemodynamic instability or a large VTEs risking organ or limb compromise call for aggressive intervention with the goal of rapidly resolving the thrombus. In addition to anticoagulation, thrombolysis should be considered in such situations.
- Bleeding risks of the intervention. Anticoagulation and thrombolysis each carry a risk of bleeding, and bleeding risk is highest for patients with evidence of bleeding such as intracranial hemorrhage, gastrointestinal hemorrhage, in patients whose vasculature has recently been challenged by surgery or trauma or in patients with preexisting bleeding tendencies (e.g. thrombocytopenia, coagulopathies, prematurity). In such patients, the risks of aggressive medical interventions such as systemic thrombolysis may outweigh the benefits for VTE resolution.
- Likelihood of long-term sequelae. Large, obstructive thrombi in the lower extremities and IVC carry a high risk of post-thrombotic syndrome (PTS) which is manifested by chronic pain, swelling, and skin abnormalities [50]. Several adult and pediatric series suggest that thrombolysis may be superior to anticoagulation alone in preventing the development of PTS.
- Expertise and proficiency of the medical team. Highly specialized interventions such as catheter-directed thrombolysis require the coordinated actions of interventional radiologists or cardiologists, hematologists, intensivists and nursing care. Given the relative rarity of pediatric VTE requiring such therapies and the proficiency that comes only from treating such patients in adequate volume, it may be difficult to amass such expertise in any given hospital, especially for the care of neonates and young children [51].

10 Anticoagulant Therapy

Anticoagulant therapy reduces the risk of thrombus extension and embolism while allowing the natural fibrinolytic mechanism to gradually reduce the size of the clot. Duration of anticoagulant therapy is mainly based on adult studies. If a causative factor can be identified and is reversible (e.g. removal of a central venous catheter), one may consider a shorter course of anticoagulation [49]. If, however, causative factors cannot be removed, for example in the setting of an underlying thrombophilia, then a longer course of anticoagulation may be indicated [52]. Similarly, resolution of the thrombus on imaging along with normalization of D-dimer and factor VIII levels favors a shorter course of anticoagulant therapy [28, 53]. On the other hand, if VTE recurs, then this warrants long term anticoagulation.

Guidelines from the American College of Chest Physicians (AACP), which many clinicians consider as generally-accepted standard of care for patients with VTE, call for anticoagulation with heparin or low molecular weight heparin followed by a vitamin K antagonist for three months for a first-time VTE if the causative factor can be identified and resolved. Similarly, six to twelve months of

anticoagulation are recommended for an unprovoked VTE. For recurrent VTEs, the recommended duration of anticoagulation is three months for VTE when a causative factor can be identified and resolved and lifelong for idiopathic, unprovoked VTE [54].

11 Anticoagulant Medications

Unfractionated heparin (UFH) acts predominantly by enhancing the inhibitory action of antithrombin on thrombin, factors Xa, IXa and XIa. UFH may be administered subcutaneously or intravenously and has a relatively short half-life (30–60 min), particularly with IV administration, which makes anticoagulation quickly reversible should a bleeding complication, trauma or need for surgery develop. The anticoagulant activity of heparin can be monitored using the activated partial thromboplastin time (aPTT) or the anti- activated factor X activity (anti-Xa). Pediatric therapeutic ranges, for the most part, are extrapolated from adult VTE studies. Since aPTTs can be higher at baseline for infants, it is difficult to define a therapeutic range for heparin in pediatrics based solely on aPTT [55]. For this reason, and because the physiologic effects of Xa inhibition are consistent across the pediatric age range, the anti-Xa test is widely considered to be a more reliable test to monitor heparin anticoagulation level in infants and children. In general, the dose of UFH should be titrated to establish an anti-Xa therapeutic range of 0.35–0.7 U/ml. Heparin works in conjunction with antithrombin, and will therefore have greatest anticoagulant effect when antithrombin levels are normal. Newborns have physiologically lower antithrombin levels and therefore may require higher UFH doses. The starting therapeutic dose for UFH, when used as a continuous infusion is 28 units/kg for neonates and 18–20 units/kg for children older than 1 year. The dose should be titrated to the desired level of anticoagulation. Bolus infusions of 75–100 U/kg UFH shortens the time to achieving the therapeutic range but may increase risk of bleeding especially in premature newborns [56]. The main risk associated with heparin use is bleeding, with estimates of major bleeding varying between 1.5 and 24 %, depending on the population and clinical setting [57]. Heparin-induced thrombocytopenia (HIT), an acquired antibody-targeted reaction against heparin that activates platelets and paradoxically increases thrombotic risk, is one of the most serious consequences of UFH therapy [58, 59]. Nonetheless, the risk of developing HIT is relatively low (1–2.3 %). Long-term heparin use may be associated with risk of bone calcium wasting and osteoporosis, but only a few cases have been reported in children. If reversal of heparinization is required quicker than can be achieved by simply discontinuing UFH, protamine can be used. Protamine is thought to antagonize heparin's anti-IIa activity but not its anti-Xa activity.

Low molecular weight heparin (LMWH), like UFH, acts through the antithrombin pathway, but exerts a comparatively stronger inhibitory effect on activated factor X (Xa). Enoxaparin, the most commonly used LMWH in children, can be administered subcutaneously and has a more predictable dose–response relationship than UFH [60]. LMWH also has a longer half-life than UFH, roughly 12 h, allowing less frequent dosing but at the cost of less reversibility [61]. LMWH is cleared predominantly renally, therefore it should be used with caution in individuals with renal insufficiency. The anticoagulant activity of LMWH is usually measured by anti-Xa activity 3–5 h after subcutaneous administration. The therapeutic range for anticoagulation is generally between 0.5 and 1 U/ml and less for thrombosis prophylaxis (typically 0.25–0.5 U/ml). The beginning dose for enoxaparin is usually 1 mg/kg administered subcutaneously every 12 h. Because of enhanced clearance of the drug, newborns generally require larger doses per kilogram, so for infants the starting enoxaparin dose is typically 1.5 mg/kg administered subcutaneously every 12 h. Obese children may require less enoxaparin per kg. of body weight to achieve targeted anticoagulation levels [62]. Anti-Xa levels should be checked after the second or third dose, and LMWH dosing titrated to the targeted

anti-Xa level [57]. Once therapeutic levels are achieved, periodic monitoring of anti-Xa activity is recommended, especially in young infants, who experience rapid weight gain and changing LMWH requirements per kilogram of body weight. The main risk of LMWH therapy is bleeding, with different authors reporting rates of major bleeding between 2.9 and 5 %. The anticoagulant activity of LMWH, like that of UFH, can be partially reversed using protamine. Osteoporosis and HIT are thought to be less frequent complications of LMWH than of UFH, but their incidence and severity in children remain uncharacterized [60].

Vitamin K antagonists antagonize the post-translational γ-carboxylation reaction needed for the activation of coagulation factors II, VII, IX and X. Importantly, γ-carboxylation is also needed for the synthesis of functional protein C and S which have a shorter half-life than that of II, IX or X [63]. Thus, vitamin K antagonists are administered along with heparin or LMWH for 4–6 days until a therapeutic INR is achieved; this approach prevents the development of a transient hypercoagulable state through the inhibition of protein C and protein S activity [57]. The most commonly used vitamin K antagonist is warfarin (Coumadin©). In children, starting doses of warfarin are usually in the range of 0.1 mg/kg. day, but therapeutic doses must be titrated to desired effect. Since warfarin antagonizes vitamin K activity, its anticoagulant effects are susceptible to dietary vitamin K intake. For this reason, patients should be advised not to alter their dietary intake of vitamin K rich foods (e.g. greens, leafy vegetables) once an appropriate therapeutic level of warfarin has been achieved [64]. Anticoagulant activity is measured by the prothrombin time (PT) / international normalized ration (INR), which is standardized between laboratories. The therapeutic range for most patients, extrapolated from adult studies, is an INR between 2 and 3, higher in certain high risk situations like artificial heart valves. In general, warfarin is not used in newborns and young infants because of difficulty in keeping such patients in the therapeutic range. Newborns have physiologically low levels of vitamin K dependent factors, they may have variable intake of vitamin K (low in breast milk, high in formula and in total parenteral infusions), and blood sampling for INR monitoring is often difficult for premature babies and low birth weight infants. Furthermore, there are no liquid formulations for warfarin, which challenges administration for very young patients. As with other anticoagulants, the main risk of warfarin therapy is bleeding, with major bleeding risk estimated at around 3 % per patient per year. Proper and continued education of the patient and family in managing of this medication and activity restrictions are important ways to minimize bleeding risk. Given the variations in the vitamin K levels, it is important to monitor INRs at regular intervals) while patients are on warfarin. Should bleeding or trauma occur, warfarin's anticoagulant effects may be reversed using vitamin K, fresh frozen plasma infusions, prothrombin protein concentrates or recombinant activated factor VII. Lastly, warfarin is well-known teratogen and is contraindicated in pregnancy. For this reason, teenage girls that must be on warfarin should receive appropriate counseling and ideally be on contraceptive therapy.

12 Newer Anticoagulants

Because of the challenges that come with heparin and warfarin therapy, the use of other anticoagulants has become more prevalent in children. Argatroban is a direct thrombin inhibitor approved for pediatric use in the United States for treatment of patients with heparin induced thrombocytopenia (HIT). It is administered as a continuous IV infusion and its anticoagulant activity monitored with the aPTT (therapeutic target aPTT 1.5–3 times normal); the steady state is reached after 2 h. of intravenous infusion. Argatroban is cleared by the liver and therefore should be used with caution in patients with hepatic dysfunction [65].

The direct thrombin inhibitor dabigatran is approved for adult use, and the pediatric experience is limited to small case series. A phase I

clinical trial (NCT00844415) done in adolescents showed that drug was well tolerated, with no major bleeding events; there are ongoing phase 2 and phase 3 pediatric clinical trials [66, 67].

Fondaparinux is a direct factor Xa inhibitor which does not interact with platelets and therefore does not trigger HIT [68, 69]. It is administered subcutaneously at daily intervals, it was studied in children in a dose finding and safety study [70] as well as in a cohort of 34 patients [71], showing a good safety and efficacy record. This drug is not yet approved for pediatric use in the US. The direct anti-Xa inhibitors rivaroxaban and apixaban are widely used in adults, however the pediatric experience is limited to a few case reports [72] There are several ongoing clinical trials to determine their safety and efficacy in children. Finally, dalteparin, a low molecular weight heparin used in adults, has been studied in children and was found to successfully achieve therapeutic anti-Xa levels with a favorable safety profile [73].

13 Thrombolysis

Thrombolysis is a more aggressive medical intervention aimed at clot dissolution and relieving vascular obstruction in a short period of time by activating the fibrinolytic system [47]. Thrombolysis is used in life- or limb-threatening thrombosis, when timing is of the essence. In addition, there is increasing interest in using thrombolysis for VTE with the goal of reducing the incidence of debilitating post-thrombotic syndrome [74]. The thrombolytic agent of choice in the pediatric population is intravenous tissue plasminogen activator (tPA) which can be administered systemically or targeted to the clot via catheter-directed infusion. AACP guidelines suggest tPA dosing of 0.1–0.6 mg/kg for 6 h for systemic thrombolysis, though alternative regimens involving lower doses and longer exposure times (0.01–0.06 mg/kg.hr for 4–48 h) have also been used. Catheter-directed thrombolysis uses lower doses of tPA delivered in the proximity of the clot for various length of time but is limited by the small diameter of blood vessels in very young children [75]. As such, catheter-directed thrombolysis may not be feasible for very young infants and children. Anticoagulation with low-dose heparin may be used concurrently with thrombolysis to prevent clot propagation and embolization.

Bleeding is the main risk of thrombolysis, with risk of major bleeding (requiring blood transfusion or medical intervention) varying considerably between trials perhaps due to the range of patient populations and thrombolytic regimens used in pediatric case series. Results of a meta-analysis of 413 cases of children receiving thrombolytic therapy placed the incidence of major hemorrhage at 15 %. Thus, it is important to understand bleeding risk factors before beginning thrombolysis. At a minimum, a platelet count, fibrinogen, PT and aPTT be determined and replacement therapy (FFP) provided to ensure adequate hemostasis before beginning thrombolysis. Furthermore, a head ultrasound should be done in premature babies and infants to rule out a pre-existing intracranial hemorrhage. Contraindications for thrombolysis based on guidelines from the International Society of Thrombosis and Haemostasis include:

- active, uncontrolled bleeding
- hypofibrinogenemia
- intractable thrombocytopenia
- prematurity (less than 32 weeks gestation)
- recent severe hypoxic event
- recent surgery or hemorrhage
- seizures within the previous 2 days
- sepsis

Because of the rarity of thrombolysis in the pediatric age range, there have been no randomized, controlled trials in children on the safety and efficacy of thrombolytic therapy. Rather, small numbers of children have been treated in scattered pediatric hospitals [34, 76–78], with the availability of thrombolysis (especially catheter-directed thrombolysis) dependent on the experience, availability and expertise of a given institution's staff and facilities [49]. Clearly, a risk-benefit assessment

must be made on a case-by-case basis when considering thrombolysis in children.

14 Inferior Vena Cava (IVC) Filters

IVC filters, designed to trap emboli that have broken loose from DVTs of the lower extremities, have been used in adults since the 1970s [79]. There are several report of their use in children, with most being placed in patients at risk for recurrent DVT and PE who may or may not be good candidates for long-term anticoagulation [80]. IVC filters have also been used for recurrent DVT despite anticoagulation therapy as well as for PE prevention during endovascular thrombolysis [81]. Because of anatomic restrictions, IVC filter use is generally limited to children larger than 10 kg. The main risk of IVC filters is thrombus formation in and around the filter, however, they can also migrate or even perforate the IVC. Long-term risks of IVC filters in the pediatric patients remain unknown. As a result, IVC filters are generally removed as soon as risk of PE decreases. Different device manufacturers recommend their removal within weeks to months after initial placement.

14.1 Thrombectomy

Surgical removal of a thrombus is generally reserved for life-threatening VTEs such as large PEs or occlusion of vascular shunts after cardiac surgery. There are no specific guidelines for surgical thrombectomy in children and procedures have a significant rate of complications, including recurrent thrombosis and vascular damage [82, 83]. Risks and benefits should be carefully evaluated on a case by case basis.

15 VTE Prophylaxis

VTE is a relatively common complication of hospitalized adult patients is a common contributor to hospital deaths. As pediatric inpatient units find themselves increasingly caring for children with complicated medical issues and more adult-type co-morbidities (e.g. obesity), VTE awareness is becoming increasingly important in pediatrics [84, 85]. Incidences of VTE and PE have both been increasing in pediatric patients (Fig. 3), prompting increasing attention toward VTE prophylaxis in hospitalized children. Although no consensus guidelines exist, VTE prophylaxis should be considered for patients with several known VTE risk factors (Table 1), especially those undergoing prolonged immobilization, after certain surgical procedures, and in adolescents, whose risk profile resembles that of adults [86]. VTE prophylaxis combines physical as well as pharmacologic approaches. Physical methods are aimed at reducing venostasis associated with bedrest and include, sequential compression devices or compression stockings. Medical VTE prophylaxis generally involves the use of anticoagulants [67]. LMWH is the most

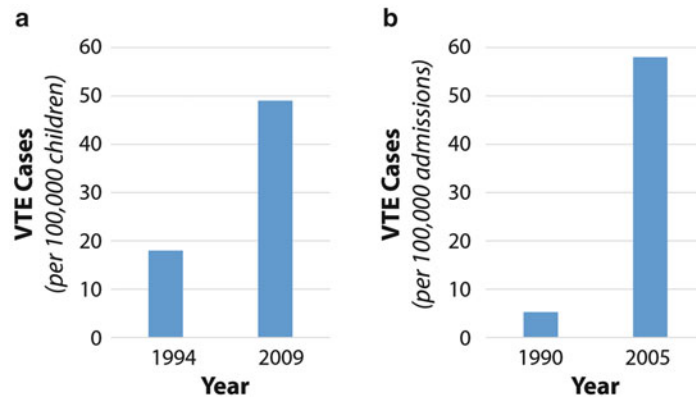

Fig. 3 Increasing incidence of VTE. (**a**) All children, (**b**) hospitalized children [5, 6]

commonly used anticoagulant for short-term prophylaxis. LMWH VTE prophylactic doses are typically half of the ones used for VTE treatment (e.g. 0.5 mg/ kg enoxaparin subcutaneously every 12 h), aiming for anti-Xa levels in the 0.25–0.5 range.

16 Infancy

Circulating levels of pro- and anti-coagulant factors as well as components of the fibrinolytic system are found in lower quantities in infants than for older children and adults [23]. Apparently these differences do not predispose toward bleeding or clotting because normal, healthy, newborns rarely develop bleeding or thrombosis even if they are carriers of inherited thrombophilic traits. Rather, 90 % of cases of neonatal thrombosis occur in the context of central venous catheter placement [87]. In addition, VTE may be favored by medical conditions that necessitated placement of central lines such as neonatal asphyxia, sepsis, dehydration, maternal diabetes and congenital heart disease. Unprovoked thromboses are rare in infants, The most common unprovoked neonatal VTE is renal vein thrombosis which can be associated with inherited thrombophilia [88]. Therapeutically, newborns require higher doses of heparin per kilogram in order to achieve adequate levels of anticoagulation. Similarly, newborns have low plasminogen levels, necessitating plasminogen supplementation or FFP to optimize tPA-based thrombolytic therapy [76]. However, infants are at risk of intraventricular hemorrhages because of the fragility of the germinal matrix, especially among premature newborns. For this reason, baseline brain imaging (e.g. head ultrasound) should be considered prior to the start of anticoagulant or thrombolytic therapy in order to determine how aggressive to be therapeutically.

17 Central Venous Catheter (CVC) Use in Children

CVCs are commonly used in the care of very ill children and in patients with complex medical conditions requiring frequent blood draws or medication infusions [89]. CVCs are a major VTE risk factor in children of all ages. In fact, CVCs are present in about 90 % of newborns with VTE and in more than 50 % of children with VTE [89]. Catheter-related thrombosis can occur at any point after placement.. CVC-related clots can begin with the deposition of a fibrin sheath around the catheter tip, leading to catheter malfunction. As CVC-related clots progress, there is thrombus deposition that adheres to both the catheter and the venous wall and may produce vascular obstruction, pulmonary embolism, and even paradoxical embolism and stroke in patients with a right to left or bidirectional shunt. Furthermore, bacteria and other microorganisms can sequester themselves from the immune system when associated with a clot, therefore the presence of a thrombus increases risk of bacteremia and line infections. CVC-related thrombi may also lead to long-term morbidity in the form of post-thrombotic syndrome. Incidence of catheter-related thrombosis varies between studies, depending on diagnostic approach, type of central line and the patient population studied. Symptomatic VTE rates range between 2.6 and 5 % per patient per year while rates of VTE diagnosed through imaging techniques – venogram, ultrasound, magnetic resonance venogram – may approach 40 % or more [90]. Risk factors for catheter related thrombosis in children are not well defined. Route of administration may be relevant. Percutaneous inserted catheters may have higher VTE risk than surgically-inserted ones, though this is controversial [91]. Anatomic location of central lines clearly plays a role. Thus, in infants, femoral catheters have a higher incidence of VTE as compared to lines in other locations. Size of the line also matters; larger catheters appear to increase risk of VTE compared with smaller ones. The duration of catheter use is also important, with VTE risk increasing the longer a line remains in place [92]. Co-morbidities are clearly important. Children with complex conditions are more likely to develop catheter related VTE than less ill counterparts [93]. Certain medication use (e.g. L-asparaginase therapy for acute lymphoblastic leukemia which depletes anticoagulation

factors by inhibiting protein synthesis) also increases risk [90, 94]. Lastly, inherited thrombophilias may independently raise CVC-related thrombotic risk [95].

CVC-related thrombosis treatment generally involves removal of the catheter, when possible, either immediately or after 4–5 days of anticoagulant therapy. If this is not possible due to the need for vascular access, ACCP guidelines suggest anticoagulation in the therapeutic range for 3 months followed by anticoagulation in the prophylactic range until the catheter can be removed. CBC-related thrombi should be monitored with imaging studies at periodic intervals. As with any intervention aimed at manipulation of the coagulation or anticoagulation cascade, risk of vascular obstruction and embolism should be balanced against risk of bleeding with anticoagulation. Various prophylactic interventions have been used in an attempt to reduce rates of catheter related VTE including heparin-bonded catheters, heparin infusions, oral warfarin and antithrombin concentrates, however none reduced the thrombotic risk in a statistically-meaningful manner [96]. As a result, aside from CVCs placed in newborns which should be flushed with continuous low-dose UFH (0.5 U/kg/h), ACCP guidelines do not support the use of CVC-related chemoprophylaxis in children due to paucity of data and risk of bleeding.

18 Pediatric Malignancy

Armand Trousseau noted an association between thrombosis and cancer more than 150 years ago. And "Trousseau's syndrome" as it has been termed, refers to repeated episodes of thrombosis that occur in the setting of malignancy, albeit most often in association with adult type malignancies (e.g. gastric or pancreatic carcinomas) rather than the typical hematologic, sarcomatous and CNS tumors of pediatrics [97]. Nonetheless, pediatric oncology patients are at higher risk of thrombosis than are children without malignancy [98]. Incidence of symptomatic VTE in children with cancer ranges from 2 to 16 % depending on the population studied and the diagnostic approach used. Asymptomatic VTEs may occur in up to 40 % of children with cancer. Most pediatric oncology-related VTEs are located in the upper and lower extremities and incidence of associated PE can be as high as 20 %. Main risk factors for this population include the presence of a central venous line – in up to 75 % of cases – and the use of certain chemotherapy agents – most particularly L-asparaginase. Older patients, patients with leukemia and sarcomas, presence of an intrathoracic mass and inherited thrombophilia all increase risk of VTE [99, 100]. Children with ALL have an increased risk of cerebral venous thrombosis. There are no guidelines for DVT prophylaxis in pediatric oncology patients. Several interventions such as LMWH, antithrombin supplementation, cryoprecipitate/ fresh frozen plasma supplementation and low dose warfarin have been evaluated in small series, however none showed a clear benefit in reducing the incidence of VTE. Clearly further studies are needed to clarify risks and therapeutic benefits in this at-risk population.

19 Pulmonary Embolism

Pulmonary embolism (PE) is uncommon in the pediatric population. The incidence data, derived mostly form institutional or regional registries, shows significant variations from 0.86 per 10,000 admissions [101] to 5.7 per 10,000 [102]. It is likely that the incidence of PE increased over the last two decades as a result of an increased number of sick pediatric patients at risk for PE as well as better imaging techniques.

Most of the pediatric PEs occur in the context of a serious illness, including congenital heart disease, malignancy, prematurity or nephrotic syndrome. Up to one third of patients diagnosed with PE have a central venous catheter in place at the time of diagnosis [102]. Inherited thrombophilia is more common in adolescents with PE compared to younger children. In contrast with the adults, PE secondary to trauma or surgery is less common, while idiopathic PE

occurs in only about 5 % of children, compared to approximately 30 % of adults.

PEs are associated with a clinically apparent thrombosis at another location in 60–70 % of the cases [102, 103] The DVTs may involve the superior vena cava tributaries in 20–60 % of cases [103, 104], in contrast with adults with PE who tend to have predominantly lower extremity DVTs.

The clinical symptoms most commonly include shortness of breath, pleuritic chest pain, hemoptysis and cough. The D-Dimer is frequently elevated, though 14–40 % of pediatric PE s have a normal D Dimer level [102, 105]. No clinical prediction score, similar to the Wells score used in adults, has been validated in children; this may be due to the high false negative rate of the D- Dimer and the fact that some of the symptoms of PE may be masked by the ones of the underlying illness.

The most commonly used imaging modality in diagnosis pediatric PE is the CT pulmonary angiography, which based on several retrospective studies yields a false positive rate of 9.3 % and a false negative rate of 2.4 % [106]. Magnetic resonance pulmonary angiography enables evaluation of the pulmonary arteries without using radiation. While adult data shows a high specificity and sensitivity of this modality, no pediatric data is available. The study has a long examination time, this the need for anesthesia in young children and it is impractical for critically ill children. Echography may visualize thrombi in the heart and central pulmonary arteries though its role in evaluation of PE is to identify signs of hemodynamic instability like right ventricular strain that may guide the choice of therapy.

The treatment of PE is based on the results of the adult clinical trials and few pediatric studies. It includes anticoagulant therapy with unfractionated heparin, LMWH and warfarin for hemodynamically stable PE with strong consideration for thrombolysis for hemodynamically unstable PE without contraindication for this modality. There is no consensus over the route of administration of thrombolytic medication – systemic vs catheter directed.

20 Conclusions

VTE has become more and more common in the pediatric population, primarily as a result of increased complexity of medical treatments and the prevalence of co-morbidities such as obesity [107]. The use of central venous catheters has steadily increased over the past decades. The factors that lead to catheter related thrombosis as well as the interventions required to reduce this complication are still a matter of debate. Larger studies are needed to determine the best interventions for reducing the risk of catheter related thrombosis. Most pediatric VTEs have an identifiable cause, with central venous catheters being the single most important risk factor. Many treatment algorithms are based on data from adult studies, and while general principles learned from adults may usually be applied, some conclusions cannot always be extrapolated to children, particularly in very young patients such as newborns or premature infants. As newer anticoagulant and thrombolytic therapies become more available, multicenter studies are needed to define their risks and benefits in the pediatric population.

Conflict of Interest Neither author discloses any conflicts of interest or pertinent financial relationships related to the topics discussed in this review.

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Deep Vein Thrombosis in Intensive Care

Maria Boddi and Adriano Peris

Abstract

Venous thromboembolism (VTE) which includes deep vein thrombosis (DVT) and pulmonary embolism (PE) is a severe complication in critically ill patients generally affected by multiorgan disfunction associated with immobilization also prolonged.

Nowadays, VTE prophylaxis is included in the requirements of hospital accreditation and evaluation of the maintenance of standards of quality of care. ICU patients are characterized by a dynamic day-to-day variation both of thromboembolic that bleeding risk and DVT incidence in presence of thromboprophylaxis ranges between 5 and 15 %.

Patient-centered methods for the assessment of both thrombotic and bleeding risk are recommended because pre-existent factors to ICU admission, diagnosis, emerging syndromes, invasive procedures and pharmacological treatments daily induce important changes in clinical condition.

General consensus currently establishes use of heparin in pharmacological prophylaxis at the time of admission to the ICU and the temporary suspension of heparin in patients with active bleeding or severe (<50,000/cc) thrombocytopenia. Individualized thromboprophylaxis regimens were proposed but there is still no consensus based on evidence.

DVT diagnosis is not clinical but imaging-based and in each ICU data on DVT incidence (DVT diagnosed 72 h after ICU admission) should be obtained by weekly ultrasound screening standardized for the anatomical sites of compression used, taking into account the persistence of DVT-risk throughout ICU stay. A role for mechanical thromboprophylaxis by elastic stockings or pneumatic compression was reported but no general consensus was reached about its use at the best. Much work has to be done but ICU remain the last frontier for VTE prophylaxis.

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Deep vein thrombosis • Thromboembolism • Intensive care unit • Critical care • Thromboprophylaxis • Heparin • Ultrasonography • Thrombotic risk • Haemorrhagic risk

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a devastating complication for critical patients who have a baseline decrease in cardiopulmonary reserve. In six studies performed between 1978 and 2000 in medical-surgical intensive care unit (ICU) setting, autoptic diagnosis of pulmonary embolism was made in 13 (7–23) % of the 463 patients who died in ICU [1, 2] and all authors agreed on the fact that clinical suspicion was mentioned in a low minority. ICU patients with DVT have a longer duration of mechanical ventilation, ICU and hospital stay than patients without DVT even when DVT is not complicated (Fig. 1) [3, 4]. Four randomized controlled trials performed between 1981 and 2000 demonstrated the efficacy of unfractionated heparin (UH) or low molecular weight heparin (LMWH) thromboprophylaxis in ICU patients [5–8] and the 9th edition of the American College of Chest Physician's (ACCP) Evidence-Based Clinical Practice Guidelines recommends prophylaxis of ICU patients with LMWH over no prophylaxis [9]. Nowadays venous thromboembolism (VTE) prophylaxis is incorporated into hospital accreditation and quality of care metrics all around the world.

The issue of "thromboembolism in intensive care units" deserves dedicated treatment because of some peculiar characteristics of critical patients. In this perspective we synthesize the most relevant: (**a**) critical patients are a heterogeneous population for thrombotic risk: in patients not receiving thromboprophylaxis was reported a DVT prevalence ranging between 10 and 80 % [10] that was usually observed in patients with major trauma or spinal cord injury, the two subpopulations at the highest risk of thrombosis. In medical-surgical ICU settings a failure rate of prophylaxis as high as 5–15 % was recently shown [11]; (**b**) in ICU DVT can rarely be diagnosed through clinical data: patients very often cannot communicate symptoms due to their underlying conditions, pharmacotherapy and mechanical ventilation. Signs associated with DVT such as oedema are common in the ICU setting and attributable to many other factors. Diagnosis of DVT needs imaging i.e. ultrasound screening that must be scheduled so that the cost/benefit ratio could be sustainable. (**c**) The individual risk stratification for DVT in ICU setting is difficult: risk assessment models for DVT diagnosis that are used for out-patients (Wells score) [12], hospitalized medical (Padua score) [13], surgical (Caprini modified score) [14] or trauma patients cannot be applied to critically ill patients. Pretest probability scores developed and validated outside ICU for diagnosis of pulmonary embolism (PE) do not correlated with clinically suspected PE in ICU [15]. In ICU patients not only risk factors such as personal or family history of VET or illness score severity at admission, but also time dependent factors due to newly acquired pathologies, iatrogen interventions or therapies concur to determine thrombotic risk which is dynamic and can change from day to day.; (**d**) ICU patients can also be at risk of major bleeding [16]. The balance between thrombotic and haemorrhagic risk must be evaluated daily, as it can change suddenly. In medical-surgical ICU patients on thromboprophylaxis the incidence of major bleeding was 6 % and was associated with a twofold increase of ICU and hospital mortality [17]. Dedicated strategies to improve compliance with thromboprophylaxis such as programs of continued education for physicians and nurses and /or

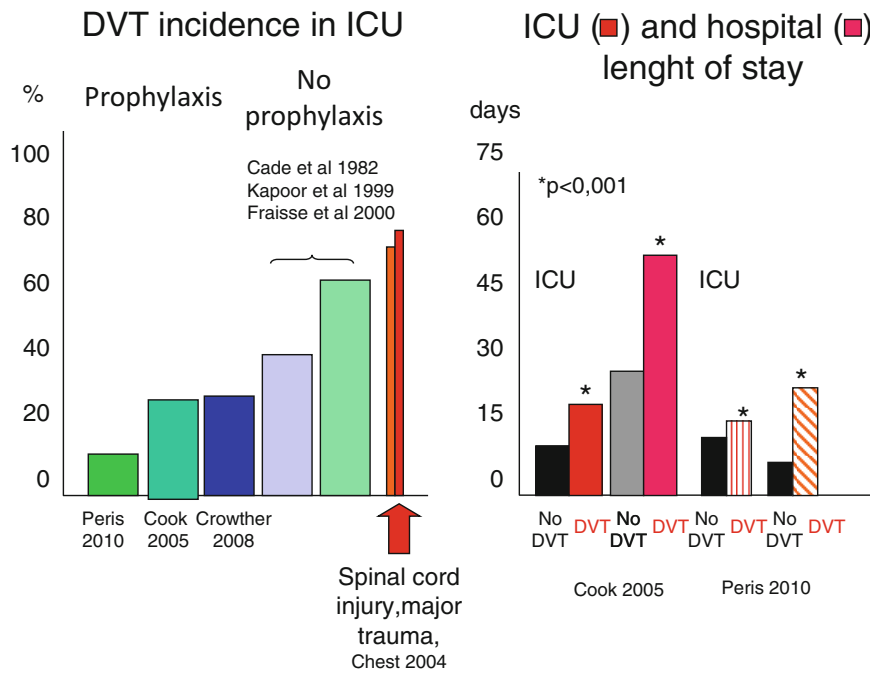

Fig. 1 **Panel A**:schematic report of changes in DVT incidence in ICU after introduction of heparin prophylaxis. **Panel B** ICU patients with DVT have a longer duration of mechanical ventilation, ICU and hospital stay than patients without DVT even when DVT is not complicated [3, 4]

electronic order sets and reminders are strongly recommended in ICU [11].

The goal of this review is to offer synthetic and critical knowledge on what we believe to be the main certainties and the main doubts regarding "DVT in ICU setting".

1 How Many Deep Vein Thrombosis in ICU?

When the "DVT problem in ICU" is investigated, data must be separately analyzed according to (a) the evaluation of DVT clinically suspected or detected by ultrasound surveillance, (b) the use or not of thromboprophylaxis in ICU patients (c) the evaluation of spontaneous and/or CVC-related thrombosis. We remind that catheter-related DVT must be considered those DVT which occur within 72 h from CVC insertion. The difference between DVT prevalence and incidence is also to be taken into account.

2 The Difference Between Prevalence and Incidence of DVT in ICU

Cook et al [3] well describe the difference between prevalence and incidence of DVT in ICU: prevalence takes into account those DVTs that are diagnosed within 48–72 h from ICU admission and that started before admission either during the preceding hospital stay or from trauma or individual thrombotic risk. Data on DVT prevalence are obtainable only when an ultrasound exam for DVT is scheduled within 48–72 h from admission. DVT prevalence depends on factors preceding ICU admission and is independent of ICU quality of care.

DVT incidence in ICU shows how many DVTs are diagnosed 72 h after ICU admission and is the result of the imbalance between prothrombotic stimuli and antithrombotic defence that can occur any time during ICU stay. Indeed, observational studies showed that

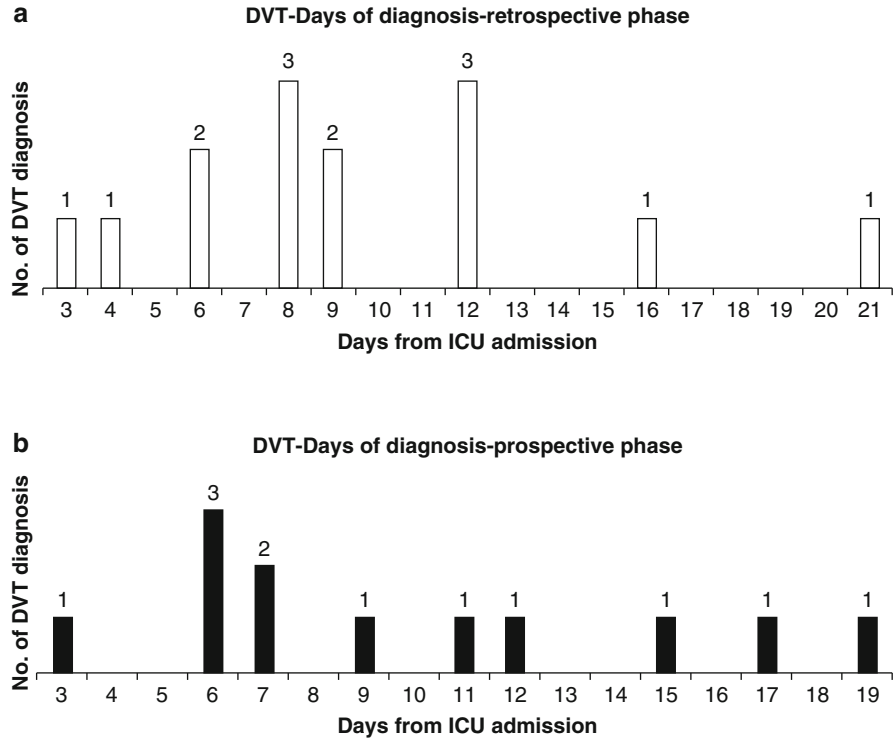

Fig. 2 New-onset DVT can occur at every day independently of the length of ICU stay [4]. During the prospective phase of the study tromboprophylaxis was optimized and DVT incidence decreased from 11 to 4 %, but no difference was observed on the time of occurrence between the prospective and retrospective phase

new-onset DVT can occur at every day independently of the length of ICU stay [4]. No ICU patient can be considered free from risk of DVT (Fig. 2).

3 Criticism About Clinical and Ultrasound Diagnosis of DVT in ICU

(**a**) In the ICU setting, the clinical suspicion of DVT is made difficult by the fact that patients with impaired consciousness through the effect of drugs or simply through their conditions often cannot refer symptoms. Signs that are part of risk assessment models for DVT in hospitalized or out-patients are therefore not easily detectable in ICU patients. Physical examination proved to have no diagnostic utility for DVT in medical-surgical patients [18]. Venous compression ultrasonography (CUS) is the most accurate non invasive test for DVT diagnosis [19, 20], even if CUS has reduced sensitivity in patients with minimal symptoms [21, 22]. Concern about underdiagnosed DVT in the medical-surgical ICU setting is highlighted by studies showing that 10 % [16, 17] to 100 % [23] of DVTs identified by ultrasound screening were clinically unsuspected. Screening test is not recommended by guidelines for DVT prevention [24], but given the common lack of clinical symptoms and signs for DVT in critical patients, DVT diagnosis can only be made by ultrasound screening that allows strict monitoring of the changes in DVT incidence related to the different interventions adopted for prophylaxis improvement. In our opinion a scheduled ultrasound screening program would increase awareness for the need of daily assessment of individual DVT risk burden. Moreover, nowadays in the ICU setting ultrasound is part of the daily clinical assessment of patients and its use for DVT ultrasound screening

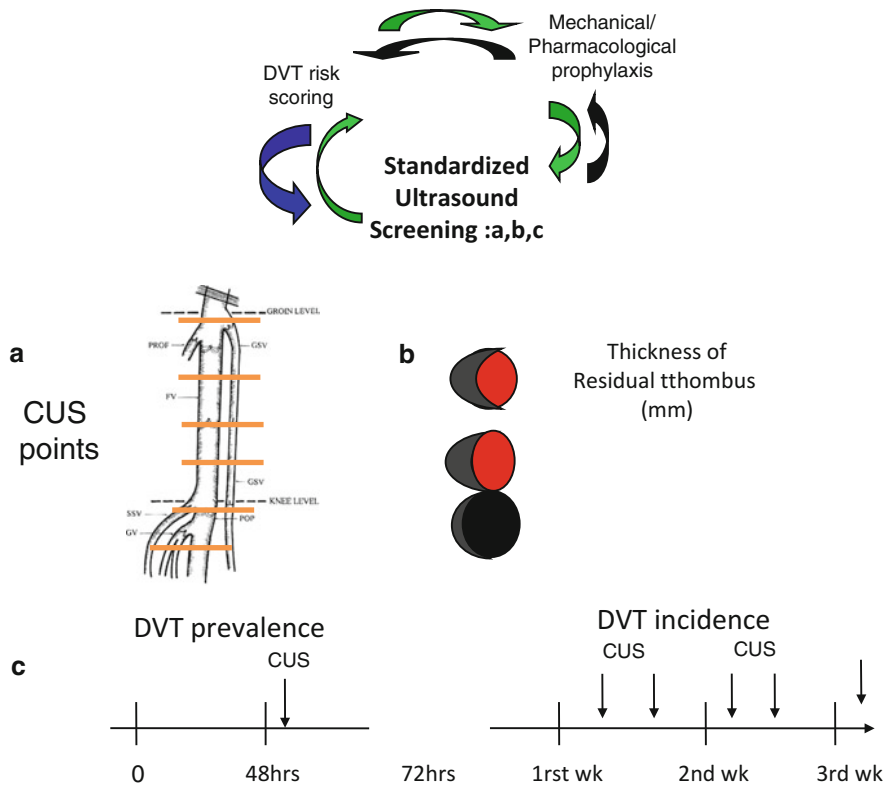

Fig. 3 Standardization of ultrasound exams for the diagnosis of DVT is a key point and is based on (**a**) the definition of anatomical points on which compressive ultrasound is to be performed, (**b**) the measurement at of the residual thrombus in mm at each CUS point and (**c**) the scheduled time of ultrasound exams during ICU stay

does not represent a supplementary cost in term of human and tool resources. Finally, we strongly encourage the use of a standard technique for Doppler ultrasound exam through (a) the application of ultrasound compression at six fixed locations from the popliteal trifurcation to the common femoral vein, (b) the measurement of residual thrombus in mm in short axis at each of the CUS fixed locations and (c) scheduled ultrasound test once or twice/a week till discharge (Fig. 3). A standardized methodology would permit optimization of DVT follow-up [3, 4] not only during ICU and hospital stay but also after hospital discharge.

It is to be underlined that DVT frequency varies among different studies because of heterogeneity in populations enrolled but most importantly because of the methods of surveillance used and when ultrasound screening is used, because of the frequency of ultrasound test. It is well known that an increased number of ultrasound test in a week, results in a higher number of diagnosed DVT [25]. This means that only studies reporting similar frequency of ultrasound screening are comparable. According to data reported by Cook et al [3] the best risk/benefit ratio is obtained when ultrasound screening is performed twice a week; ultrasound screening carried out less than once a week is therefore unadvisable for a correct control of DVT prophylaxis. When ultrasound screening is scheduled once or twice a week, an incidence of 5–10 % is reported in medical-surgical ICU [3, 4, 26].

4 Does Differentiating Between Symptomatic and Asymptomatic DVT in ICU Have Sence?

Early studies reported that symptomatic or asymptomatic DVT without thromboprophylaxis

develops in 13–31 % of medical –surgical critically ill patients [27], whereas in ICU patients receiving LMWH the frequency of DVT at any site ranged between 5.1 and 15.5 % [11]. Due to the extreme difficulty in clinical diagnosis already cited many times, we believe that a reliable distinction between symptomatic and asymptomatic DVT is impossible in ICU settings and that the need for ultrasound screening is absolute when the issue "DVT in ICU" is investigated.

5 What About CVC-Related Thrombosis?

Central venous catheter (CVC)-related DVTs are to be considered those diagnosed within 72 h of CVC insertion. CVCs are included among time dependent acquired DVT risk factors in ICU in all dedicated studies, but some issues must be considered that differentiate CVC-related DVT from idiopathic DVT. The majority of studies on DVT in ICU investigated DVT of the lower limbs, whereas CVC-related thromboses are located in the veins of the upper limbs [28]. The veins of upper limbs are usually not evaluated during ultrasound screening except under specific clinical questions. In patients enrolled in the PROTECT study the incidence of non leg DVT diagnosed in patients with clinical signs or symptoms that prompted ultrasound screening was 2 % [29]. Most importantly, CVC related DVT are mainly due to endothelial damage and in the pathophysiology of CVC-related DVT the role of other risk factors can be different when compared to the role played in idiopathic thrombosis. This is very true when we consider the cannula-related DVT during Extra Corporeal Membrane Oxygenation (ECMO) treatment: the cannulas used in ECMO, expecially the venous cannulas, have a diameter very close to that of the affected vessels with a marked increase in the endothelial damage [30]. Considering all the above points, we believe that CVC-related DVT in ICU deserves dedicated treatment that is beyond the goals of this review.

6 What Is Important to Know About DVT Incidence in ICU?

Data on DVT frequency are extensively reported in literature and according to recent trials DVT incidence in ICU patients under thromboprophylaxis ranges between 5 and 15 %; this means that if in an ICU DVT incidence is above 15 %, an optimization of thromboprophylaxis is called for. Further, it is no longer acceptable for an ICU not to record and not to report the relative data on DVT incidence. A retrospective investigation of what has taken place in the past is necessary in order to form the basis for creating a quality improvement program for the future [4, 26].

6.1 Risk Factors for DVT in ICU

Recognized risk factors for DVT are related to one or more elements of Virchow's triad (flow stasis, vessel injury and hypercoagulability). In ICU patients, flow stasis plays a major role because of immobility due to trauma, use of sedatives and neuromuscular block that markedly decreases the velocity of limb venous blood flow [31, 32]. In addition, mechanical ventilation and abdominal hypertension, found in many situations, decrease venous return of blood to the heart and can further facilitate the stasis of venous blood in veins of the lower limbs [33] Vessel injuries are mainly due to catheter insertion in central and peripheral veins and/or surgical interventions. Finally, hypercoagulability can be due to sepsis, renal failure or hemodynamic impairment with administration of vasoactive drugs. Under such pathophysiological conditions, the occurrence of additional DVT risk factors during ICU stay added to risk factors present at admission can precipitate thrombosis.

Figure 4 shows that according to the triad of Virchow in ICU setting, several factors occur contemporarily in each patient that facilitate flow stasis and/or endothelial damage and/or hypercoagulabity. We should wonder why not

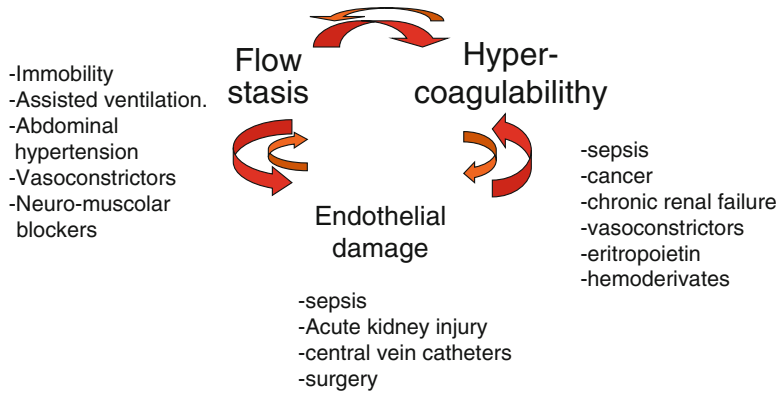

Fig. 4 Virchow's triad in ICU. Schematic synthesis of different factors that can concur to lower the thrombotic threshold in ICU patients because of their physio-pathological role/s on each of the components of the Virchow's triad

all ICU patients develop DVT. Really, humans are endowed with a very good fibrinolytic system.

To calculate the risk for DVT in ICU patients a risk assessment model must be used that takes into account not only the thrombophilic profile of each patient at ICU admission with different items for medical, surgical and trauma patients, but also transient risk factors acquired during ICU stay, the major part related to iatrogenic interventions. In the ICU setting thrombofilic profile is not static, but dynamic; the persistence of DVT occurrence shown in all studies performed in ICU despite an extensive application of thromboprophylaxis, can be partly due to the variability of the thrombotic threshold that is hardly detectable compared with a fixed dosage of anticoagulants. ICU has been called the last frontiere of prophylaxis" [34].

7 DVT Risk Assessment Model in ICU-One for Each ICU?

– ***pre-existent risk factors-a proposal for calculating DVT risk at admission***

Pre-existent risk factors are in major part common to the risk factors that in recent years have been included in models for the assessment of thrombotic risk in hospitalized medical and surgical patients. Among those available in literature, the Padua score for medical patients [13] and the Caprini [14] modified score for surgical patients, also applied in the PROF-ETEV study [35] are the most extensively used and we propose that they would be applied in the evaluation of individual thrombotic risk at ICU admission. Remarkably, both Padua and Caprini modified models classify as at high thrombotic risk those patients who have a positive history for TEV, that was also selected together with end-stage renal failure as strongest pre-existent risk factor in ICU medical surgical setting by Cook et al 2005. Moreover, chronic cardiac and/or respiratory failure that select ICU patients at very high DVT risk are identified by Padua and Caprini scores [36]. In ICU intensivists have too short time to do too many things and having an electronic format for thrombotic scoring to complete could be a good methodological approach for the standardized calculation of individual thrombotic profile. In ICU patients the thrombotic risk scoring at admission would not have the goal to decide the start of anticoagulation, but could help to quickly calculate a baseline individual risk threshold which should be daily modified according with the evolution of clinical conditions.

– ***specific of admission diagnosis***

Dedicated score are available for hospitalized medical, surgical o trauma patients each taking into account DVT risk factors that play the major role in that specific subpopulation such as underlying inflammatory conditions, minor or major surgery due or not to cancer, number and kind of

injured bones. However when patients are admitted to ICU beyond the mentioned risk factors, hemodynamic instability with the need of vasopressor therapy and/or compromised ventilation with the need of mechanical ventilation complicate the clinical picture of the majority of patients. These acute illness are always associated with a very high risk of thrombosis and determine per se the immediate start of anticoagulation [36].

– **newly acquired and not specific of admission diagnosis**

As a whole newly acquired risk factors in ICU can be differentiated in those related to the evolution of the clinical conditions, or secondary to pharmacological or invasive or surgical iatrogenic interventions, as below shown, or rather according to the component of the Virchow's triad they mainly act on.

(a) *Related to onset of new medical pathologies*
Sepsis, kidney failure, systemic hypotension-hypoperfusion, abdominal hypertension
(b) *Related to procedures*
surgical procedures, peripheral or central catheter insertion
(c) *Related to mechanical ventilation*
(d) *Related to pharmacological therapies-amine neuromuscular blockers*
(e) *Related to hemoderivate administration.*

Risk factors described according to the effect on each component of the Virchow's triad

Negative action on flow stasis:
Abdominal hypertension, mechanical ventilation, amine, neuromuscular blockers
Negative action on hypercoagulability:
Sepsis, renal failure, amine, hemoderivate, erythropoietin
Negative action on endothelium:
For direct endothelium damage:surgical intervention, CVC
For endothelium dysfunction: sepsis renal failure amine

In recent years a protective effect of statins on DVT was reported and related with their positive effect on endothelial dysfunction; the clinical relevance of these data for thromboprophylaxis in ICU needs dedicated studies [37].

We think that when the pathophysiologic mechanisms of the different DVT risk factors is considered, the dynamic change in individual thrombotic threshold would be better assayed during ICU stay. Dedicated studies are needed to understand whether this approach could have clinical relevance supporting the individual adjustment of pharmacological and/or mechanical prophylaxis.

No "official" risk assessment model is available for ICU patients. Given the high number of risk factors for DVT that may differently coexist and concur to lower the threshold of the risk of thrombosis, risk factors are reported in different studies as having different impact. It is always difficult to apply recommendations by trials or meta-analysis to real clinical practice but it is even more difficult in ICU setting.

We suggest that a specific model should be prepared in each ICU according to the risk factors that characterize that specific population taking into account but not rigidly applying the indications given in the literature.

7.1 DVT Prophylaxis in ICU

(A) **Pharmacological prophylaxis is recommended in medical-surgical ICU patients**

Starting from the first trial by Kapoor et al in 1999 [7] that reported a 50 % risk reduction of screening detected VTE vs placebo, in medical-surgical ICU patients randomly selected and treated with UFU 5,000 units subcutaneously twice daily, in these decades an evidence-based efficacy of pharmacological UFH or LVWH prophylaxis in reducing the risk of VTE in ICU patients has been clearly shown [11, 37]. In a recent systematic review and meta-Analysis of randomized trials on the efficacy and safety of

any heparin (UFH or LMWH) thromboprophylaxis vs no anticoagulant prophylaxis, that enrolled 7,226 medical surgical ICU patients, any heparin compared with no heparin was associated with a 50 % lower risk of DVT and of PE with a number needed to prophylax to prevent one DVT of 20, using an assumed control risk of 10 %, and to a number needed to prophylax to prevent one PE of 52, using an assumed control risk of 4 %[38]. Heparin thromboprophylaxis did not influence the risk of major bleeding or mortality.

Laboratory-based variables to define optimal thromboprophylaxis such as thrombin generation and thromboelastometric assay of hypercoagulability have been proposed but dedicated studies are needed to understand how and whether use these data in clinical practice [37].

(B) **Which heparin?**

LWMHs are prepared from UFH by different chemical or enzymatic processes and we know that they have different physical, biochemical and pharmacological properties but we do not know whether this translates in different clinical outcome, specifically in ICU setting. In absence of comparative data among different LWMH, each LWMH should be used at the recommended doses when efficacy and safety data exist [39]. The major advantage of UFH over LMWH is that it avoids a renal clearance that allows UFH administration in patients with impaired renal function. LMWH are associated with a reduced likelihood of heparin-induced thrombocytopenia, that requires administration only once-daily and is commercially available in a unit dose. All the three randomized controlled trials performed between 2000 and 2011 that compared UFH with LMWH for VTE prophylaxis in ICU patients, did not find significant difference in the DVT rate between the two groups [40–42]. Only the multicentric Prophylaxis for Thromboembolism in Critical Care Trial (PROTECT) reported a significant lower incidence of PE (2.3 vs 1.3 %, $p = 0.01$) in the dalteparin group [43]. Pooled outcomes from the meta-analysis of Alhazzani et al are in agreement with the PROTECT's results that LMWH was not associated with a lower risk of DVT, but with a reduction of asymptomatic and symptomatic pulmonary embolism when compared with UFH. The risk of DVT, major bleeding, mortality and HIT was similar in the two groups [38].

A recent systematic review with meta-analysis and trial sequential analysis by Beitland et al [44] that included also ICU patients with trauma showed that LMWH compared with UFH reduced the risk of any DVT (RR 0.84,95 % CI 0.71–0.98), $p = 0.03$) and resulted in a net clinical benefit. There were no statistically significant differences in the risk of any PE, major bleeding or mortality.

The different findings reported by these two meta-analyses highlight the importance of a critical interpretation of all data reported by meta-analysis of trials performed in ICU patients when we want to transfer reported results into clinical practice. We should consider whether and how much the characteristics of ICU patients enrolled in studies or meta-analysis fit with those of our ICU.

8 Heparin Thromboprophylaxis in High Risk Subgroups

8.1 Sepsis

Heparin at prophylactic dosage can significantly reduce 28-day mortality in patients with severe sepsis i.e. sepsis complicated by organ dysfunction and tissue hypoperfusion; the use of heparin for sepsis is not associated to an increased risk of bleeding (Wang et al Critical Care 2014;18:563) [45]. Heparin has no effect on 28-day mortality in patients with no severe sepsis. The positive effect of heparin on mortality in ICU patients with severe sepsis can be explained by (a) the reduced occurrence of deep venous thromboembolism, (b) the negative modulation of coagulation activation and (c) the heparin anti-inflammatory effect through the reduction of

inflammatory mediators (histamine) and the increase in TFPI release.

8.2 Renal Failure

Patients with renal failure have an increase of both thrombotic and hemorrhagic risks, with the transitional prevalence of one over the other depending on underlying nephropathies (nephrotic or nephritic syndrome), hemodialysis treatment, eritropoietin administration and associated comorbidities. End-stage renal failure was selected with a positive familial or individual history of VET as the two strongest risk factors for DVT pre-existent to ICU admission in medical-surgical critical ill patients [3]. No specific indications are reported about the role of renal failure in the thrombotic risk stratification by the algorithm proposed by Laport and Mismetti [36] that is dedicated to medical critically ill patients and by Caprini modified score [14] that is used in the surgical setting. It must be underlined that beyond the effect on haemostatic balance, renal failure signifies a reduction of creatinine clearance and often results in the anticoagulant therapy to be stopped or in its excessive reduction without proven data on possible bioaccumulation. Heparin bioaccumulation would be investigated through the determination of anti-Xa units after the third heparin dose when the steady state has been achieved. Regarding prophylaxis, data on bioaccumulation are reported only for enoxaparin that should be used at reduced dose (30 mg once daily) for VET prophylaxis. Therapeutic doses of enoxaparin were associated with increased in major bleeding in patients with a creatinine clearance of 30 ml/min or less compared with UFH (8.3 % vs 2.4 %,95 % CI 1.78–8.45) in a meta-analysis of 12 studies that had enrolled about 5000 patients [39].

9 What About Obesity?

No doubts remain about the role of obesity as independent risk factor for DVT in all hospitalized patients and also in ICU patients, but whether or not a patient with a BMI >30 need a higher dosage of heparin is still a matter of debate [46]. Increasing BMI demonstrates the strongest relationship with thromboprophylaxis failure, suggesting an underdosing of anticoagulants with a fixed dose regimen (36a). Due to the lability of thrombotic threshold in ICU patients, we suggest that in these patients heparin concentration should be monitorized by the dosage of anti Xa levels. The decision to increase heparin dosage would be taken account of the level of global individual DVT risk.

10 When the Bleeding Risk Is Not Acceptable for Prophylaxis-Major Bleeding

The absolute contraindication to anticoagulation in patients at high risk for DVT are active bleeding and severe thrombocytopenia (<50000/cc); both are transient controindications and prophylaxis or therapy must be started immediately after these controindications are corrected [9]. All other clinical situations that are associated with increased risk of bleeding do not represent an absolute controindication for heparin prophylaxis but a daily individual evaluation of bleeding risk is needed in ICU patients. According to what indicated in the paragraph for the evaluation of the thrombotic risk, we think that the use of bleeding risk assessment models proposed for hospitalized medical patients could be also applied for ICU patients [47]; to answer to a standardized electronic form for bleeding scoring would shorten the dedicated time and undoubtedly would reduce the intra and interassay variability.

11 Only Heparin as Anticoagulant for DVT Prophylaxis in ICU?

Recently, new oral anticoagulants (NAO) that are direct thrombin or factor Xa inhibitors, have become available for primary and secondary prevention of venous thrombosis and of

embolization in atrial fibrillation. None of the new anticoagulants have been studied in the ICU population and the results of the MAGELLAN trial, rivaroxaban vs enoxaparin, [48] and the ADOPT trial, apixaban vs enoxaparin,[49] studies performed in acute medical illness cannot be transferred tout-court to ICU setting. At the moment the lack of data on efficacy and safety of NAO in ICU setting and of antidote for controlling bleeding, are against the use of NAO in critical ill patients.

12 Doubts on the Role of Mechanical Thromboprophylaxis in ICU Patients

Mechanical prophylaxis includes graduated compression stocking (GCS) and intermittent pneumatic compression (IPC) devices; however, for their use in ICU setting, general agreement only exists for patients at very high risk for VET in association with pharmacological prophylaxis or in patients for whom contraindications to pharmacological prophylaxis exists. These indications are reported in ACCP guidelines. Vignon et al [50] randomized ICU patients with high risk of bleeding to IPC plus GCS or GCS alone and found no difference in the DVT rate between the two groups (5,6 vs 9.2 %).In only one two-phase study that examined the effect of an educational program on the implementation of DVT prophylaxis in medical-surgical-trauma patients, the increased use of graduated compression stockings combined with pharmacological prophylaxis was associated with a significant reduction in DVT incidence during ICU stay from 11.6 to 4.7 %, $p = 0.017$despite no changes in the LWMH dosage and in the use of pneumatic mechanical compression [4]. These findings had had scarce relevance in the scientific community, but they sound not surprising taking into account the pathophysiology of DVT (i.e. Virchow's triad): ICU patients have a marked decrease in venous blood flow velocity because they are immobile, under sedation and/or often ventilated. When a neuromuscolar block is activated the venous blood velocity falls to about zero. In these unfavourable conditions the application of graduated compression stockings can be effective in increasing blood velocity in veins of the lower limbs so that the key event for the start of thrombus formation can be limited, especially when anticoagulation is administered contemporarily [51]. Moreover, the daily application of compression stockings is necessarily associated with an increased passive mobilization of ICU patients.

Recently two randomized controlled trials analyzed the efficacy of pneumatic compression in reducing thrombotic risk in medical surgical ICU patients when compared with no anticoagulation and showed that pneumatic compression significantly reduced DVT (3.8 vs 19.28 %, $p < 0.0$), PE (0 vs 9.64 %, $p < 0.01$), separately analyzed in the first study, and VTE from 7.2 to 4.8 % in the second study [52, 53].

13 Strategies to Improve Thromboprophylaxis Compliance in ICU

Nowadays DVT incidence during ICU hospital stay is used as a marker of quality care and given the epidemiology and the clinical impact of DVT in ICU population, clear evidence exists that DVT prophylaxis must be optimized by dedicated educational programs. On the contrary, the passive dissemination of guidelines has little effect on the improvement and maintenance of DVT prophylaxis prescription [54]. In ICU setting the presence of combined active and dynamic clinical conditions influencing the attention of the medical staff, together with the complexity and heterogeneity of medical in-patients, hinder the systematic application of prophylaxis. Remarkably, Ho et al [55] showed that omission of thromboprophylaxis within the first 24 h following ICU admission was associated with an increased risk of mortality in 175,665 critically ill adult patients admitted to 134 ICUs in Australia and New Zealand between 2006 and 2010, despite patients with early omission of prophylaxis being associated with a

slightly lower acuity of illness (mean APACHE [Acute Physiology and Chronic Health Evaluation] III model predicted mortality, 13 % vs 14 %; *P* 5.001). The estimated attributable mortality effect of omitting early prophylaxis was more relevant in patients with high acuity of illness such as multiple trauma, sepsis, cardiac arrest, and pre-existing metastatic cancer.

A recent review on venous thromboembolism prophylaxis [11] in critically ill patients clearly summarizes that studies performed all around the world- Asia, Australia and New Zeland, China, Japan, Spain and United States- have shown that more than 80 % ICU patients received appropriated prophylaxis; principal barriers to prophylaxis are fear of bleeding and underestimated risk of thrombosis.

Among studies based on the activation of educational programs for physicians and nurses, a three-phase prospective longitudinal study investigated the implementation of pharmacological prophylaxis in medical-surgical ICU by minimizing errors of omission through a 1-year period of interactive multidisciplinary educational in-services, verbal reminders to ICU team, computerized daily nurse recording of prophylaxis, weekly graphic feedback, publicly displayed graphic feedback on group performance. At the end of the educational period, days of heparin administration increased from 60 % observed under baseline period (phase 1) to 100 % ($p < 0.01$) [56]. The use of a daily quality round checklist (QRC) including DVT prophylaxis in a surgical ICU during a 2-year program with routine implementation of QCR, was associated to a final DVT prophylaxis compliance of 98 % [57].

Boddi et al [4] showed that a-1 year ICU-based educational program aimed at optimization of pharmacological and mechanical prophylaxis, combined with a twice a week scheduled ultrasound screening, was significantly associated with a marked decrease in DVT incidence from 11.6 to 4.7 %.

Several studies have demonstrated that electronic reminders associated with educational programs clearly improved the use of both pharmacological and mechanical DVT prophylaxis through the direct involvement of ICU clinicians and daily assessment of prophylaxis prescription [11]. Recently, an Italian study by Peris's group [26] showed that multiple interventions aimed at improving DVT prophylaxis rate (electronic alert for automatic pharmacological prophylaxis activation at ICU admission, nurse protocol with check list including graduated compression stockings application to be applied within 12 h from ICU admission) can reduce DVT incidence to low levels (2.6 %) in high risk ICU patients and result in a decrease in ICU length of stay. Most importantly, the 4-year-long quality improvement program of DVT prophylaxis was sustained and was active in a busy 10-bed mixed trauma, medical and surgical ICU despite the high turnover of patients.

14 Additional Problems Due to the Increased Dosage of Heparin from Prophylaxis to Therapy

The diagnosis of DVT is associated with the need of increasing dosage of anticoagulants and a higher risk of over dosing in patients with impaired renal function, peripheral hypoperfusion because of low cardiac output, hypotension and vasopressor use, altered binding to albumin, acute phase reactants and generalized edema. Risk factors that may be associated with under dosing are multiple organ dysfunction, high body mass index and the use of vasodepressor.

To monitor the LWMH anticoagulant effect the dosage of anti-Xa levels is used but a correlation between bleeding and thrombosis and anti Xa levels was not clearly proved (r na). Indeed, anti-factor Xa measure a drug concentration, not an effect [37]. Recently, the use of a weight-based LMWH dosing regime has been reported to avoid subtherapeutic anti-factor Xa levels in critically ill population [58]. In clinical conditions with risk of over or underdosing of heparin, the use of mechanical prophylaxis should be optimized and additional risk of bleeding such as thrombocytemia, antiplatelet therapy

and surgical intervention that should be delayed whenever possible.

15 Key Messages

Main Certainties

(a) ICU patients are at high risk for DVT thrombosis and ICU population is characterized by a dynamic day-to-day variation in the thrombotic threshold and bleeding risk. Pharmacological prophylaxis by heparin should be immediately start at ICU admission and stopped only in those few patients at very high bleeding risk, till the risk is not resolved (Fig. 5).

(b) In each ICU data on DVT prevalence and incidence obtained by scheduled ultrasound screening should be available and regularly (monthly) updated.

(c) Electronic form for individual thrombotic and bleeding risk assessment models should be available in every ICU and used daily. The models for calculating thrombotic risk would consider the additive effect of the different risk factors on each of three components of the Virchow's triad. The application of pharmacological and mechanical prophylaxis should be optimized by individual checklist-form for intensivists and nurses.

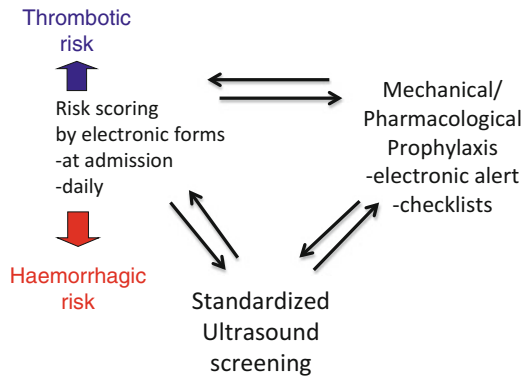

Fig. 5 How to approach DVT in ICU. Schematic synthesis of key points to be adopted for the optimization of thromboprophylaxis in ICU shown as a therapeutical triad

Doubts

(a) Individualized thromboprophylaxis regimens in ICU is invoked, expecially in renal failure and obesity, but how to monitor is still a matter of debate.

(b) A role for mechanical thromboprophylaxis in ICU is proved, but how to standardize its use at the best is a question to be addressed.

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Cerebral Venous Thrombosis

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Abstract

Cerebral venous thrombosis is an important cause of stroke in the young. Unlike venous thromboembolism (VTE), women are affected three times more often than men by CVT. The most common symptoms are headache, seizures and focal neurological deficits. The diagnosis can be confirmed with MRI, CT-venography, or catheter angiography. An intracerebral hemorrhage is found on cerebral imaging in approximately 40 % of patients, and can range from small juxtacortical hemorrhages to large space-occupying lesions. Many risk factors for CVT have been reported, most of which overlap with those of VTE. The primary therapy for CVT is anticoagulation with heparin, based on limited evidence from randomized trials. Both unfractionated or low-molecular weight heparin can be used to treat CVT, although the latter is generally preferable. Small studies have shown promising results of endovascular treatment in severe patients, but these data require confirmation in a randomized trial. In patients who develop clinical and radiological signs of impending herniation decompressive surgery can be both life-saving and result in a good functional outcome. The prognosis is nowadays favorable in most cases, especially compared to arterial stroke, although a significant proportion of patients do suffer from chronic symptoms.

Keywords

Cerebral venous thrombosis • Dural sinus thrombosis • Stroke • Intracerebral hemorrhage • Seizures • Anticoagulation • Endovascular thrombolysis

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1 Introduction

Cerebral venous thrombosis (CVT) is a rare cerebrovascular condition that was first described by a French physician in the nineteenth century

[1]. Patients with CVT have an occlusion of one or more of the dural sinuses of the brain, often in combination with cortical vein thrombosis. A small proportion of patients only have an occlusion of a cortical vein, which is termed isolated cortical vein thrombosis. CVT leads to a diminished outflow of blood and cerebrospinal fluid, which in about 50 % of patients results in development of a venous infarct. In contrast to arterial infarcts, CVT mostly affects young adults and children and it is an important cause of stroke in the young.

2 Objectives

The aims of this chapter are to:

- Provide an overview on the epidemiology and clinical manifestations of CVT.
- Describe the pathophysiology of CVT, differentiating between thrombosis of the dural sinuses and the cortical veins.
- Summarize which ancillary investigations can be used to diagnose CVT and the value of D-dimer to exclude CVT.
- Provide a framework on how to treat CVT and summarize the scientific evidence for the efficacy and safety of each therapy.

3 Epidemiology

Two recent studies estimated that the incidence of adult CVT is approximately 1.3 per 100 000 person-years [2, 3]. Prior to these studies, the incidence of adult CVT was believed to be between 0.2 and 0.5 per 100 000 per year. This estimate was derived from an extrapolation of mortality and autopsy data from studies that were performed several decades ago [4]. Increased awareness of CVT and improved imaging techniques, especially MRI and CT-venography, are the most important explanations why these contemporary studies show a higher incidence [2]. The incidence is higher in patients aged 31–50 years (1.7 per 100 000), and especially in women of that age (2.8 per 100 000) [2]. In the elderly, CVT is very uncommon; less than 10 % is older than 65 [5]. In children, the incidence of CVT has been estimated at 0.7 per 100 000 per year, with a peak among neonates [6].

4 Anatomy and Pathophysiology

The venous drainage system of the brain can be divided into a superficial and deep part. The superficial system collects blood from the cerebral cortex and the outer 1–2 cm of white matter. Small subcortical and intracortical veins transport blood to the larger cortical veins, which in turn drain into the dural sinuses [7, 8]. Most of the cortical veins drain into the superior sagittal sinus, although some, like the inferior anastomotic vein (vein of Labbé) usually connect with the lateral sinus. The superior sagittal sinus transports blood to the transverse sinuses, of which one is often dominant. The blood flow then continues to the sigmoid sinuses and leaves the skull through the jugular veins. The deep cerebral system drains blood from the deeper white matter and basal ganglia. Blood is transported from the deep cerebral veins (internal cerebral veins, basal vein of Rosenthal, vein of Galen) to the straight sinus, which drains into the transverse sinuses (Fig. 1) [9]. Many anastomoses connect the different parts of the cerebral venous system and the anatomy can vary considerably from person to person.

It is helpful to differentiate between two different mechanisms in the pathophysiology of CVT: thrombosis of the cortical veins and thrombosis of the cerebral sinuses. Depending on the extent of the thrombus and the availability of venous collaterals, occlusion of a cortical vein can cause an increase in the venous and capillary pressure and breakdown of the blood-brain-barrier. This process results in localized brain edema, which can progress to venous infarction. A unique characteristic of venous infarcts is that they are often hemorrhagic. Clinically, venous infarcts cause focal neurological deficits and, often, epileptic seizures. The second

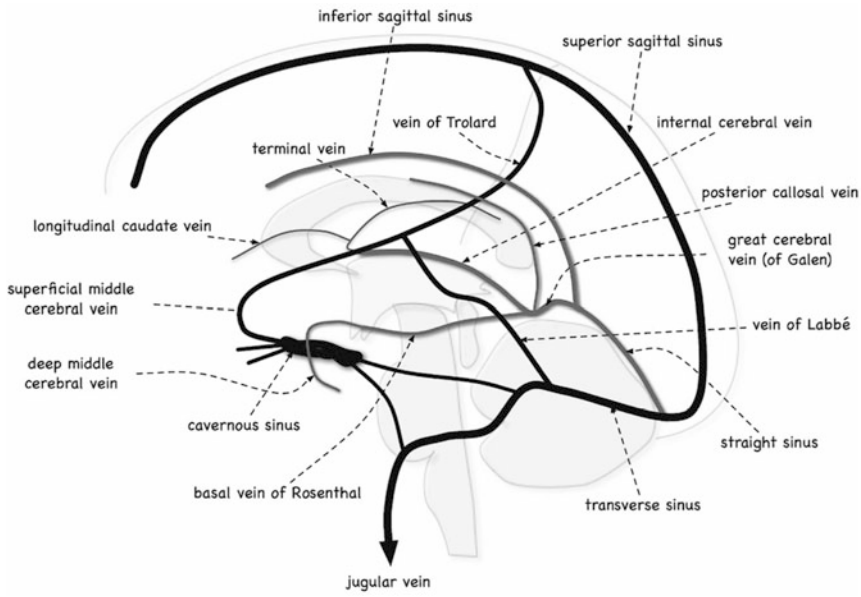

Fig. 1 Anatomy of the normal cerebral venous circulation (Reproduced with kind permission from An Atlas of Neonatal Brain Sonography, 2nd edition, by Paul Govaert and Linda de Vries, published by Mac Keith Press (www.mackeith.co.uk) in its Clinics in Developmental Medicine Series 2010 [ISBN 978-1-898683-56-8])

pathophysiological mechanism, thrombosis of the cerebral sinuses, results in a restricted outflow of cerebrospinal fluid, leading to intracranial hypertension. Major symptoms of intracranial hypertension are headache and decreased visual acuity [10].

5 Risk Factors

In young and middle-aged adults, CVT is three times more common in women than men. This skewed sex ratio is the result of female specific risk factors: oral contraceptive use, hormone replacement therapy, and pregnancy/puerperium [11–14]. These risk factors are generally absent in children and elderly, which explains why in these groups the sex ratio is more evenly distributed [5, 6, 15].

Many different risk factors have been associated with CVT (Table 1). In part these overlap with risk factors for venous thromboembolism (VTE), such as genetic thrombophilia, cancer, obesity, and the previously mentioned female specific risk factors. Other risk factors, mostly those that affect the head and neck region, are specific for CVT. Examples include local infections (otitis, mastoiditis, and meningitis), head trauma, neurosurgical operation, and lumbar puncture. While septic CVT was common in the past, the frequency of infection related CVT has declined over time, probably due to improved antibiotic therapy [10]. Inherited thrombophilias that have been associated with CVT include the prothrombin G20210A mutation, Factor V Leiden mutation, protein S deficiency, protein C deficiency, increased factor VIII levels, JAK2 V617F mutation, and hyperhomocysteinemia [16]. Inflammatory bowel disease and acute lymphoblastic leukemia (ALL) are associated with both VTE and CVT, but, for reasons that are unknown, these conditions are more strongly associated with CVT than VTE [17]. In the case of ALL, the increased risk of CVT appears to be related to the use of asparaginase, possibly in combination with lumbar punctures for intrathecal methotrexate

Table 1 Risk factors for cerebral venous thrombosis

Genetic thrombophilia	**Cancer**
	Especially hematological malignancies
Infections	**Gender specific risk factors**
Otitis / Mastoiditis	Oral contraceptive use
Meningitis	Pregnancy / Puerperium
Systemic infectious disease	Hormone replacement therapy
Iatrogenic	**Medication**
Catheterization jugular vein	Asparaginase
Neurosurgical intervention	Methotrexate
Lumbar puncture	
Miscellaneous	**Systemic diseases**
Anemia	Inflammatory bowel disease
Head trauma	Steroids
Dehydration	Thyroid disease
Severe obesity	Behçet disease
Spontaneous intracranial hypotension	Systemic lupus erythematosus
Dural arteriovenous fistula	Antiphospholipid syndrome
Arteriovenous malformation	

therapy. Anemia has also been associated with CVT and is present in 10–20 % of patients [15, 18]. Severe obesity was recently also found to be a risk factor for CVT. Subjects with a body mass index of 40 or more have an almost ten-fold higher risk of CVT than those with a normal weight. The association between obesity and CVT is especially strong in women of reproductive age who use oral contraceptives [19].

At least one risk factor can be identified in 85 % of patients with CVT, and 44 % has multiple risk factors [15]. The most common acquired risk factor for CVT is oral contraceptive use. The reported proportion of women with CVT who use oral contraceptives varies, depending of the country where the study was performed, but percentages of 50 % or higher are not uncommon [2, 15]. Most women with pregnancy related CVT develop symptoms in the puerperium and the risk appears to be increased up to 12 weeks after delivery [12, 20, 21].

6 Symptoms and Signs

The clinical manifestations of CVT are variable, and the disease can be difficult to diagnose. In the International Study on Cerebral Vein and dural sinus Thrombosis (ISCVT), the median delay from symptom onset to admission was 4 days, and the median delay from onset of symptoms to diagnosis was 7 days [15]. A chronic onset of symptoms occurs in less than 10 % of patients and less common in women than men [11].

The most common symptom of CVT is headache, which is found in about 90 % of patients. Although any type of headache can occur, most often it is diffuse and severe. A subgroup of patients present with thunderclap headache, mimicking subarachnoid hemorrhage [22]. Presentation without headache is rare, but occurs more often in older patients, men, and in some associated conditions like isolated cortical vein thrombosis [23, 24]. Focal neurological deficits, such as paresis, aphasia, and hemianopia are found in about half of all patients, and these patients usually have a venous infarct [15]. Seizures occur in approximately 40 % of patients, which is much higher than arterial stroke. A decreased consciousness can also occur, and one in seven patients is comatose at admission, usually as a result of large venous infarcts or bilateral edema of the basal ganglia and thalami [15]. The latter is usually due to thrombosis of the deep venous system and this can also result in behavioral symptoms such as confusion, amnesia, bradyphrenia and mutism [25, 26].

7 Diagnosis

Three different imaging modalities are available to diagnose CVT: CT-venography, MRI with MR-venography, and catheter angiography. Non contrast CT is insufficient to diagnose CVT, but it can show abnormalities that suggest the diagnosis. For example, a thrombus in a dural sinus or cortical vein can appear hyperdense. The latter finding is termed “cord sign” (Fig. 2) [27].

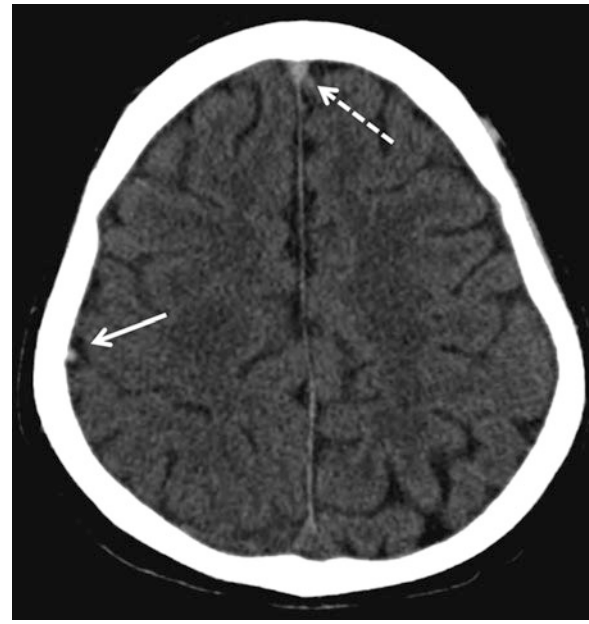

Fig. 2 Axial non-contrast CT-scan of a 27-year-old man with CVT. He had a history of acute lymphoblastic leukemia and presented with generalized seizures. Note the hyperdense signal in the anterior part of the superior sagittal sinus (delta sign; *dashed arrow*) and in one of the cortical veins overlaying the right hemisphere (cord sign; *filled arrow*)

The most frequently occluded sinus is the superior sagittal sinus (62 %), followed by the left and right lateral sinus (each around 40 %), and straight sinus (18 %) [15]. Although catheter angiography is still considered the gold standard, it is rarely required anymore. Given the cost and associated risk to the patient, catheter angiography should only be performed if there is doubt about the diagnosis after MRI and CT-venography. When using MRI, it is important to perform both MR-venography and regular MR sequences, because the combination of a signal alteration in the sinus and absent flow on venography is required to make the diagnosis. The precise sensitivity and specificity of MRI and MR-venography are unknown because sufficiently powered studies comparing MRI to catheter angiography have not been performed [27]. Time-of-flight and contrast-enhanced MR-venography can both be used, although the venous system can visualized better with the latter technique [28]. It is also useful to include a susceptibility weighted sequence, since this is the most sensitive technique to visualize a thrombus in a cortical vein [29].

CT-venography is a good alternative to MRI to diagnose CVT. A small study that compared CT-venography to catheter angiography showed a sensitivity of 95 % and specificity of 91 % for the detection of the thrombosis of the cerebral venous system [27]. Advantages of CT-venography include a wide availability, quick image acquisition, and the ability to image patients with a pacemaker or other ferromagnetic devices. Disadvantages of CT venography are the need for intravenous contrast material and exposure to ionizing radiation, which limits its applicability in children and pregnant women. Moreover, CT is inferior to MRI to detect parenchymal lesions and cortical vein thrombosis [24, 30].

Parenchymal brain lesions are found in approximately 40–60 % of patients with CVT, and usually consist of hemorrhagic infarcts or cerebral edema. The shape and size of hemorrhagic lesions can vary from small petechial hemorrhages to large intracerebral hemorrhages (Fig. 3). Juxtacortical hemorrhages, which are small (<2 cm in diameter) hemorrhages that are located just below the cortex, are very typical for CVT and rarely seen in other conditions [31]. Large space-occupying hemorrhagic infarcts of the temporal lobe are usually caused by thrombosis of the vein of Labbé or one of the

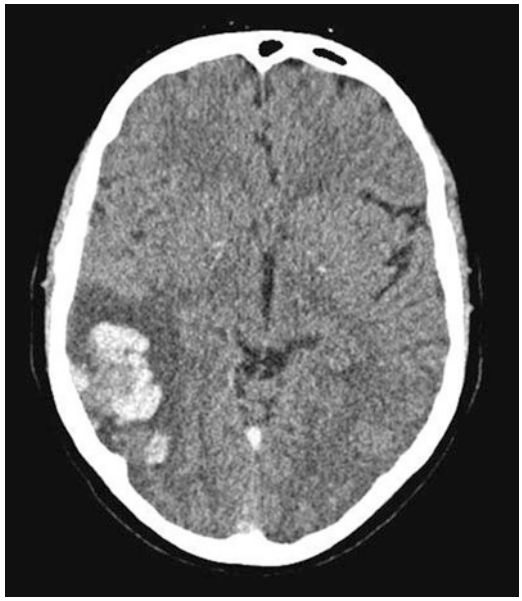

Fig. 3 Axial non-contrast CT-scan of a patient with CVT. In the right hemisphere (*left* side on the CT) a large hemorrhagic infarct is visible. *Darker* areas in the lesion indicate edema and the *white* areas blood

inferior middle cerebral veins that drain into the transverse sinus [32].

Standard blood tests should be performed in all patients with CVT, consisting of a complete blood count, chemistry panel, prothrombin time and activated partial thromboplastin time [27]. Routine screening for genetic thrombophilia is not recommended, since it usually does not change clinical practice, but it may be performed in selected patients with high a pre-test probability for severe thrombophilia (i.e. recurrent thrombosis, a family history of venous thrombosis, or CVT without a risk factor) [16]. Prior to screening for thrombophilia, it is advisable to consult with a thrombosis specialist. A meta-analysis showed that the sensitivity of D-dimer measurement in patients with CVT is 94 % [33]. Among patients with a chronic headache or isolated headache, however, the sensitivity was considerably lower, 83 % and 82 %, respectively. Since these are exactly the patients in whom D-dimer measurement could be helpful, since there may be no other reason to perform brain imaging other than to exclude CVT, the value of D-dimer measurement in the diagnostic work-up of CVT is limited.

8 Treatment

8.1 Anticoagulation

The primary therapy for patients with CVT is anticoagulation with heparin in the acute phase, followed by oral anticoagulation in the chronic phase. The efficacy and safety of heparin treatment has been investigated in 3 small-randomized trials [34–36]. A meta-analysis showed a pooled relative risk of death and dependency of 0.46 (95 % CI 0.16-1.31) after heparin treatment as compared to placebo [37]. Hence, the limited data that is available suggests a beneficial effect of heparin treatment, but the difference was not statistically significant. Importantly, heparin treatment was not associated with increased risk of hemorrhagic complications. Both low-molecular weight and unfractionated heparin are used to treat CVT, although based on data from two studies, low molecular weight heparin is preferable [38, 39]. The optimal duration of anticoagulant therapy is not known, but most physicians treat for a period of 3–12 months [40]. Factors such as whether the thrombosis was provoked and the preference of the patient should be taken into account when determining the duration of treatment. In some patients, for instance in case of a recurrent thrombosis or in the presence of severe genetic thrombophilia, indefinite treatment with anticoagulation is recommended.

8.2 Endovascular Treatment

During endovascular thrombolysis a catheter is introduced into the cerebral venous system, with the aim to remove the thrombus. Access is usually acquired using a transfemoral or transjugular approach, although direct puncture of a sinus through a burr hole has been reported. Thrombolysis can be achieved using chemical thrombolysis (urokinase or rt-pa), mechanical

thrombectomy, or a combination of both. Although many case reports and case series have been published reporting promising results with endovascular treatment, no controlled studies have assessed the efficacy and safety of this therapy [41, 42]. Therefore, endovascular treatment should not be routinely performed in patients with CVT, although it can be considered in selected patients with a severe form of CVT or who deteriorate despite heparin treatment. Currently, there is a randomized controlled trial ongoing in which the efficacy of endovascular therapy is being assessed (TO-ACT trial) [43]. At the time this manuscript was written, 52 patients were included in this study.

8.3 Decompressive Surgery

Decompressive surgery is indicated in a small subset of patients with signs of transtentorial herniation. Clinically, these patients develop a depressed consciousness, with or without 3rd nerve palsy. Imaging will generally shows a large venous infarct with mass effect and shift of midline structures. During decompressive surgery, a hemicraniectomy (or sometimes bilateral) is performed, thereby removing the immediate threat of fatal herniation. Recent studies have shown that this procedure can be lifesaving and result in a good outcome in many patients [44, 45]. The largest retrospective study on this subject included data from 69 patients [45]. The mortality was 16 %, and at follow up 57 % of the patients was functionally independent. Good outcomes have even been reported in patients with advanced stages of transtentorial herniation [46].

8.4 Steroids

The rationale behind the use of steroids in patients with CVT is that it may reduce vasogenic edema.

The efficacy of steroid treatment has only been assessed in one, non-randomised, study [47]. Overall, there was no difference in poor outcome in patients who did or did not receive treatment with steroids, but patients without a parenchymal lesion had a worse outcome if treated with steroids. Although residual confounding may have biased the results of this study, until more data become available, the use of steroids in patients with CVT cannot be recommended, especially not in those without parenchymal lesions.

9 Complications

9.1 Seizures

As mentioned previously, seizures occur frequently in the acute phase of CVT. In patients with early seizures, most already have had their first seizure prior to diagnosis. The risk of early seizures (within 2 weeks after the diagnosis) is especially increased in patients with venous hemorrhagic infarcts [48]. There is general agreement to treat all patients with CVT who develop early seizures with antiepileptic drugs, with the aim to prevent early recurrences [27, 39]. Late seizures and epilepsy are much less common and occur in approximately 10 % of patients, although there is little data on this topic [49]. The optimal duration of treatment in patients with early seizures is unknown. Personally, we start tapering anti-epileptic drugs after 3–9 months in most patients, unless a patient has had a recurrent seizure. It is unknown if longer duration decreases the risk of late seizures.

9.2 Hydrocephalus

There is little data on the frequency of hydrocephalus in CVT. A recent study observed hydrocephalus in 14 % of patients [50]. In this study, the most important risk factor for hydrocephalus was edema of the basal ganglia and thalami and, in these patients, hydrocephalus probably resulted from obstruction of the foramen of Monro. The presence of hydrocephalus was also a risk factor for poor outcome, with an associated mortality rate of approximately 30 %. A direct

causal relation between hydrocephalus and poor outcome, however, has not been established, and it is more likely that hydrocephalus is a marker of severe parenchymal involvement. Routine shunting procedures are therefore not recommended in patients with CVT, although this decision has to be carefully weighed in each individual patient. The fact that placement of a ventricular drain requires stopping of anticoagulation makes this decision more difficult [50].

9.3 Intracranial Hypertension

Intracranial hypertension is present in the acute phase in most patients with CVT. Besides prescription of analgesics, specific treatment for intracranial hypertension is usually not required at that stage, but frequent monitoring of the visual acuity and the presence of papilledema should be performed. This is especially important in patients with a decreased consciousness or aphasia who are unable to report decreased vision. Acetazolamide can be prescribed to reduce the production of cerebrospinal fluid, although the effect is probably limited. Performing a therapeutical lumbar puncture is generally inadvisable, because the effect is only short lasting and it requires discontinuation of heparin treatment. We only perform a lumbar puncture in an emergency if a patient develops acute visual loss. In that situation, averting imminent blindness outweighs the small risk of hemorrhagic complications. The effect of a lumbar puncture, however, is only temporarily, and patients with a threatened vision will usually require a shunting procedure.

10 Prognosis

The prognosis of CVT is generally good, especially compared to arterial stroke. Approximately 80 % of the patients recover without disability, although many of these patients do suffer from chronic symptoms such as headache, diminished concentration and mood disorders [15, 51, 52]. These long-term symptoms often have a negative impact on the quality of life and employment status of patients [51]. Risk factors for an unfavorable outcome are: male sex, older age, an intracerebral hemorrhagic lesion, mental status disorder, coma, thrombosis of the deep cerebral venous system, central nervous system infection, and malignancy [15]. Follow-up studies have shown that recanalization occurs in about 90 % of patients. In most, this process takes place early, and by 3 months, 70–80 % of patients will have partial or complete recanalization [53, 54]. Whether or not there is a relation between recanalization and clinical outcome is uncertain, as the data on this issue are conflicting [53, 54]. Venous collaterals also develop in the majority of patients, but limited data on this subject do not suggest an association between collaterals and outcome [55].

The risk of a recurrent thrombosis is around 4 per 100 person-years, although the estimates of recurrence risk vary considerably between studies. About 1/3rd of the recurrent thrombotic events are CVT and the rest are VTEs. Risk factors for the recurrence of VTE are male sex and polycythemia/thrombocytosis. Of all recurrences, the majority occurs within the first year after CVT [56].

The mortality of patients with CVT has declined steeply over time [57]. In the past, mortality rates of 50 % were not uncommon and some even believed that CVT was almost uniformly fatal [58]. In recent studies, however, the reported mortality is between 5 and 10 %. Although part of the decline in mortality is probably due to better therapy and a shift in risk factors, the most important reason is that with modern imaging, less severe cases are identified. If a patient dies in the acute phase, death is often directly attributable to CVT. Most of these patients die from transtentorial herniation due to large venous infarcts [59]. In contrast, death in the chronic phase is usually caused by co-morbid conditions, especially cancer.

11 Conclusion

Although an uncommon condition, CVT is an important cause of stroke in the young. Due to variable clinical manifestations, CVT can be difficult to diagnose. Early recognition is important, because adequate treatment with heparin can prevent development of venous infarcts. In severe cases, endovascular treatment or decompressive surgery should be considered, but more evidence on the efficacy and safety of these therapies is required. The mortality has decreased steeply over the past decades, predominantly thanks to better imaging, and the outcome is now favorable is most patients.

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Endovascular Treatment of Thrombosis and Embolism

Ahmet Yigit Goktay and Cagin Senturk

Abstract

Deep venous thrombosis (DVT) is a common disorder with a significant mortality rate. Successful endovascular treatment of acute DVT is most likely to be achieved in patients with recently formed thrombus, (<10–14 days) with acute iliofemoral DVT. Endovascular treatment options include: Catheter-directed thrombolysis (CDT), pharmacomechanical catheter-directed thrombolysis (PCDT), percutaneous aspiration thrombectomy (PAT), vena cava filter protection, venous balloon dilatation and venous stent implantation. Current practice shows strong clinical tendency for the use of PCDT with or without other endovascular methods and an individualized approach for each DVT patient. PMT has not received general acceptance because of the associated risk of PE and damage to venous valves caused by thrombectomy devices. PAT is most commonly used as an adjunctive endovascular technique like balloon maceration to fragment thrombus, balloon angioplasty, stent implantation and vena cava filter placement. Interventional endovascular therapies for DVT have the potential to provide PE protection and prevention of PTS. Patient centered individualized approach for endovascular DVT treatment is recommended to optimize the ideal clinical result.

Acute stroke is the leading cause of death for people above the age of 60 and the fifth leading cause in people aged 15–59. Mortality during the first 30 days of ischemic stroke is 20 % and 30 % of survivors will remain permanently disabled. Acute stroke patients within the therapeutic window must receive IVrtPA unless there is a contraindication. In case of contraindication to IVrtPA or for patients out of the therapeutic window

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for thrombolytics, standart of care is the intraarterial treatment. Patients have to be transferred to a comprehensive stroke center with capacity of dedicated neurovascular imaging and interventional neuroradiology. Noncontrast head CT that is used to rule out hemorrhage is followed by imaging studies dedicated to show if there is reasonable penumbra to save. Intraarterial thrombolysis has the main advantage of extended therapy window, earlier and more efficient recanalization and less risk of hemorrhage due to lower doses of thrombolytics. Mechanical thrombectomy has several advantages over IV/IA fibrinolysis including faster recanalization and less risk of hemorrhage especially in large artery occlusions. ASA guidelines recommend choosing stent retrievers over other devices for mechanical thrombectomy. Better recanalization rates and less infarct volume after mechanical thrombectomy result in higher numbers of functionally independent patients compared with other treatments. Two landmark studies that were published recently, SWIFT PRIME and MR CLEAN, showed that IA treatment especially with the new stent retrievers lead to a significant increase in functional recovery and independence in daily life after an acute stroke.

Cerebral venous and sinus thrombosis (CVST) comprises nearly 0.5–1 % of all stroke cases. CVST causes different neurological deficits depending on the sinus/cortical vein involved. CVST may cause death and dependency in 13.4 % of patients. CT/CT venography and MR/MR venography can be effectively used to diagnose and to follow up CVT cases. Anticoagulation with heparin is the most widely accepted therapy to prevent the expansion of the thrombus. Patients deteriorating despite heparinization and patients presenting with very severe neurological deficits must receive endovascular treatment. Endovascular methods include intrasinus infusion of thrombolytics or heparin, balloon angioplasty, mechanical thrombectomy or a combination of different techniques. There is a higher rate or recanalization with endovascular methods compared to other medical therapies.

Keywords

Endovascular • Deep venous thrombosis • Catheter • Thrombolysis • Thrombectomy • Stroke • Stent retrievers • Cerebral venous thrombosis

1 Endovascular Treatment of Deep Venous Thrombosis

Deep venous thrombosis (DVT) is a common life-threatening disorder with a significant mortality rate. Even after appropriate medical therapy, DVT recurs frequently and may cause serious complications such as *pulmonary embolism* (PE) and postthrombotic syndrome [1–3]. Despite these risks of major complications and potentially permanent sequelae, no single effective treatment modality for DVT yet exists. There has been growing experience in the treatment of deep vein thrombosis, but major clinical challenges and a wide variation in practice still remain [4, 5].

The main purpose of any DVT treatment is to improve symptoms and to prevent the development of PE and *postthrombotic syndrome* (PTS)

by eliminating the thrombus material. Conventionally, there have been three acceptable basic treatment options for DVT and the rationale, risks, benefits, and uncertainties associated with these methods are summarized below.

1. **Anticoagulant Therapy:** The main objectives of anticoagulant therapy are to prevent progression of existing thrombi and to lower the incidence of PE by preventing development of recurrent thrombosis. Anticoagulants do not exert a recanalization activity. Recanalization occurs by natural thrombus resorption over time. Many studies have reported that anticoagulation therapy prevented progression of popliteal and tibial vein thrombosis and allowed development of near-complete recanalization in 95 % of patients in the long term. However, recanalization rates are poor (20 %) in patients with iliofemoral vein thrombosis [6].
2. **Systemic Thrombolytic Therapy:** Systemic thrombolytic therapy is markedly superior to anticoagulation therapy (heparin) in terms of reestablishment of venous blood flow [7]. Thrombolytic agents only resolve thrombi with which they come into contact. Thus, if venous occlusion is complete, such agents sometimes do not penetrate blood clots, and treatment failure may result. The most significant concern of thrombolytic therapy is the increased risk of bleeding. Although the efficacy of systemic thrombolytic therapy used to treat DVT is widely acknowledged, the risk of bleeding, the potential development of serious related complications, uncertainties in terms of dosage and route of administration, the requirement for admission to the intensive care unit, a prolonged hospitalization period, and the need to conduct numerous laboratory tests to monitor health status, all indicate that this therapeutic modality is associated with limited indications [6, 7].
3. **Surgical Thrombectomy:** As another therapeutic alternative, surgical thrombectomy, can be used to treat a limited number of patients and is especially preferred in patients with phlegmasia caerulea dolens [8]. However, even in patients with this rare pathological abnormality, it is not possible to achieve adequate venous patency with preservation of venous valvular function using surgical techniques [9].
4. **Endovascular treatment:** Endovascular interventional treatments have been used in the management of DVT for many years, and recently endovascular options increased in number with many different technical advances and new devices. The limitations of conventional treatment options encouraged the progress in endovascular treatment of DVT, and advances in endovascular therapies have delivered a wide range of new treatment options. Acceptable recanalization rates have been reported using endovascular therapeutic methods such as: *catheter-directed thrombolysis (CDT), pharmacomechanical catheter-directed thrombolysis (PCDT), percutaneous aspiration thrombectomy (PAT), vena cava filter protection, venous balloon dilatation and venous stent implantation* [4, 5, 10]. In recent years, endovascular techniques are also undergoing evaluation in many multicenter randomized controlled trials to determine their clinical benefit [4, 5].

Patient Selection for Endovascular Acute DVT Therapy All patients, in whom endovascular DVT therapy is planned, should undergo a detailed evaluation with clinical assessment that covers information from past medical history, physical examination and imaging findings. Patients should be evaluated for the thromboembolic risk factors and previous treatments, and preexisting comorbidities. Successful endovascular treatment of acute DVT is most likely to be achieved in patients with recently formed thrombus, (<10–14 days) with acute iliofemoral DVT [10–12]. Patients with a left-sided iliofemoral DVT are likely to have *May-Thurner Syndrome* with left common iliac vein stenosis that can be eliminated with venous stent placement [4, 13].

According to the *Society of Interventional Radiology (SIR) and Cardiovascular and Interventional Radiological Society of Europe (CIRSE) guidelines,* imaging proven symptomatic DVT in inferior vena cava or iliac, common femoral, and/or femoral veins in a recently ambulatory patient with DVT symptoms for less than 28 days and in whom there is strong clinical suspicion for recently formed DVT are the primary indications for endovascular interventions for lower-extremity DVT thrombus removal [10]. Contraindications for endovascular pharmacologic catheter-directed DVT thrombolysis are summarized in Table 1.

Table 1 Contraindications to catheter-directed thrombolysis and pharmacomechanical thrombolysis for lower extremity DVT

Absolute contraindications:
*Active internal bleeding or DIC
*Recent cerebrovascular event (including TIA)
*Recent neurosurgery or intracranial trauma (<3 months)
*Absolute contraindication to anticoagulation
Relative contraindications:
*Recent CPR, major surgery, obstetrical delivery (< 7–10 days)
*Recent organ biopsy, major trauma, or cataract surgery (<7–10 days)
*Intracranial tumor, other intracranial lesion, or seizure disorder
*Recent major GIS bleeding or internal eye surgery (<3 months)
*Serious allergic reaction to thrombolytic agent, anticoagulant or contrast media
*Known right-to-left cardiac or pulmonary shunt, left heart thrombus
*Severe dyspnea or severe acute medical illness precluding safe procedure
*Suspicion for infected venous thrombus
*Renal failure (GFR < 60 mL/min)
*Short life expectancy
*Severe thrombocytopenia
*Uncontrolled hypertension
*Bacterial endocarditis
*Pregnancy or lactation
*Severe hepatic dysfunction
*Diabetic hemorrhagic retinopathy

DIC disseminated intravascular coagulation, *CPR* cardiopulmonary resuscitation, *BP* blood pressure, *GIS* gastrointestinal system, *DVT* deep vein thrombosis, *GFR* glomerular filtration rate, *TIA* transient ischemic attack

1.1 Endovascular Interventional Options for Deep Vein Thrombosis

1.1.1 Catheter-Directed Thrombolysis (CDT) for DVT

Image-guided, catheter-directed, intra-thrombus drug delivery has been developed for improving the safety and efficacy of thrombolytic therapy for thromboembolic disease. CDT has several advantages for DVT patients and can be used:

1. To achieve high intra-thrombus thrombolytic agent concentrations.
2. To avoid bypass of the drug via collaterals around the thrombosed vein.
3. To reduce thrombolytic agent dose, treatment time, intensive care utilization and hospitalization time.
4. To decrease bleeding complications.
5. To treat underlying venous abnormalities by other endovascular techniques.

Catheter-directed thrombolysis (CDT) means delivery of a thrombolytic drug (rtPa, Urokinase) directly into the thrombus using a catheter or catheter-like device that is embedded within the thrombus by using Doppler ultrasound and fluoroscopy guidance. Usually a standard multisidehole catheter might be used but recently a multisidehole catheter that simultaneously applies ultrasound energy (EkoSoniccatheter; EKOS) to improve drug delivery into the thrombus has also been developed and this device is expected to increase safety and efficacy [4, 5, 10] (Fig. 1).

Currently, the most commonly used fibrinolytic drug for DVT is the *recombinant tissue plasminogen activator (rtPA).* The drug is infused continuously and directly into the thrombus at a low dose (0.5–1.0 mg/h) with systemic intravenous infusion of unfractionated heparin at subtherapeutic levels. Mostly the patient is closely monitored in an intensive care unit.

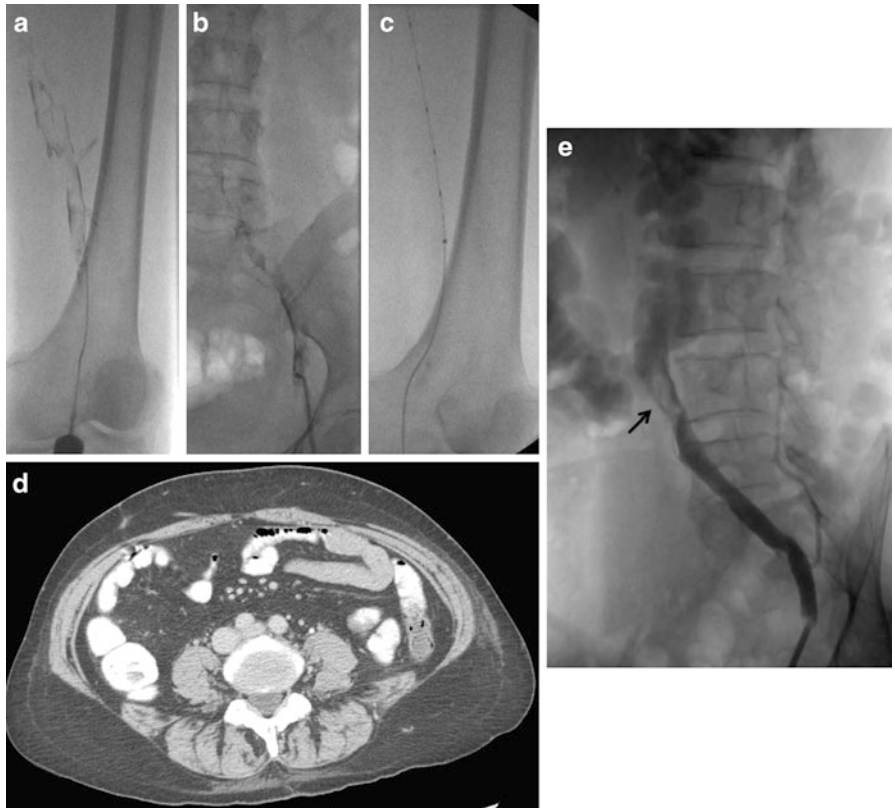


Fig. 1 Left iliofemoral DVT (**a**, **b**), placement of ultrasonic EKOS catheter with improved drug delivery into the thrombus (**c**), CT examination was obtained because of the suspicion of May-Thurner syndrome but the compression on left common iliac vein was moderate (**d**), only a small partial thrombus (*arrow*) was visible after the treatment (**e**)

Infusion might be stopped in case of active bleeding or severely abnormal coagulation parameters. Patients are evaluated by venography 1–2 times a day until the patency is achieved. Venous balloon angioplasty with thrombolytic infusion may also be used after partial thrombolysis [4, 5]. Left iliac anatomical venous stenosis (May-Thurner Syndrome) is usually treated by venous stent implantation and other venous stenoses might also be treated by balloon angioplasty and/or stent placement [4, 13]. Venography is performed to confirm the patency of the venous system. Before the patient is discharged anticoagulant therapy is arranged and compression stockings are prescribed. CDT has been evaluated in many case series and prospective multicenter trials. Major bleeding was observed in 5–12 % of patients in some older studies. However, more recent series with RCT reported much lower major bleeding rates [4, 5, 11, 12]. Fatal PE after CDT has also been reported very rarely [4, 14]. Although CDT is effective, currently the technique is not used widely because of long infusion times with intensive monitoring that are associated with longer hospital stays, and the risk of systemic bleeding still exists.

1.1.2 Pharmacomechanical Catheter-Directed Thrombolysis

Pharmacomechanical catheter-directed thrombolysis (PCDT) includes intrathrombus thrombolytic agent infusion with mechanical thrombectomy devices to improve drug penetration into thrombus and macerate thrombus for aspiration or

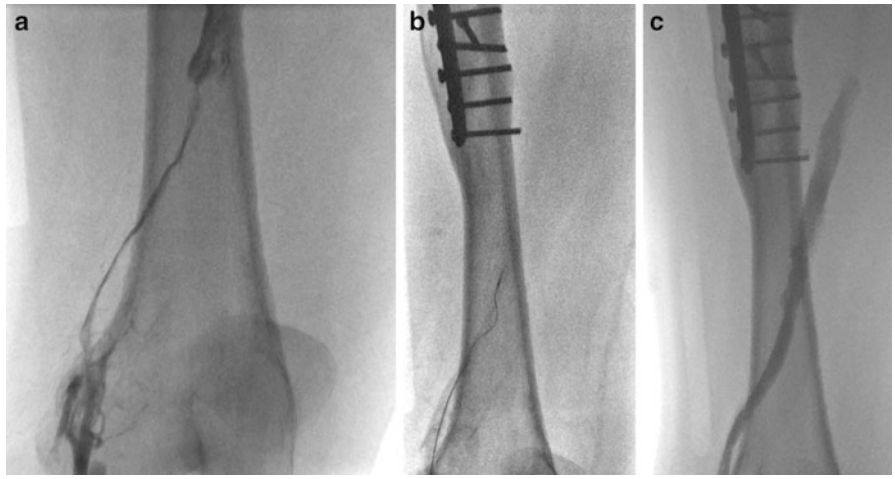


Fig. 2 Right iliofemoral DVT, thrombus is occlusive at the popliteal segment (**a**), oscillating wire activation of the pharmacomechanical thrombectomy device (**b**), recanalization of the thrombosed segment within minutes (**c**)

percutaneous thrombectomy [5, 11]. These devices enable faster penetration of thrombolytic agent within the thrombus, accelerating successful thrombolysis and improving safety by reducing drug dose and exposure time. Successful use of PCDT has been described in a number of published DVT studies [15–17]. Recently, new PCDT devices have been introduced that can enable endovascular DVT therapy to be completed in a single procedure session without the need for further drug infusions or intensive care monitoring. AngioJet Thrombectomy System (Boston Scientific) gives forceful pulse-spray bolus dose of the thrombolytic drug directly into the thrombus [18]. The drug is allowed to interact within the thrombus for a while and the device is used to aspirate the residual thrombus at the end. Isolated thrombolysis is another method performed by Trellis Peripheral Infusion System (Covidien) [5, 19]. With this device two catheter-mounted balloons are inflated to isolate a segment of vein and a bolus dose of a thrombolytic drug is injected directly into the thrombus. Activation of an oscillating wire for 10 min is then used to mechanically disperse the drug within the thrombus, and then the drug and liquefied debris are aspirated through a port on the device. Another similar device is Reya Thrombectomy catheter (Biolas Health) that is designed to use with the implantation of a temporary retrievable vena cava filter for protection before activation of an oscillating wire (Fig. 2). There are also many different endovascular venous thrombus aspiration systems such as Aspirex S Catheter (Straub Medical) and Angiovac Cannula and Circuit (AngioDynamics).

Although definitive multicenter RCTs comparing the most recent PCDT, CDT and combined methods have not been published yet, current practice shows strong clinical tendency for the use of PCDT with or without other endovascular methods and an individualized approach for each DVT patient [4, 5, 20].

1.1.3 Percutaneous Mechanical Thrombectomy

Stand-alone *percutaneous mechanical thrombectomy* (PMT) refers to the percutaneous use of catheter-based mechanical devices that contribute to thrombus removal via fragmentation, maceration, and/or aspiration, without administration of a thrombolytic drug. These methods are not always suitable for every patient and in most of the cases they are reserved for the patients with serious risk of bleeding and/or other contraindications for the thrombolytic therapy. *PMT has not received general acceptance*

because of the associated risk of PE and damage to venous valves caused by thrombectomy devices [10, 13].

1.1.4 Percutaneous Aspiration Thrombectomy

Percutaneous aspiration thrombectomy (PAT) technique can be defined as using a syringe to aspirate thrombus from the vein via a catheter, device, or sheath. PAT has been routinely used to effectively eliminate thrombi located in hemodialysis fistulae with a patency rate of 86 % at 6 months after PAT [21]. PAT also has been accepted as a rapid, safe, and effective method of management of iliofemoral vein thrombosis and provides higher recanalization rates than alternative treatments [13]. However, few clinical studies have been performed. Previous studies reported a recanalization rate of 88.9 % with PAT for the lower extremity DVT. Mechanical thrombectomy devices are not required during PAT and, therefore, the risk of trauma to the vascular wall and valves is thought to be low. Thrombolytic agents are not given to PAT patients, and the bleeding complications associated with systemic therapy are therefore absent [13, 22]. However there is no standardized PAT aspiration method and the technique is not widely accepted. PAT is most commonly used as an adjunctive endovascular technique like balloon maceration to fragment thrombus, balloon angioplasty, stent implantation and vena cava filter placement (Fig. 3).

Interventional endovascular therapies for DVT have the potential to provide PE protection and prevention of PTS. There is increasing number of scientific evidence in support of endovascular treatments. However, patient centered individualized approach for endovascular DVT treatment is recommended to optimize the ideal clinical result.

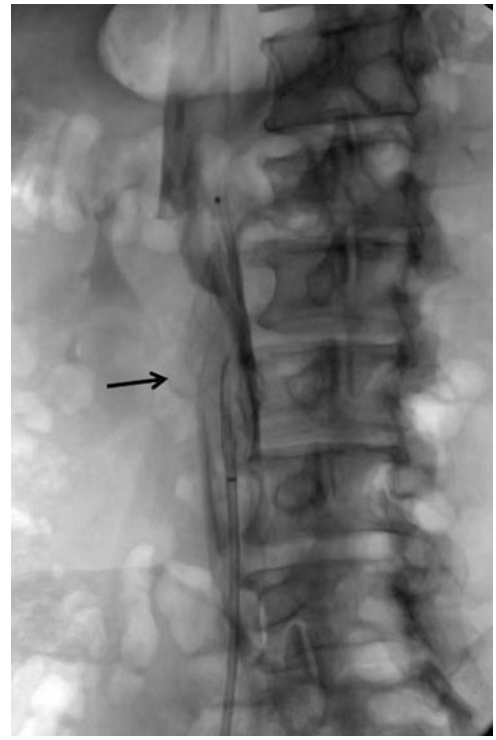


Fig. 3 Retrievable IVC filter was placed for periprocedural PE prophylaxis during pharmacomechanical thrombolytic treatment. Significant thrombus material (*arrow*) was captured by the filter just after the treatment

2 Endovascular Treatment of Acute Stroke

According to the World Health Organization (WHO), *stroke* is the leading cause of death for people above the age of 60 and the fifth leading cause in people aged 15–59 [23]. Stroke is the most common cause of disability worldwide [23, 24]. Every 6 s someone in the world will either be permanently disabled or will die due to stroke. More than 80 % of stroke cases are acute ischemic stroke cases due to cessation or diminution of blood supply to a certain part of the brain after arterial occlusion or hypoperfusion. Acute ischemia occurs mostly due to thromboembolism or local occlusion. Less frequently global hypoperfusion may cause acute cerebral ischemia. Immediate and prompt treatment of acute stroke is very important because of the heavy burden of this disease on a person and the society. Mortality during the first 30 days of ischemic stroke is 20 % and 30 % of survivors will remain permanently disabled [25].

2.1 Primary Management of Acute Stroke Patients

An acute stroke patient first seen in a hospital with the capability of intravenous (IV) fibrinolysis must have a *nonenhanced computerized tomography (NECT)* of the head to rule out cerebral hemorrhage. Patients without significant improvement after IV fibrinolysis can be immediately transferred to higher-level stroke centers. Patients that are seen by the emergency medical services in the field will benefit more if they can be sent to the nearest stroke center with the capability of both intravenous and intraarterial therapy and dedicated neurovascular imaging capabilities. *IV recombinant tissue plasminogen activator (alteplase, rtPA)* was the first approved treatment for acute ischemic stroke within 3 h of stroke onset after the *NINDS* (National Institute of Neurological Disorder and Stroke) trial. There are several exclusion criteria for the IV fibrinolytic therapy (Table 2).

The American Stroke Association (ASA, 2013) published guidelines for the early management of patients with acute ischemic stroke [26] (Tables 3, 4 and 5).

Recommendations with the highest level of evidence and that are directly related with the endovascular management of acute stroke are included. Recommendations regarding the intensive care management of acute stroke patients are not within the scope of this article. According to these guidelines an algorithm for management of acute stroke patients can be formed (Table 6).

2.2 Endovascular Therapy

Recanalization rates after *IV rtPA* in internal carotid artery terminus and MCA M1 segment occlusions range between 10 and 50 % and less than 40 % of patients regain functional independence [27]. Endovascular therapy has the main advantage of extended therapy window, earlier and more efficient recanalization and less risk of hemorrhage due to lower doses of thrombolytics. Endovascular therapies include

Table 2 Inclusion and exclusion characteristics for patients with ischemic stroke who could be treated with IV rtPA within 3 h from symptom onset

Inclusion criteria
Diagnosis of ischemic stroke causing measurable neurological deficit
Onset of symptoms <3 h before beginning treatment
Aged ≥18 years
Exclusion criteria
Significant head trauma or prior stroke in previous 3 months
Symptoms suggest subarachnoid hemorrhage
Arterial puncture at noncompressible site in previous 7 days
History of previous intracranial hemorrhage
Intracranial neoplasm, arteriovenous malformation, or aneurysm
Recent intracranial or intraspinal surgery
Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)
Active internal bleeding
Acute bleeding diathesis, including but not limited to
Platelet count <100,000/mm
Heparin received within 48 h, resulting in abnormally elevated aPTT (activated partial thromboplastin time) greater than the upper limit of normal
Current use of anticoagulant with international normalized ratio (INR) >1.7 or partial thromboplastin time (PT) >15 s
Current use of direct thrombin inhibitors or direct factor Xa inhibitors with
elevated sensitive laboratory tests (such as aPTT, INR, platelet count), and
ECT (ecarin clotting time); TT (thrombin time); or appropriate factor Xa activity assays
Blood glucose concentration <50 mg/dL (2.7 mmol/L)
CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)
Relative exclusion criteria Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV rtPA administration carefully if any of these relative contraindications are present:
Only minor or rapidly improving stroke symptoms (clearing spontaneously)
Pregnancy
Seizure at onset with postictal residual neurological impairments
Major surgery or serious trauma within previous 14 days
Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
Recent acute myocardial infarction (within previous 3 months)

Table 3 ASA recommendations for the evaluation of the stroke patient in the emergency service

1. An organized protocol for the emergency evaluation of patients with suspected stroke (Class 1; Level of evidence B). The goal is to complete and begin fibrinolytic treatment within 60 min of the patient's arrival in an ED (Emergency department). Designation of an acute stroke team. Patients with stroke should have a careful clinical assessment, including neurological examination
2. The use of stroke rating scale preferably the NIHSS (National Institute of Health Stroke Scale) (Class 1; Level of evidence B)
3. A limited number of hematologic, coagulation and biochemistry tests are recommended during the initial emergency evaluation, and only the assessment of blood glucose must precede the initiation of intravenous rtPA (Class 1; Level of evidence B). Because hypoglycemia may mimic stroke signs and hyperglycemia is a risk factor for unfavorable outcomes

Table 4 ASA recommendations for the radiologic evaluation of the stroke patient

1. Either head NECT (Nonenhanced computerized tomography) or MRI (Magnetic resonance imaging) is recommended before intravenous rtPA administration to exclude intracerebral hematoma which is an absolute contraindication (Class 1; Level of evidence A)
2. Intravenous fibrinolytic therapy is recommended in the setting of early ischemic changes (other than frank hypodenisty) on CT, regardless of their extent (Class I; Level of evidence A)
3. A noninvasive intracranial vascular study is strongly recommended during the initial imaging evaluation of the acute stroke patient if either intraarterial fibrinolysis or mechanical thrombectomy is contemplated for management but should not delay intravenous rtPA if indicated (Class I; Level of evidence A)
4. CT perfusion and MRI perfusion and diffusion imaging, including measures of infarct core and penumbra, may be considered for the selection of patients for acute reperfusion therapy beyond the time windows for intravenous fibrinolysis. These techniques provide additional information that may improve diagnosis, mechanism, and severity of ischemic stroke and allow more informed clinical decision making (Class IIb; Level of Evidence B)
5. Frank hypodensity on NECT may increase the risk of hemorrhage with fibrinolysis and should be considered in treatment decisions. If frank hypodensity involves more than one third of the middle cerebral artery (MCA) territory, intravenous rtPA treatment should be withheld (Class III; Level of Evidence A)

Table 5 ASA recommendations for intravenous fibrinolysis

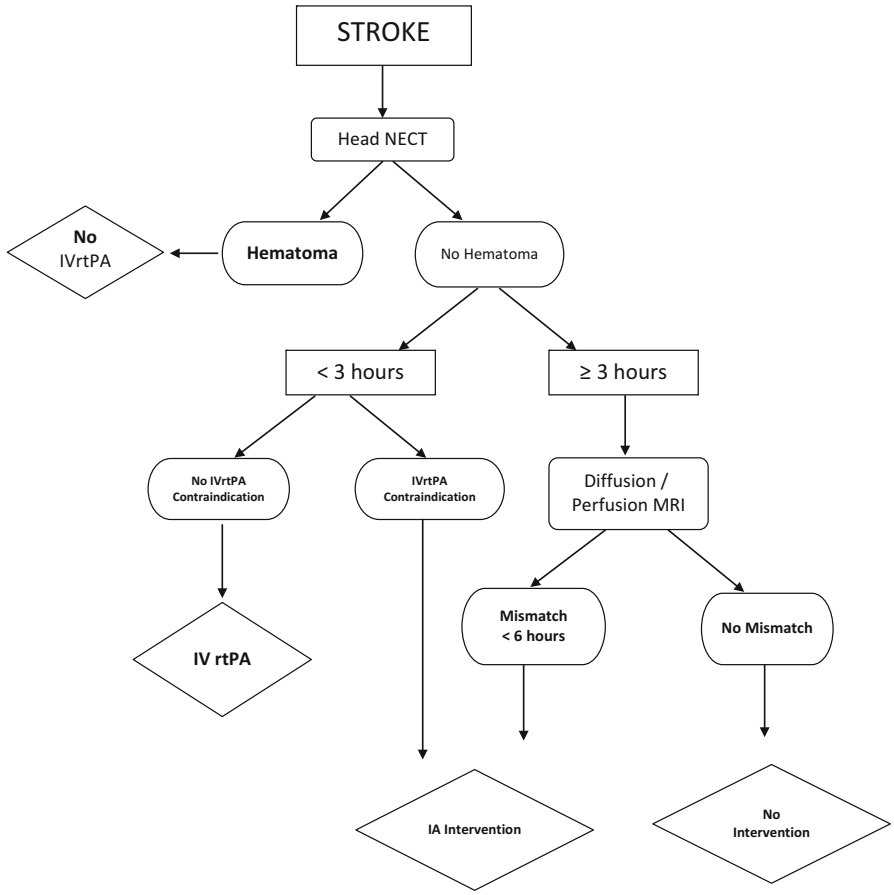
1. Intravenous rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for selected patients who may be treated within 3 h of onset of ischemic stroke (Class I; Level of Evidence A). Physicians should review the criteria outlined in Table 2 (which are modeled on those used in the NINDS Trial) to determine the eligibility of the patient
2. Intravenous rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for administration to eligible patients who can be treated in the time period of 3–4.5 h after stroke onset (Class I; Level of Evidence B). The eligibility criteria for treatment in this time period are similar to those for people treated at earlier time periods within 3 h, with the following additional exclusion criteria: patients >80 years old, those taking oral anticoagulants regardless of INR, those with a baseline NIHSS score >25, those with imaging evidence of ischemic injury involving more than one third of the MCA territory, or those with a history of both stroke and diabetes mellitus

either application of local intraarterial thrombolytics in the occluded intracranial segment or mechanical removal of the clot with a thrombectomy device or another endovascular device like a balloon or stent. *According to most recent guidelines safe therapy window for endovascular treatment is the first 6 hours after the stroke onset* [26]. After the development of dedicated mechanical thrombectomy devices, including stent retrievers, the balloon angioplasty has been put aside. Major disadvantages of endovascular therapies include low availability due to requirement of high level of expertise of specialists and complex neurointerventional infrastructure, delay in therapy initiation and invasive nature of the endovascular methods. Potential complications of endovascular stroke treatment are reperfusion hemorrhage, distal emboli, intracranial dissections, hematomas and subarachnoid hemorrhage [28, 29].

2.2.1 Intraarterial Fibrinolysis

The first positive randomized trial [28] to evaluate the efficiency of intraarterial fibrinolysis was PROACT 2 (Prolyse in Acute Cerebral Thromboembolism). In this study IA fibrinolysis with recombinant prourokinase (r-pro-UK) yielded

Table 6 Algorithm for management of acute stroke patients



higher middle cerebral artery recanalization rates than the control group (66 % vs % 18, $p < 0.001$). Fibrinolytics used in acute stroke treatment work as plasminogen activators. Prourokinase did not achieve FDA approval and it is not available any more and today the most frequently used IA fibrinolytic is *Alteplase (rtPA)*. Alteplase is applied directly within the thrombus through a microcatheter. Most neurointerventional specialists would use a maximum dose of 22 mg of IA rtPA [30, 31]. Adjunct mechanical disruption of the clot can be used with microwire maneuvers to increase the interaction surface area of the clot and the medicine. Recanalization rates in large artery occlusion including internal carotid artery, basilar artery or MCA M1 segment is not as high as distal and smaller arteries [32, 33]. Due to this reason in most centers first line treatment for large artery occlusions causing stroke is the mechanical thrombectomy. However, IA fibrinolysis is still used very efficiently in distal small artery occlusions like MCA M2-M3 segments, ACA paricallosal/callosomarginal branches and posterior cerebral artery occlusions. Bridging therapies as combination of IV rtPA and IA rtPA can further increase recanalization rates. Three consecutive trials, interventional management of stroke (IMS) 1, 2 and 3, showed better outcomes with comparable rates of symptomatic intracranial hematoma and mortality compared with NINDS rtPA trial [30, 34, 35].

2.2.2 Mechanical Thrombectomy

Mechanical thrombectomy has several advantages over IV/IA fibrinolysis. First of all, recanalization with mechanical techniques is faster. There is less risk of hemorrhage due to lower dose of fibrinolytics. Atherosclerotic emboli rich of calcium or cholesterol causing stroke are more resistant to pharmacological lysis and this brings the potential benefit of better recanalization by mechanical thrombectomy in these cases. Patients with contraindication to IV/IA fibrinolysis due to recent surgery and abnormal coagulation parameters can be treated only by means of mechanical thrombectomy [36]. Although there are several commercially available mechanical thrombectomy devices, only devices that are most frequently used, and that have been thoroughly studied in the literature, will be mentioned in this chapter. All mechanical thrombectomy devices are deployed in the intracranial arteries through microcatheters. Depending on the device they are either deployed within or distal to the clot and engage with the thrombus when deployed. Then the whole system, device, microcatheter and proposedly engaged clot are retrieved (Fig. 4). For documenting the recanalization/reperfusion rates after IA intervention a scale was proposed by Higashida et al. [37]. TICI (Thrombolysis in Cerebral Infraction) scale is

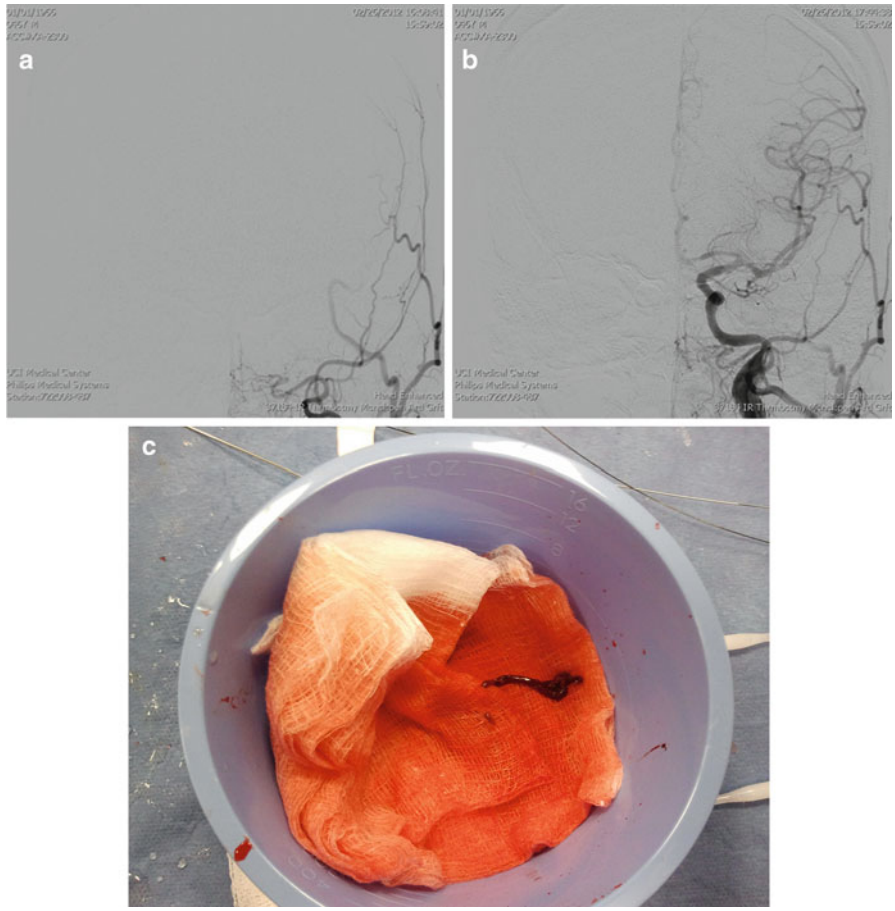


Fig. 4 (**a**) Left common carotid angiogram in an acute stroke patient shows complete occlusion of the internal carotid artery. There is no cerebral blood flow but only external carotid artery branches can be seen. (**b**) Complete recanalization of the left ICA and MCA after aspiration and mechanical thrombectomy. (**c**) Clot that occluded ICA was taken out by the thrombectomy device

commonly used in stroke centers to document the results of their therapies [38]. First FDA approved (2004) device *MERCI* (Concentric Medical, Mountain View, California) is a flexible nitinol wire with coil loops [39, 40]. *Penumbra* (Penumbra, Alameda, California) is another device that works by thromboaspiration by a microcatheter connected to an aspiration pump after mechanical disruption of the clot with a separator [41]. After the Penumbra Pivotal Stroke Trial [42], the Penumbra device was approved by FDA (2008). Newest and most frequently used devices are *stent retrievers including Solitaire* (Covidien, Irvine, CA), *Trevo* (Stryker Neurovascular, Fremont, California), *Catch* (Balt Extrusion, Montmerency, France) and *Preset* (Phenox, Bochum, Germany). ASA guidelines recommend choosing stent retrievers over other devices for mechanical thrombectomy in addition to other recommendations (Table 7).

Table 7 Recommendations for endovascular therapy

1. Patients eligible for intravenous rtPA should receive intravenous rtPA even if intra-arterial treatments are being considered (Class I; Level of Evidence A)
2. Intra-arterial fibrinolysis is beneficial for treatment of carefully selected patients with major ischemic strokes of <6 h duration caused by occlusions of the MCA who are not otherwise candidates for intravenous rtPA (Class I; Level of Evidence B)
3. As with intravenous fibrinolytic therapy, reduced time from symptom onset to reperfusion with intraarterial therapies is highly correlated with better clinical outcomes, and all efforts must be undertaken to minimize delays to definitive therapy (Class I; Level of Evidence B)
4. Intra-arterial treatment requires the patient to be at an experienced stroke center with rapid access to cerebral angiography and qualified interventionalists. An emphasis on expeditious assessment and treatment should be made. Facilities are encouraged to define criteria that can be used to credential individuals who can perform intra-arterial revascularization procedures. Outcomes on all patients should be tracked (Class I; Level of Evidence C)
5. When mechanical thrombectomy is pursued, stent retrievers such as Solitaire FR and Trevo are generally preferred to coil retrievers such as Merci (Class I; Level of Evidence A)
6. Intra-arterial fibrinolysis or mechanical thrombectomy is reasonable in patients who have contraindications to the use of intravenous fibrinolysis (Class IIa; Level of Evidence C)

These devices are self-expandable and retrievable stents that are deployed within the thrombus, jail the thrombus in between the stent struts and the artery wall and remove the thrombus by retrieving (Fig. 5). Both pivotal studies for Solitaire and Trevo showed superiority in recanalization rates compared with Merci [43, 44]. FDA approved both devices in 2012. The main advantage of stent retrievers is that once they are deployed temporary restoration of the blood flow to the deprived brain parenchyma occurs. By technological improvements, smaller microcatheter systems are used to navigate these stent retrievers in distal cerebral vasculature. Two landmark studies that were published recently, *SWIFT PRIME* and *MR CLEAN,* will potentially revolutionize the management of acute stroke [44–47]. *MR CLEAN* (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) [47] assessed whether intraarterial treatment plus usual care would be more effective than usual care alone in patients with a proximal arterial occlusion in the anterior cerebral circulation that could be treated intraarterially within 6 h after symptom onset. 195 patients (81.5 %) out of 233 patients treated with IA treatment had mechanical thrombectomy with stent retrievers. Only one patient (0.4 %) had IA thrombolytic agents as monotherapy. This represents the paradigm shift toward a more frequent use of mechanical thrombectomy devices as the first line therapy for IA treatment of acute stroke [48]. There were better recanalization (75.4 % vs 32.9 %), less infarct volume and more functionally independent patients (32.6 % vs 19.1 %) in the IA treatment group than the IV fibrinolysis group. *SWIFT PRIME* (Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment) trial evaluated the efficacy and safety of mechanical thrombectomy with the stent retriever in conjunction with intravenous t-PA versus intravenous t-PA alone in patients with acute ischemic stroke. Successful reperfusion rates were significantly higher (83 % vs 40 %) in the stent retriever group. Both studies showed that IA treatment especially with the new stent retrievers lead to a

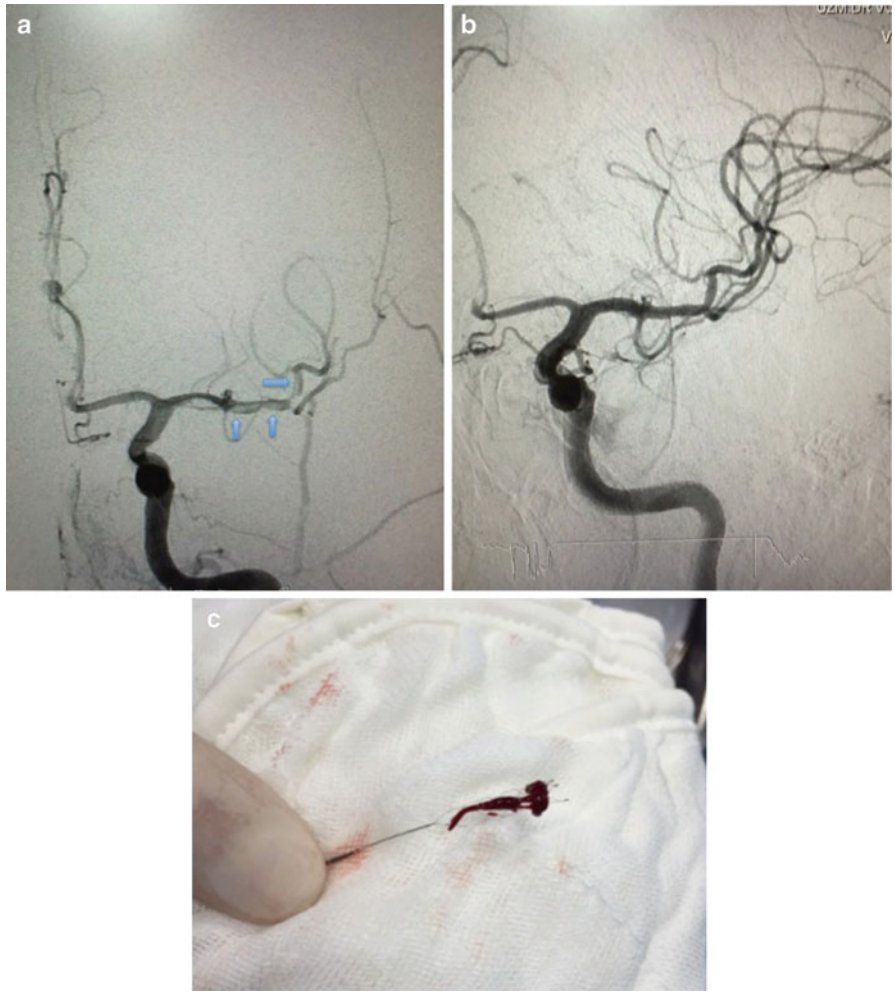


Fig. 5 (**a**) Acute stroke caused by a clot in left MCA M1 and M2 segment that is causing a linear filling defect within the artery. (**b**) Complete recanalization by a stent retriever and normal filling of the left MCA branches. (**c**) Clot engaged to the stent retriever device is seen. Shape and size of the clot correspond well with the angiographic image of the thrombosis in MCA (Fig. 5a)

significant increase in functional recovery and independence in daily life after an acute stroke.

3 Endovascular Treatment Cerebral Venous and Sinus Thrombosis

Cerebral venous and sinus thrombosis (CVST) comprises nearly 0.5–1 % of all stroke cases. Incidence of CVST is 3–4 cases per million in adults and incidence in pediatric population is 0.67 per 100.000 children [49]. In adult population it is more common in women and female predominance is most likely related with oral contraceptive use and hormonal disturbances during pregnancy. Other causes of CVST are infection, dehydration, hypercoagulable states, cardiac disease, surgery and trauma [50–53]. Most commonly affected intracranial venous structure is the *superior sagittal sinus* (SSS) followed by the transverse sinus. Other dural sinuses and cortical veins may also be involved. Clinical presentation is highly variable from completely asymptomatic cases to severe

intracranial hypertension, cerebral hematoma and herniation. Most common symptoms are headache, nausea, seizures, visual disturbances, decreased consciousness level and focal neurological deficits like hemiparesis, aphasia. Different neurological deficits are seen depending on the location of the thrombosis in the cerebral venous system and the affected cerebral lobe drained by that specific vein. For example, whereas thrombosis of the middle 1/3 of the SSS may cause hemiparesis, occlusion of the posterior 1/3 of the SSS may lead to cortical blindness due to occipital lobe involvement. Occlusion of the anterior 1/3 of the SSS may be asymptomatic. Occlusion of the dural sinus accompanied by the thrombosis of a cortical vein may potentially cause a higher risk of hemorrhagic infarct. Ferro et al. in the largest prospective multicenter international study found out 13.4 % death and dependency in 624 CVST patients [54]. Risk factors for an unfavorable outcome were male sex, age >37 years, coma, mental status disorder, intracranial hemorrhage on admission, thrombosis of the deep cerebral venous system, central nervous system (CNS) infection, and cancer [54, 55].

3.1 Radiological Work-up

Computerized tomography of the head is the most frequently used noninvasive radiological exam in patients presenting with headache or focal neurologic deficits. Cerebral infarct with or without hemorrhage can be seen in head CT of severe cases (Fig. 6). Cerebral infarct in venous thrombosis will not follow the arterial territories and will have a more atypical appearance and location than the arterial thromboembolism. The "*empty delta sign*" can be seen in enhanced head CT as enhancement of dura around the nonenhanced thrombosed sinus segment (Fig. 7). The "*cord sign*" defined as a homogeneous, hyperattenuated appearance of thrombosed venous sinuses on nonenhanced CT scans is highly specific and sensitive for deep venous system thrombosis [56].

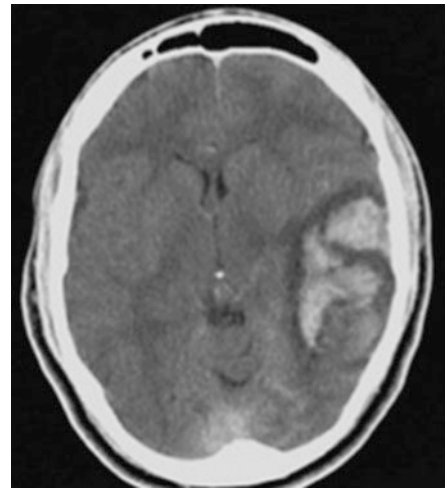


Fig. 6 NECT shows hemorrhagic infarct of the left frontoparietal lobes and mass effect due to cerebral vein thrombosis

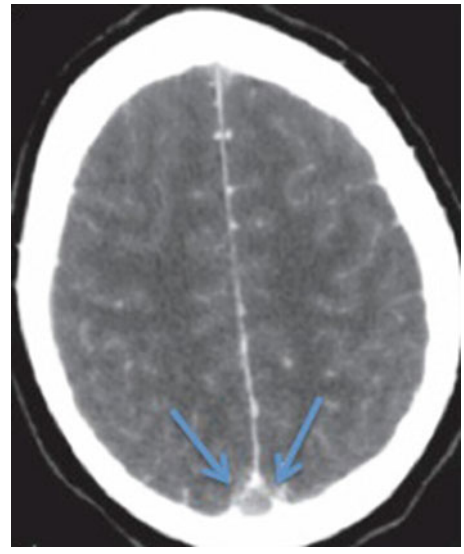


Fig. 7 "Empty delta sign" due to thrombosis of the superior sagittal sinus in contrast enhanced head CT

CT or Magnetic resonance (MR) angiography of the cerebral veins will depict the thrombus and its expansion within the venous system (Fig. 8). *"Cord sign"*, cerebral edema, infarct, subdural hematoma and subarachnoid hemorrhage due to cerebral venous thrombosis can be seen in CT or MR imaging. Both modalities *CT/CT venography* and *MR/MR venography* can be

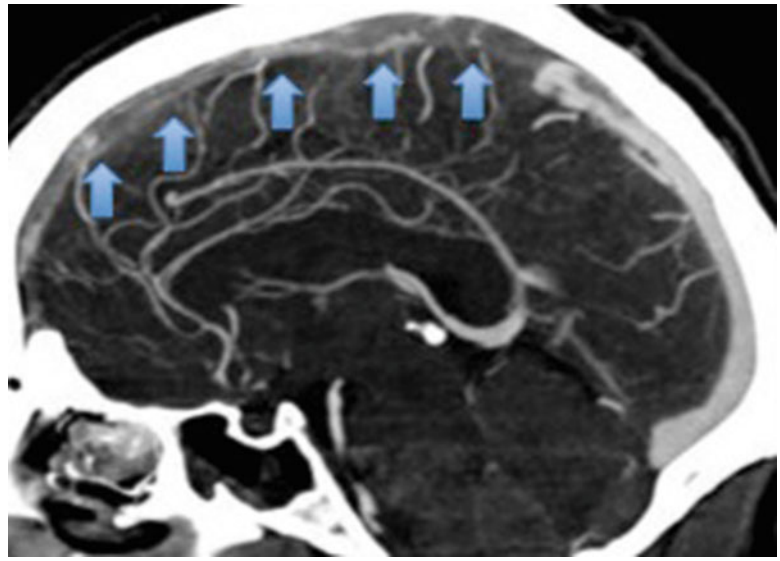


Fig. 8 Occlusion of the anterior 2/3 of the superior sagittal sinus in head CT venography (*Arrows*)

effectively used to diagnose and to follow up CVT cases [57–59].

3.2 Medical Management

Stabilization of the general status of the patient with hydration, treatment for intracranial hypertension and management of symptoms like seizures and headaches are first line measures. *Anticoagulation with heparin* is the most widely accepted therapy to prevent the expansion of the thrombus. Several studies showed better outcomes in CVST patients treated with heparin [60, 61].

Effective systemic anticoagulation targets activated partial thromboplastin times (aPTT) between 60 and 80 s. Cerebral hemorrhage is not a contraindication for heparin use in CVST and a substudy from *ISCVT (International Study on Cerebral Vein and Dural Sinus Thrombosis)* study group suggested a better efficacy and safety of low–molecular weight heparin over unfractionated heparin [62].

3.3 Endovascular Treatment

Despite heparinization, some CSVT patients with negative prognostic factors will fail to recover and mortality rate can be as high as 10 % in these patients [63]. Patients with rapid decompensation despite medical therapies will need more aggressive treatments. Rahman et al. [64], based on their literature review for endovascular treatment of CSVT, proposed a treatment algorithm for CSVT patients. Patients who present with severe neurological deficits (Glasgow coma scale score ≤ 8) are strongly considered for direct thrombolysis/thrombectomy immediately. Patients with Glasgow coma scale score (GCS) scores between 9 and 12 may be considered for immediate endovascular treatment. For other patients (GCS score > 12), direct thrombolysis/thrombectomy would be considered only after a trial of systemic anticoagulation. Endovascular methods include intrasinus infusion of thrombolytics or heparin, balloon angioplasty, mechanical thrombectomy or a combination of different techniques [65–70]. For pharmacological lysis of the clot, intrasinus heparin or thrombolytic infusion can be performed. Either urokinase or tissue plasminogen activators can be used as thrombolytics [71–75]. Infusion of local thrombolytics may increase the size of the hemorrhagic infarct in addition to complications including pulmonary embolism and hemorrhage. Mechanical thrombectomy can be achieved with rheolytic

catheters, balloon angioplasty, Fogarty catheter or dedicated mechanic thrombectomy devices including stent retrievers. There is a higher rate of recanalization with endovascular methods compared to other medical therapies. Even with partial recanalization of the sinus significant clinical recovery may happen. Until today there is no controlled randomized trial to compare the efficacy of intrasinus infusion of thrombolytics/heparin with mechanical thrombectomy for the treatment of CSVT.

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Venous Thromboembolism in Brain Tumor Patients

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Abstract

Venous thromboembolism (VTE) is a common medical condition, particularly after surgical interventions. Many studies have shown that development of VTE, including both deep vein thrombosis (DVT) and pulmonary embolism (PE), is more common in surgical patients with cancer than in patients without cancer. This chapter focuses on VTE in brain tumor patients, including their pathogenesis, presentation, diagnosis, and treatment. Topics discussed included a brief overview of VTE followed by an in-depth discussion of the VTE risks brain tumor patients face in the post-operative period. We conclude with a summary of various recommendations on VTE prophylaxis and a discussion of the controversial nature of VTE chemoprophylaxis for patients undergoing transcranial operations for brain tumors.

Keywords

Venous thromboembolism • Deep venous thrombosis • Neurosurgery • Brain tumors • Brain surgery • Prophylaxis • Thromboprophylaxis • Anti-coagulation • Pulmonary embolism

1 Introduction

Venous thromboembolism (VTE) is a term that encompasses two distinct but similar pathologies: deep venous thrombosis (DVT) and pulmonary embolism (PE). VTE has been studied extensively, mostly because it is relatively common and can also lead to significant morbidity and death. Statistics from Center for Disease Control (CDC) show that VTEs account for more than half a million admission annually. The scope of the problem is large, as VTE is a major contributor to mortality among patients hospitalized for a wide range of illnesses, despite advances in diagnosis, prevention, and treatment.

This chapter focuses on VTE in brain tumor patients, including pathogenesis, presentation, diagnosis, and treatment. Topics discussed

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included a brief overview of VTE followed by an in-depth discussion of the VTE risks brain tumor patients face in the post-operative period. We conclude with a summary of various recommendations on VTE prophylaxis and a discussion of the controversial nature of VTE chemoprophylaxis for patients undergoing transcranial operations for brain tumors.

2 Epidemiology of VTE

VTE is a significant contributor to mortality and morbidity and has been recognized as a serious public health issue. In 2008, the U.S. Surgeon General issued a "call to action" initiative to address the problem of VTE, and similar initiatives have also been started in the UK and Canada [1–3].

VTE occurs regularly in 1–2 % of the general population, with an annual incidence of 1 in 500 [4, 5] According to the Centers for Disease Control and Prevention (CDC), it is estimated that over a 3-year period (2007–2009), there was an annual average of 547,596 hospitalizations among patients 18 years and older, during which VTE was diagnosed [6]. In terms of mortality, which mainly occurs as a result of PE, it is estimated that the prevalence of VTE-related deaths annually is somewhere between 100,000 and 300,000 [7].

Non-fatal VTE contributes significantly to morbidity and lowers quality of life. VTE can result in pain, edema, and post-thrombotic syndrome, a form of venous reflux that occurs secondary to DVT. VTE can also cause chronic thromboembolic pulmonary hypertension, which usually results in shortness of breath and cardiac disability.

To understand the magnitude of the burden VTE places on the healthcare system, a study of the economic impact of the morbidity associated with such an illness will be useful. A review of ten cost-of-illness studies of several geographic locations displayed the magnitude of this burden [8]. In the United States of America, initial costs associated with VTE were approximated to range from US$3,000 to US$9,500. Total costs of US $5,000, US$10,000, and US$33,000, were associated with VTE care over 3 months, 6 months, and 1 year, respectively. These figures were similar for Europe, with an addendum inpatient costs of €1,800 after 3 months and €3,200 after 1 year. The burden is not constituted by inpatient care only, but also by the associated complications of commonly used interventions and treatments. For instance, such costs can be as high as US $11,700 for the treatment of post-thrombotic syndrome, and as high as $41,133 for heparin-induced thrombocytopenia. This doesn't only indicate that treating complications costs more than treating the disease itself, but also sheds the light on the hidden burden of this illness on disabling active members of the society, and the effect this has on their dependents and the economy as a whole, which remains to be investigated.

Patients undergoing operations for brain tumor resection are more likely to develop VTE as a result of three additive risk factors: cancer, natural thrombotic responses to operative injury, and limited post-operative mobility. Harboring cancer is an independent risk factor for VTE, with studies demonstrating that up to 10 % of cancer patients have clinically apparent VTE [9]. Overall, patients harboring brain tumors are even more likely to develop VTE than patients who have cancers in other sites, making them one of the most vulnerable populations to VTE development (Table 1) [10–29].

3 Pathogenesis of VTE in Patients with Brain Tumors

Virchow's triad delineates the three most commonly cited pathogenic mechanisms for the development of VTE: venous stasis, a hypercoaguable state, and endothelial damage. Most patients who develop VTE have at least one of these typical risk factors, and many have two or more.

Beyond Virchow's triad, recent literature has suggested that a wide range of additional factors are related to the development of VTE in cancer patients [30]. Data on VTE development in brain tumor patients, however, are limited. When discussing the pathogenesis of VTE in brain

Table 1 Rate of VTE in patients with various types of cancer[a]

Cancer type/Site	Diagnoses/100 hospitalizations		
	VTE	PE	DVT
Pancreas	4.3	1.2	3.5
Brain	**3.5**	**1.0**	**2.8**
Myeloproliferative, other lymphatic/hematopoetic	2.9	[b]	2.5
Stomach	2.7	0.7	2.3
Lymphoma, lymphosarcoma, reticulosarcoma	2.5	0.6	2.0
Uterus	2.2	0.5	1.8
Trachea, bronchus, and lung	2.1	0.6	1.6
Esophagus	2.0	[b]	1.3
Prostate	2.0	0.6	1.6
Rectum, rectosigmoid junction, anus	2.1	0.7	1.4
Kidney	2.0	0.5	1.6
Colon	1.9	0.6	1.4
Ovary	2.0	0.5	1.6
Liver, gallbladder, intra- and extrahepatic ducts	1.8	0.9	1.1
Leukemia	1.7	0.4	1.4
Breast (female)	1.7	0.4	1.3
Cervix	1.6	[b]	1.4
Bladder	1.0	0.3	0.8
Lip, oral cavity, pharynx	<0.6	[b]	[b]
No cancer	1.0	0.3	0.8

[a]Table adapted from Stein et al. [22]
[b]Insufficient data

tumor patients, it is convenient to categorize the risk factors for VTE development by dividing them into patient-related, tumor-related, and host tissue-related mechanisms [5, 31, 32].

VTE is far more common during the post-operative period than it is in the general population [33–41]. Proposed explanations for this phenomenon include limited post-operative mobility, which can promote venous stasis, and damage to endothelial tissue. So from one stand point, brain tumor patients are at risk for VTE simply by undergoing an operation. Additionally, certain procedures confer more VTE risk than others. Orthopedic procedures, for example, increase the risk of VTE development: Day et al. recently reported a VTE rate of 1.2 % for lower extremity arthroplasties, and 0.53 % for shoulder arthroplasties [42]. Craniotomy, the most common operation for brain tumor resection, has also been implicated in increasing VTE risk compared to other operations [43]. Several studies have also shown that patients harboring brain tumors develop DVT at a higher rate than patients with cancer at other sites or patients undergoing procedures for diseases other than cancer (Table 1) [10, 29].

Patient with brain tumors are also more commonly afflicted with motor deficiencies that can render them bed ridden or immobile [44]. This limited mobility can result in relatively slower venous blood flow, one of the chief risk factors for VTE development [32, 45]. The use of indwelling central venous catheters for delivery of chemotherapeutic agents involved in the treatment of brain tumors can also contribute to the development of DVTs and PEs [46]. Patient specific genetic factors, such as factor V Leiden or an excess of pro-thrombotic factors can also be implicated in VTE development in brain tumor patients [24].

Many other risk factors have been reported as potential contributors to the development of VTE [44] (Table 2). Incidence of DVT and PE almost double when comparing those aged 65–69 to those above 85 years of age [47]. A similar trend is seen in a study comparing those aged 30–39 to younger patients with a twofold

Table 2 Factors associated with VTEs in patients with brain tumors and their corresponding odds ratios

Factor[a]	Odds Ratio	95 % Confidence Interval	P-Value
Increase the likelihood			
Intraluminal thrombosis (ILT) [11]	17.8	[4–79.3]	<0.0001
Sex (Female) [24]	14.2	[3.3–62.0]	<0.001
Perivascular Lymphocytic infiltrates (moderate – severe) [11]	12.0	N/R	<0.05
Prior history of DVT/PE [24]	7.6	[1.6–35.8]	0.01
Prior history of DVT/PE [20]	7.1	N/R	<0.001
Necrosis (moderate – severe) [11]	4.4	N/R	<0.05
Seizure [21]	2.4	N/R	0.005
Decrease the likelihood			
Ethnicity (Caucasian) [24]	0.5	[0.3–0.9]	0.04
Post-operative ICU days (1 Day earlier exit) [24]	0.2	[1.1–1.4]	0.003

N/R not reported, *ICU* intensive care unit
[a]Only includes statistically significant results

increase in the risk of VTE [48]. Traditionally, patients above the age of 40 are considered at a higher risk of VTE development [49]. A BMI >25–35 has also been implicated as a risk factor for VTE in other studies, along with increased operative duration, increased post-operative complications (all-types), and increased hospital stay [50, 51]. Gender, post-operative ICU days, anti-coagulation state, and blood type have also been studied as potential factors related to VTE in cancer patients [24, 42, 49]. Steroids and some chemotherapy protocols, often prescribed after cranial surgeries for brain tumors, have also been reported to contribute to VTE formation [44, 51].

Beyond these general risk factors for patients harboring brain tumors, there are many mechanisms specific to brain tumors that increase the risk of VTE development, most notably increased production of tissue factor (TF) and other pro-coagulants [21, 24, 52]. A study by Bastida et al. demonstrated that micro-vesicles from the cell-free supernatant of U-87 MG (a cell line of human glioblastoma cells) results in platelet aggregation and coagulation [52]. This is clinically correlated with a higher rate of VTE in patients with gliomas, one of the most common types of brain tumor [21, 24]. Khorana et al., in a series of pancreatic cancer patients, demonstrated that increased plasma TF correlates with the formation of VTE [53]. This has been suggested as a possible mechanism through which malignancies increase the risk of VTE [54].

Other studies have investigated this, but found negative immuno-histochemical staining for TF in a glioma specimen. Thus the models supporting this hypothesis (linking the increase of TF in brain tumors to VTE) remain limited to cell cultures, and are not in-vivo models [52, 55].

Another brain tumor-specific risk factor for VTE development are TF-bearing micro-particles (TFMP). In a group of 96 patients with advanced malignancies including glioblastoma, increased levels of TFMP tissue factor antigens were found to be 3.72 times more likely to result in VTE [56]. In 2011, Sartori et al. studied the pro-coagulant activity of circulating MPs in patients harboring glioblastoma multiforme (GBM). They found that MP activity levels increased in 63.6 % of 61 patients who underwent resection of GBM, a statistically significant association ($chi^2 = 4.93$, $p = 0.026$) [57] (Table 3).

Host tissues also contribute to the formation of VTE in patients with brain tumors. Collagen-rich endothelial membranes stimulate platelet aggregation, and thus the collection of white blood cells and ultimately VTE formation [31, 58]. Animal models also demonstrate that tumor interaction with platelets can lead to aggregation [59]. Both local and systemic tissue inflammation are also thought to take part in development of VTE through inflammatory markers, such as C-reactive protein (CRP),

Table 3 DVT development by brain tumor type[a]

Tumor type	DVT+/total patients (%)
Metastasis	44/185 (23.8)
High Grade Glioma	53/248 (21.4)
Low Grade Glioma	5/28 (17.6)
Meningioma	16/196 (8.2)
High Grade Oligodendroglioma	3/15 (20.0)
Low Grade Oligodendroglioma	2/16 (12.5)
Mixed	3/9 (33.3)
Sarcoma	0/3 (0.0)
Schwanomma	4/22 (18.2)
Acoustic Neuroma	0/1 (0.0)
Medulloblastoma	0/6 (0.0)
Lymphoma	8/27 (29.6)
Pituitary Adenoma	0/10 (0.0)
Ependymoma	0/6 (0.0)
Hemangiopericytoma	1/4 (25.0)
Choroid	0/3 (0.0)
Hemangioblastoma	2/9 (22.2)
Other	15/88 (17.0)

[a]Table adapted from Smith et al. [21]

which is considered a potential indicator of the presence of VTE [60]. Evidence also suggests the involvement of tumor necrosis factor (TNF), a known inflammatory mediator, in the process of VTE development [61]. In addition to inflammation, disruption of the endothelium during operations leads to a pro-thrombotic state via the release of pro-thrombotic factors [31]. Cell adhesion molecules like P-selectin and E-selectin also promote leukocyte margination and adhesion [31]. P-selectins found in alpha granules of platelets and Weibel-Palade bodies of endothelial cells increase tissue factor expression and were found to be pro-thrombotic in animal models [62]. This has been clinically correlated by a study that displayed their increased presence in patients with cancer who developed VTE [63].

4 Presenting Signs and Symptoms

VTE presentation in afflicted patients can vary widely depending on the region involved. In some patients, VTE (especially DVT) can be asymptomatic. The most common presenting symptoms for DVT include pain and edema of the affected limb [64–66]. Symptoms can also include severe tenderness of the extremity, a palpable mass, blanching of the skin, and excessive warmth or redness in the extremity [23, 64, 67, 68]. PE, on the other hand, commonly present with signs and symptoms that include dyspnea, pleuritic pain, cough, hemoptysis, and palpitation [64, 69]. The location of these presenting symptoms can greatly aid in diagnosis and localization of the thrombus.

Definitive diagnosis of VTE often requires radio-graphical investigation. A low threshold of suspension should provoke the work up for DVT, which typically involves an upper/lower extremity ultrasound to locate the embolus [38, 69]. Well's score is the most widely used tool for assessment of likelihood of VTE occurrence, despite the availability of other scoring systems [70]. A systematic review of 17 articles evaluating the use of such scores reported a median positive likelihood ratios of 6.62, 1, and 0.22 when patients had a high, moderate, and low pretest probability for the use of Well's score, respectively [71]. Another study showed that the use of compression ultrasonography had a negative predictive value of 97–98 % after a normal result, which rose to 99 % after serial testing in an outpatient setting [72]. In a recent report, basing the choice of investigation on symptoms and clinical signs in such clinical scores was found to be less accurate than the use of biomarkers. For instance, clinical signs were found to be statistically less useful in aiding the diagnosis of DVT (Area under the curve (AUC): 0.69), as compared to serum protein S (AUC: 0.82) and albumin (AUC: 0.80) [73].

In the case of PE, however, workup is more complex and should include radiographic imaging techniques such as chest CT scans and V/Q scans, depending on the risk and the profile of the patient [21, 66, 67, 74]. The use of Well's score was similarly useful for detection of PE as DVT, with median positive likelihood ratios of 6.75, 1.82, and 0.13 when patients had a high, moderate, and low pretest probability,

correspondingly [71]. Helical spiral computed tomography (CT) has a negative prediction value of >99 % to diagnosing PE, and can thus safely replace the gold standard of angiography [72].

5 Prophylaxis and Treatment

There are multiple modalities available for physicians to achieve thrombo-prophylaxis in their patients. The methods of achieving thrombo-prophylaxis can be broadly divided into two categories: pharmacological or mechanical. The ideal method depends on multiple factors, and physicians should always aim to achieve thrombo-prophylaxis without conferring additional health risks to patients. Viewing the patient holistically, physicians can determine how to tailor the ideal method of thrombo-prophylaxis based on several factors, including prior history of VTE, presence of a malignancy, pertinent contraindications to anti-coagulation, and the overall type of patient (e.g. medical vs. surgical; neurosurgical vs. general surgical).

These factors, in addition to the risk factors mentioned earlier, may guide physicians towards optimal prophylaxis. For general surgical patients, the Modified Caprini risk assessment model for VTE can be used to categorize patients by risk from very low to high [75, 76]. Patients with a high Modified Caprini risk ($\geq$5) are estimated to have a six percent chance of developing VTE if left untreated. Based on this risk score, an appropriate method of prophylaxis is then prescribed.

A scoring system like the Modified Caprini scale has not been developed or validated specifically for neurosurgical patients. Based on evidence from observational studies, however, the nature of neurosurgical procedures and central nervous system malignancy are both significant contributors to risk of VTE [54]. Craniotomy patients are thus considered at high risk for acquiring VTE. Furthermore, brain tumor patients undergoing craniotomy have a higher risk for developing VTE compared to patients undergoing craniotomy for other pathologies (e.g., elective aneurysm surgery).

An important complicating factor in thromboprophylaxis for neurosurgical patients is the risk of intracranial hemorrhage (ICH). Patients undergoing transcranial operations for tumors or vascular lesions are already at an increased risk for hemorrhage. The addition of anti-coagulant medication has been proposed as a potential risk factor for higher rates of hemorrhage among neurosurgical patients. Data on this association have been mixed. Some studies have demonstrated an increased rate of intracranial hemorrhage when VTE chemoprophylaxis is initiated pre-operatively [77]. In contrast, other studies have failed to demonstrate any evidence of increased hemorrhage risk with VTE chemoprophylaxis [78–81]. One study estimated that craniotomy patients have approximately 1 % risk for developing ICH in the absence of thromboprophylaxis [82]. Other studies report even a lower risk [83]. Despite this relatively low risk, the consequences of ICH are great (e.g., disability, paresis or paralysis, speech impediment, diminished neurological function, or death), emphasizing the need to approach medical prophylaxis thoughtfully.

5.1 Pharmacological Prophylaxis

The use of anticoagulants in the prophylaxis of VTE is extremely common. Several medical options are available and involve the administration of one of the following drugs:

Low-Dose Unfractionated Heparin Low-dose unfractionated heparin interrupts the coagulation cascade through augmenting the function of antithrombin III, which in turn affects the activity of factor Xa and IIa [84]. In a meta-analysis of general surgical patients, Clagett et al. demonstrated that the administration of low-dose unfractionated heparin was effective in preventing the formation of DVT [84, 85]. Another study, however, has demonstrated that heparin is ineffective in preventing VTE in critically injured patients [86]. Overall, evidence from meta-analyses shows significant reduction of VTE risk, with some studies reporting a decrease of fatal PE by

Table 4 Occurrence of hemorrhagic complications with various pharmacological VTE prophylactic regimens in patients with brain tumors

Pharmacological drug	Hemorrhagic complications % in treatment group	Hemorrhagic complications % controls group	P-value
Heparin (5000 units, BD, SC) / Enoxaparin (40 mg, OD) [21]	0.00 %	1.30 %	–
Heparin (5000 units, BD, SC) [103]	2.00 %	N/R	–
Heparin (5000 units, BD, SC)	3.78 %	N/R	–
Dalteparin (2500 units, OD) [103]	4.00 %	N/R	–
Nadroparin [104]	2.50 %	0.80 %	0.87
CY 216 (Fraxiparin) [105]	19.8 %	N/R	–
Pooled data analysis[a]	RR	95 % CI	P-Value
UFH vs Control [83]	0.50	(0.11–2.38)	–
LMWH vs UFH [83]	1.46	(0.61–3.51)	–

N/R not reported
[a]Including studies involving brain neoplasms

60 % compared to no prophylaxis [87]. Patients given unfractionated heparin should have their platelets monitored in order to detect heparin-induced thrombocytopenia (HITT), a complication that presents as a consumptive coagulopathy [88]. In case of overdose, protamine sulfate is used as an antidote to unfractionated heparin [89].

Low Molecular Weight Heparin (LMWH)
LMWH has been studied extensively for reducing the rate of VTE development. It has a similar mechanism of action as unfractionated heparin, working to interrupt the coagulation cascade through antithrombin III. It is however different in that it mainly inhibits the action of factor Xa. - Meta-analyses have shown that LMWH is at least as efficacious as unfractionated heparin for reducing VTE [75]. Advantages LMWH has over unfractionated heparin is that can be administered subcutaneously, and has a much lower incidence of HITT. This makes it generally more effective in the clinical setting.

In brain tumor patients, what is more important is not choosing between LMWH or unfractionated heparin, but whether the method of chemoprophylaxis should be used at all. Several trials have compared the efficacy of the two drugs, showing similar results [83] (Table 4). As we have discussed previously, these agents will reduce the risk of VTE at the cost of potentially increasing the risk of ICH. In brain tumor patients undergoing craniotomy, administering LMWH or unfractionated heparin is safe and indicated, as the benefit of reducing the already much higher VTE risk outweighs the increase in risk for developing ICH. Other pharmacological alternatives exist, some of which are becoming more commonly used. These include fondaparinux, warfarin, asprin, and novel direct thrombin/factor Xa inhibitors.

5.2 Mechanical Prophylaxis

The second approach available to achieve thrombo-prophylaxis is through mechanical methods. The two most common forms of mechanical prophylaxis for VTE are intermittent pneumatic compression (IPC) and compression stockings [90].

It is thought that IPC not only reduces venous stasis, but also stimulates endogenous fibrinolytic activity [91]. This is likely because of a reduction in plasminogen activator inhibitor-1 (PAI-1), resulting in an increased fibrinolytic activity through tissue plasminogen activator (tPA) activity [91]. In a systematic meta-analysis, Vanek et al. demonstrated that IPC decreased the risk of DVT by 62 % compared to a placebo, 47 % compared to high-pressure stockings, and 48 % compared to low molecular weight heparin [92]. In a randomized trial of

Table 5 Mechanical prophylaxis efficacy compared to pharmacological prophylactic regimens for VTEs in patients with brain tumors

Reference	% developed VTE with mechanical prophylaxis	% Developed VTE (*Method of Prophylaxis*)	RRR	P-value
Nurmohamed et al. [104] – CS	11.5 %	6.90 % (LMWH)	40.2 %	0.065
Macdonald et al. [103]-	4.41 %	1.89 %(LMWH)	N/R	–
Skillman et al. [106]– IPC	8.30 %	–	N/R	–
Turpie et al. [93]– CS	8.80 %	19.8 %(None)	N/R	–
Turpie et al [93]– CS + IPC	9.00 %	19.8 %(None)	N/R	–
Pooled LMWH + IPC [83]	5.7 %	–	N/R	–
Pooled UFH + IPC [83]	1.5 %	–	N/R	–
Pooled data analysis[a] [83]	**RR**	**95 % CI**	**RRR**	**P-Value**
IPC vs CS	0.81	(0.32–1.78)	N/R	–
IPC vs placebo	0.41	(0.21–0.78)	N/R	–
LMWH vs CS	0.60	(0.44–0.81)	N/R	–
LMWH vs IPC	0.79	(0.30–2.12)	N/R	–

N/R not reported
[a]Including studies involving brain neoplasms

neurosurgery patients, Turpie et al. corroborated this data by reporting the incidence of DVT at 8.8 % in patients using high-pressure stockings, 9 % in patients using IPC, and 19.8 % in an untreated control group [93]. Kurtoglu et al. similarly reported that IPC was as effective as low molecular weight heparin in DVT prophylaxis following head and spinal trauma [84]. Although effective at preventing DVT, Vanek et al. report that IPC and compression stockings have no effect on the rate of PE formation [92]. Overall, IPC has limited adverse effects, and is an alternative for patients who are contra-indicated to receive anticoagulants.

Compression stockings have been studied less than IPC, but nevertheless have been demonstrated to be effective in preventing DVT. One meta-analysis showed that compression stockings reduced the risk of developing DVT by 65 % compared to no prophylaxis [94]. Most often, compression stockings are combined with other thrombo-prophylactic measures.

Because paresis and limited post-operative mobility are often reported as risk factors for the development of DVT, post-operative ambulation is encouraged for prophylactic purposes. Intervention with physical therapy for patients who are not ambulatory is often employed as an additional prophylactic. Post-operative ambulation and exercise can help prevent venous stasis, which contributes to the development of VTE as described above [34, 36, 49, 85, 95].

5.3 Combined Prophylaxis

Because both mechanical and chemical prophylaxis are effective at reducing the rate of VTE development during the post-operative period, they are frequently prescribed simultaneously. Several studies have compared the effectiveness of chemical anticoagulation with the effectiveness of mechanical prophylaxis [14, 40, 77, 84, 86, 96, 97]. Many of these studies show that combined prophylaxis has a higher effectiveness in preventing VTE than either method alone, without increasing risk to the patient (Table 5) [97].

5.4 Timing of Prophylaxis

Proper timing of prophylaxis for development of VTE in surgical patients is an issue that is more difficult to address, and remains controversial. In the case of patients with brain tumors, neurosurgeons are often wary of prescribing pre-operative anticoagulants that may be employed in other types of surgery due to the risk of ICH intra- or immediately post-op [98]. ICH poses a serious risk to the patient's cognitive and functional outcome, and can lead to re-operations and iatrogenic morbidity. In other disciplines, the administration of pre-operative chemical anti-coagulants remains more generally accepted because of lower danger of complications from intra-operative bleeding. As such, for patients with brain tumors, pre-operative anticoagulation is generally discouraged [12, 14, 24, 40, 41, 85, 99, 100].

For the same reason, neurosurgeons are often overly cautious of prescribing chemical anticoagulants during the post-operative period. Carman et al. surveyed American neurosurgeons and reported that, generally, they underestimate the risk of DVT after brain surgery, and tend to avoid the use of chemoprophylaxis [98]. They remain committed to VTE prophylaxis via mechanical means, however, almost universally providing patients with some form of mechanical prophylaxis (e.g., ICP). This mechanical prophylaxis is often used without combined chemical prophylaxis, however [98]. Another point worth considering is that ICH typically occurs within 12–24 h post-operatively, while the majority of VTE occurs one week after craniotomy. Despite mounting evidence of both their safety and efficacy, chemical anticoagulants remain under-prescribed by neurosurgeons during the post-operative period [78, 80, 81, 84, 97, 98].

5.5 Treatment for VTE

There are several methods for treating VTE. The first line of treatment is chemical anticoagulation, usually with heparin [31, 65, 68, 93]. Treatment with heparin often resolves VTE and its associated symptoms. In some cases, however, anticoagulation is contraindicated. Contraindicated patients include patients who are non-ambulatory or comatose. Treatment with anticoagulants in these cases can lead to hemorrhage and associated morbidity and mortality.

When anticoagulants are contraindicated, VTE can be treated endovascularly, most often with filters. VTE filters are placed most frequently in the inferior vena cava (IVC) to prevent a circulating clot from becoming a PE. IVC filters have been shown to be extremely effective in preventing the development of PE and in decreasing the morbidity and mortality of patients known to be harboring DVT [17, 18, 84, 101].

5.6 Clinical Recommendations for VTE Prophylaxis

The American College of Chest Physicians, in 2012, recommended that VTE chemoprophylaxis for craniotomy patients should include mechanical prophylaxis, preferably with IPC, rather than no prophylaxis or pharmacologic prophylaxis [75]. For craniotomy patients at very high risk of VTE (e.g., those harboring malignancies), the ACCP recommended the addition of pharmacologic prophylaxis in addition to mechanical prophylaxis, once hemostasis has been established (Grade 2C).

The American Society of Clinical Oncology also released VTE prophylaxis guidelines, which stated that all surgical patients with malignant disease should receive pharmacological prophylaxis with LMWH or unfractionated heparin, unless contraindicated, and that the prophylaxis should be commenced preoperatively and continued for 7–10 days.

Lastly, the international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer state that a brain tumor is not a contraindication for anticoagulation for diagnosed VTE, per se, but that decisions should be based on individual

clinical assessment [102]. These recommendations also state that chemoprophylaxis with LMWH or UFH should be commenced post-operatively for neurosurgical patients with cancer, with preference given to subcutaneous injections (Grade 1A).

Based on the body of evidence, despite being relatively low quality, the best practice for thrombo-prophylaxis in brain tumor patients undergoing surgery would be administering pharmacologic prophylaxis with either LMWH or unfractionated heparin, post-operatively up to a period of 10 days, in addition to IPC.

6 Conclusion

Brain tumor patients are at a higher risk for development of VTE during the post-operative period due to both the process of undergoing an operation (i.e., general anesthesia, limited mobility, endothelial damage) and the pro-thrombotic nature of brain tumors themselves.

Neurosurgeons are still overly cautious of prescribing VTE chemoprophylaxis in the post-operative period due to a fear of ICH. Despite this risk, a growing body of evidence suggests that chemoprophylaxis in the post-operative period for brain tumor patients is safe and should be prescribed as soon as hemostasis has been secured.

7 Key Points

- VTE is a common complication in patients with brain tumors, and poses a great economic burden on the health system.
- Patients with brain tumors are susceptible to VTEs due to physical factors, and tumor pathology, and thus VTE prophylaxis is vital in this patient cohort.
- Chemoprophylaxis for VTE is a safe option prior to and following cranial operations, and is beneficial despite the minimal increased risk of associated intra-cranial hemorrhage.
- Combined prophylaxis (mechanical and chemical) of VTE in the post-operative can effectively decrease the risk.

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Portal Vein Thrombosis: Recent Advance

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Abstract

Portal vein thrombosis is a life-threatening vascular disorder of the liver. In this chapter, I will review the recent advance regarding the epidemiology, etiology, management, and prognosis of portal vein thrombosis.

Keywords

Portal vein • Splanchnic vein • Thrombus • Portal hypertension • Liver • Hepatic

1 Introduction

Portal vein thrombosis (PVT) refers to the development of thrombus within the extra-hepatic main portal vein and/or intra-hepatic portal vein branches. With the improvement of imaging techniques, PVT may not be a rare disease any longer. It is caused by a variety of etiologies, including cancer, cirrhosis, inherited or acquired prothrombotic disorders, local inflammatory lesions and injury to the portal venous system. The pathophysiology of PVT may include the hypercoagulability, portal vein injury, and portal blood flow stasis. The primary therapeutic strategy of PVT is to deal with the predisposing factors, to recanalize the thrombosed vessels, and to prevent from the development of PVT-related complications. As for the patients without liver cirrhosis or hepatocellular carcinoma, the prognosis of PVT is relatively favorable. By comparison, as for the patients with liver cirrhosis, occlusive PVT may significantly increase the mortality; and as for the patients with hepatocellular carcinoma, PVT is one of the most important prognostic markers. In this chapter, I review the recent advances regarding the epidemiology, etiology, management, and prognosis of PVT.

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2 Epidemiology

The prevalence/incidence of PVT greatly varies according to the characteristics of study population. At least two Swedish population-based studies have evaluated the prevalence of PVT in the general population. Ögren et al. conducted a large-scale population-based study involving 23796 autopsies in Malmö city, Sweden between 1970 and 1982 to evaluate the prevalence of PVT

(Ogren et al. 2006). Surprisingly, the population prevalence of PVT was up to 1.0 % (254/23796). The underlying etiology included liver cirrhosis (28 %), primary and secondary hepatobiliary malignancy (67 %), major abdominal infectious or inflammatory disease (10 %), and myeloproliferative disorders (3 %). Rajani et al. also performed a retrospective multi-center study in eleven Swedish hospitals to estimate the incidence and prevalence rates of PVT (Rajani et al. 2010). They identified a total of 173 patients with PVT. The underlying etiology included liver disease (40 %), malignancy (27 %), thrombophilic factors (22 %), and myeloproliferative disorders (11 %). Importantly, the mean age-standardized incidence and prevalence rates were 0.7 per 100,000 per year and 3.7 per 100,000 inhabitants, respectively.

Fimognari et al. elegantly reviewed 25 relevant literatures regarding the prevalence of PVT in patients with liver cirrhosis (Fimognari and Violi 2008). The prevalence of PVT varied from 5 to 20 % in cirrhotic patients. This heterogeneity might be primarily due to the different diagnostic modalities employed among the studies (autopsy, surgery, and ultrasound) and the exclusion or inclusion of hepatocellular carcinoma. Additionally, the severity of liver dysfunction might influence the incidence of PVT in liver cirrhosis. In a prospective study by Zocco et al., the incidence of PVT in liver cirrhosis was 16.4 % (12/73) per year (Zocco et al. 2009). Notably, 49 % (36/73) of patients had MELD score of > 13. In another prospective study by Nery et al., the 5-year cumulative incidence of PVT in 1243 cirrhotic patients was 10.7 % (Nery et al. 2015). Notably, a majority of patients had Child-Pugh class A (69.4 %, 863/1243), and the remaining patients had Child-Pugh class B (30.6 %, 380/1243).

3 Etiology

In the absence of liver cirrhosis or hepatocellular carcinoma, the development of PVT mainly originates from the presence of local and systemic hypercoagulable states. Abdominal surgery is the major local hypercoagulable state, such as splenectomy, pancreatic surgery, bariatric surgery, etc. Notably, laparoscopic surgery may be associated with a higher risk of postoperative PVT, due to an increased intra-abdominal pressure during the surgery. According to the recommendations from practice guidelines and expert reviews, the systemic hypercoagulable states primarily include inherited deficiencies of natural anticoagulant proteins (i.e., antithrombin [AT], protein C [PC], and protein S [PS]), factor V Leiden (FVL) mutation, prothrombin G20210A mutation, myeloproliferative neoplasms (MPNs), paroxysmal nocturnal hemoglobinuria (PNH), Behcet's diseases, hyperhomocysteinemia, methylenetetrahydrofolate reductase (MTHFR) C677T gene mutation, antiphospholipid syndrome, etc. (Table 1) (de Franchis 2010; De Stefano and Martinelli 2010; DeLeve et al. 2009).

Table 1 Major systemic risk factors in non-cirrhotic and non-malignant PVT

Major risk factors	Prevalence
Inherited	
Inherited antithrombin deficiency	3.9 %[a]
Inherited protein C deficiency	5.6 %[a]
Inherited protein S deficiency	2.6 %[a]
Factor V Leiden mutation	6 %–32 %[b]
Prothrombin G20210A mutation	14 %–40 %[b]
Acquired	
Myeloproliferative neoplasms	31.5 %[a]
JAK2V617F mutation	24 %[a]
Paroxysmal nocturnal hemoglobinuria	0 %–2 %[b]
Behcet's diseases	0 %–31 %[b]
Hyperhomocysteinemia	12 %–22 %[b]
MTHFR C677T gene mutation	11 %–50 %[b]
Antiphospholipid syndrome	6 %–19 %[b]

Notes: [a]results of meta-analyses, [b]recommendations from AASLD guidelines

Inherited AT, PC, and PS deficiencies are the first causes of inherited thrombophilia in patients with venous thrombosis. However, the nature of AT, PC, and PS deficiencies is readily confused in patients with liver diseases, because PVT can result in the occurrence of liver dysfunction, thereby reducing the AT, PC, and PS concentrations. Qi et al. conducted a systematic review and meta-analysis regarding the prevalence of inherited AT, PC, and PS deficiencies in patients with portal vein system thrombosis (Qi et al. 2013a). Although the pooled prevalence of inherited AT, PC, and PS deficiencies were

relatively low in patients with portal vein system thrombosis (3.9 %, 5.6 %, and 2.6 %, respectively), they were closely associated with an increased risk of portal vein system thrombosis. The pooled odds ratios (ORs) of inherited AT, PC, and PS deficiencies for portal vein system thrombosis were 8.89 (95 % confidence interval [CI]: 2.34-33.72, P = 0.0011), 17.63 (95 % CI: 1.97-158.21, P = 0.0032), and 8.00 (95 % CI: 1.61-39.86, P = 0.011), respectively.

FVL and prothrombin G20210A mutations are often considered as the two most common causes of hereditary thrombophilia in patients with venous thrombosis. Qi et al. conducted a systematic review and meta-analysis regarding the association between FVL and prothrombin G20210A mutations and PVT (Qi et al. 2014a). In non-cirrhotic patients, the presence of PVT was significantly associated with the FVL mutation (OR = 1.85; 95 %CI: 1.09-3.13) and prothrombin G20210A mutation (OR = 5.01; 95 %CI: 3.03-8.30).

Philadelphia-chromosome negative MPNs, which primarily include polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF), may be considered as the most frequent systemic etiological factors of PVT in non-cirrhotic patients. Smalberg et al. performed a meta-analysis regarding the prevalence of MPNs in patients with PVT (Smalberg et al. 2012). The mean prevalence of MPNs was 31.5 % (95 %CI: 25.1-38.8 %). In details, the mean prevalence of PV, ET, MF, and unclassifiable MPNs in such patients was 27.5 % (95 %CI: 19.0-38.1 %), 26.2 % (95 %CI: 19.1-34.8 %), 12.8 % (95 %CI: 8.0-19.9 %), and 17.7 % (95 %CI: 9.9 %-29.7 %), respectively. Indeed, it is often difficult to meet the traditional diagnostic criteria for MPNs (i.e., a significant change in the regular blood tests) in patients with chronic PVT, especially in those with portal hypertension-related bleeding and/or hypersplenism. The identification of JAK2 V617F mutation greatly simplifies the diagnostic strategy of MPNs. A meta-analysis demonstrated that the pooled prevalence of JAK2 V617F mutation in patients with PVT was 24 % (95 %CI: 15.5-33.3) (Smalberg et al. 2012). However, most of data included in this meta-analysis were from Western countries. Subsequently, an observational study also confirmed these findings in Chinese patients with PVT (Qi et al. 2012).

PNH is widely recognized as a major thrombotic risk factor for PVT. A systematic analysis reported that portal vein was one of the most common sites affected by PNH (Ziakas et al. 2007). However, several recent studies just identified a very low prevalence of PNH in patients with PVT (Qi et al. 2013b; Ageno et al. 2014; Ahluwalia et al. 2014). Thus, the role of routine screening for PNH in patients with PVT remains unclear.

Hyperhomocysteinemia is regarded as a major thrombotic risk factor for venous and arterial thrombosis. MTHFR C677T gene mutation is the most precipitating factor for the occurrence of hyperhomocysteinemia. However, in a meta-analysis, the prevalence of homozygous or heterozygous MTHFR mutation was not significantly different between non-cirrhotic patients with PVT and healthy controls (homozygous mutation: OR = 1.72, 95 %CI: 0.90-3.29, P = 0.10; heterozygous mutation: OR = 1.14, 95 %CI: 0.49-2.68, P = 0.76) (Qi et al. 2014b). Notably, a recent observational study demonstrated a very high prevalence of MTHFR C677T gene mutation in Chinese patients with non-cirrhotic PVT (76 %, 29/38) (Qi et al. 2015a). Thus, it might be worthwhile to further evaluate whether or not MTHFR C677T gene mutation contributed to the occurrence of PVT in Chinese patients. Until now, only one study compared the prevalence of hyperhomocysteinemia between non-cirrhotic PVT patients and healthy controls. A statistical significance was achieved (OR = 4.21, 95 %CI: 1.01-17.54, P = 0.05), but a small sample size limited the generalization of the conclusions.

Antiphospholipid syndrome is characterized by arterial and/or venous thrombosis, recurrent fetal loss, and thrombocytopenia in the presence of antiphospholipid antibodies. A systematic review with meta-analysis demonstrated that only positive immunoglobulin G anticardiolipin antibody was more frequently observed in non-cirrhotic patients with portal vein system thrombosis than in healthy controls (Qi et al. 2015b). However, other antiphospholipid antibodies, such as immunoglobulin M anticardiolipin antibody, lupus anticoagulants, anti-β_2-glycoprotein-I antibody, and anti-β_2-glycoprotein-I oxidized low-density

lipoprotein antibody were not associated with portal vein system thrombosis in non-cirrhotic patients. Thus, only immunoglobulin G anticardiolipin antibody should be recommended.

In the setting of liver cirrhosis, the development of PVT is more closely associated with a decreased portal flow caused by the liver architectural derangement. Recently, a prospective study confirmed that a reduced portal flow velocity was the most important predictive variable for the development of PVT in patients with cirrhosis (Zocco et al. 2009). In this study, a portal flow velocity of < 15 cm/s was identified as the cut-off value for the development of PVT. Its sensitivity and specificity was 85.7 % and 78.0 %, respectively. Furthermore, the presence of systemic thrombotic risk factors and the changes of the coagulation and anticoagulation factors might be associated with the development of PVT in liver cirrhosis. However, a meta-analysis found that reduced AT, PC, and PS concentrations were not associated with the development of PVT in such patients (Qi et al. 2013c). Indeed, the reduction should be explained by the occurrence of liver dysfunction. In the patients with hepatocellular carcinoma, tumor invasion accounts for the development of PVT.

4 Prevention

Ideally, the prevention of PVT should include the two major considerations: (1) eradication of predisposing factors; and (2) use of anticoagulants in high-risk patients. As for the PVT in patients with liver cirrhosis, the portal flow velocity should be accelerated. As for the PVT in patients without liver cirrhosis, the acquired or inherited thrombotic risk factors should be corrected.

In patients with definite thrombotic risk factors and without PVT, the use of anticoagulants may be a promising choice for the prevention of PVT. Their potential safety and limited efficacy should be fully balanced. A recent randomized controlled trial by Villa et al. demonstrated that the enoxaparin (4000 IU/day, subcutaneously for 48 weeks) could significantly decrease the incidence of de novo PVT in patients with liver cirrhosis without hepatocellular carcinoma (Villa et al. 2012). The incidence of PVT at 48 weeks was significantly different between the enoxaparin and no treatment groups (0/34 versus 6/36, $P = 0.025$). Notably, the investigators did not record any relevant side effects or hemorrhagic events. Furthermore, the hepatic decompensation events and mortality were significantly decreased. The impressive findings inspired us to explore the prophylactic anticoagulation in cirrhotic patients.

A meta-analysis also evaluated the prophylactic measures for decreasing the incidence of PVT after splenectomy (Qi et al. 2014c). Overall analysis demonstrated that the incidence of PVT after splenectomy was significantly reduced by the preventive measures (OR = 0.33, 95 %CI: 0.22-0.47, $P < 0.00001$). The risk of bleeding was not significantly increased by the preventive measures (OR = 0.65, 95 %CI: 0.10-4.04, $P = 0.64$). However, it should be noticed that the number of included studies is relatively low and the quality is relatively poor.

5 Treatment

Currently, there are lots of treatment modalities for PVT. However, no consensus is clearly provided about the indications and contraindications for various treatment modalities.

5.1 Anticoagulation in Non-Cirrhotic Patients with PVT

Anticoagulation is the most frequently used and readily available choice for therapy of PVT. Anticoagulation therapy significantly increased the rate of portal vein recanalization in patients with recent portal or mesenteric venous thrombosis. In a retrospective study by Condat et al., the rate of recanalization was 25/27 in patients who were treated with anticoagulation and 0/2 in patients who were not treated with anticoagulation (Condat et al. 2000). Additionally, anticoagulant therapy did not increase the risk or the severity of bleeding in non-malignant and non-cirrhotic patients. If anticoagulation therapy was lacking, the risk of thrombosis

would be significantly increased (Condat et al. 2001). They also found that the incidence of splanchnic venous infarction was significantly decreased by anticoagulation therapy (0.82 versus 5.2 per 100 patient-years, P = 0.01). By comparison, Spaander et al. found that anticoagulation therapy was a significant predictor of (re)bleeding (hazard ratio [HR] = 2.0, P < 0.01) and did not significantly reduce the risk of recurrent thrombosis (HR = 0.2, P = 0.1) (Spaander et al. 2013).

Recently, a European multi-center prospective study found that the incidence of portal vein recanalization after early anticoagulation was 33 % in non-malignant and non-cirrhotic patients with acute PVT (Plessier et al. 2010). In this large study enrolling 95 patients with acute PVT receiving anticoagulation, the investigators also found that the presence of ascites (HR = 3.8, 95 %CI: 1.3-11.1) and an occluded splenic vein (HR = 3.5, 95 %CI: 1.4-8.9) predicted the failure to recanalize the portal vein. Maruyama et al. also suggested that intra-thrombus enhancement on the contrast-enhanced sonogram before anticoagulation was associated with the portal vein recanalization after anticoagulation (Maruyama et al. 2012). Collectively, these findings were helpful to guide the physicians to predict the outcome of anticoagulation and to provide an early decision of other aggressive treatment modalities.

More recently, Silva-Junior et al. reported that long-term anticoagulation successfully reconstructed the portal vein patency in a case with portal cavernoma (Silva-Junior et al. 2014). This case potentially supported the clinical utility of anticoagulation in chronic PVT.

5.2 Anticoagulation in Cirrhotic Patients With PVT

Experimental studies by using a global test of thrombin generation found a fragile re-established balance between thrombotic and bleeding tendency in liver cirrhosis. Even an increased ratio of factor VIII to protein C indicated the probability of developing thrombosis in liver cirrhosis (Tripodi et al. 2009). At present, the old dogma that liver cirrhosis has only a bleeding diathesis is being challenged, and the new perspective that anticoagulation therapy may be feasible for the treatment of thrombotic events in liver cirrhosis is gradually accepted (Tripodi and Mannucci 2011).

Several case series disclosed the efficacy and safety of anticoagulation therapy in recanalizing the thrombotic portal vein in liver cirrhosis (Amitrano et al. 2010; Delgado et al. 2012). A systematic review of observational studies reported a low incidence of major anticoagulation-related complications, but no lethal complications (Qi et al. 2015c). The rate of anticoagulation-related bleeding ranged from 0 to 18 % with a pooled rate of 3.3 % (95 %CI: 1.1-6.7 %). In addition, the pooled rate of portal vein recanalization was 66.6 % (95 % CI: 54.7-77.6 %), regardless of complete or partial recanalization. The pooled rate of complete portal vein recanalization 41.5 % (95 %CI: 29.2-54.5 %). Compared with non-anticoagulation group, the anticoagulation group achieved a significantly higher rate of complete portal vein recanalization (OR = 4.16, 95 %CI: 1.88-9.20, P = 0.0004). More recently, Chung et al. have conducted a propensity score matching analysis to compare the outcome of anticoagulation for the treatment of PVT in 14 patients who received warfarin and 14 patients who received no anticoagulation (Chung et al. 2014). In the warfarin treatment group, thrombus resolution was observed in 11 patients. By comparison, in the control group, thrombus resolution was observed in only 5 patients. A statistically significant difference was observed between the two groups (P = 0.022). Generally speaking, we had to acknowledge that only a small number of non-randomized comparative studies were reported (Qi et al. 2015c). The current evidence was weak. High-quality evidence from well-designed randomized controlled trial should be warranted.

5.3 Thrombolysis

Thrombolysis is often employed for the treatment of acute or recent PVT. However, the evidence regarding its efficacy and safety

originates from numerous scattered cases reports and small case series (Robin et al. 1988; Bizollon et al. 1991). Thrombolytics primarily include streptokinase, urokinase, and recombinant tissue plasminogen activator. They can be administered via the local and systemic approaches.

In a single-center study, Smalberg et al. analyzed the risks and benefits of transcatheter thrombolysis in 12 patients with acute, extended splanchnic venous thrombosis (Budd-Chiari syndrome, n = 6; non-cirrhotic PVT, n = 4; cirrhotic PVT, n = 2) (Smalberg et al. 2008). The duration of symptoms was less than 14 days. Among them, 3 thrombotic events were completely resolved and 4 thrombotic events were partially resolved after thrombolysis. However, 50 % (6/12) of patients developed major procedure-related bleeding and 17 % (2/12) of patients developed minor bleeding. Two of them died of procedure-related bleeding. This finding did not recommend thrombolysis in such patients.

By comparison, De Santis et al. suggested that systemic thrombolysis should be safe and effective in 9 cirrhotic patients with recent PVT (De Santis et al. 2010). In this study, PVT was completely resolved in 4 cases, partially resolved in 4 cases, and stable in 1 case. No episodes of thrombolysis-related bleeding occurred. In addition, Wang et al. indicated that transcatheter selective superior mesenteric artery urokinase infusion therapy via the radial artery could be safely performed in 16 patients with acute extensive portal vein and superior mesenteric vein thrombosis (Wang et al. 2010). Notably, all of them achieved compete (n = 9) and partial (n = 7) recanalization of portal vein and superior mesenteric vein thrombosis. No episodes of bleeding were observed. The same team also indicated that catheter-directed thrombolytic therapy via a transjugular intrahepatic route should be safe in 12 patients with acute superior mesenteric venous thrombosis (Wang et al. 2011). Notably, all of them achieved nearly complete disappearance of superior mesenteric venous thrombosis. Certainly, it should not be neglected that the selection of appropriate candidates for thrombolysis and high interventional skills might largely influence the risk of bleeding.

5.4 Transjugular Intrahepatic Portosystemic Shunt

Transjugular intrahepatic portosystemic shunt (TIPS) refers to an interventional radiological procedure in which an expandable stent is inserted into the liver parenchyma between the portal vein and the inferior vena cava (Rossle 2013). The invention of a TIPS originally aims to simplify the technical complexity of a surgical portosystemic shunt. Indeed, shunt surgery has been largely replaced by TIPS in the contemporary era of management of portal hypertension. The main advantages of TIPS for the treatment of PVT include: (1) a direct endovascular manipulation of recanalizing the thrombosed portal vein via an intrahepatic channel (i.e., mechanical agitation of thrombus by using guidewires and catheters or balloon dilation); (2) a direct infusion of thrombolytics and anticoagulants into the occluded vessels; and (3) an accelerated blood flow from the portal vein to the inferior vena cava in order to produce the scouring effect on the thrombosed portal vein (Qi and Han 2012; Qi et al. 2010).

The technical difficulties of TIPS in the setting of PVT are also significant. The first point is how to target the portal vein, especially in the circumstance of occlusive PVT without any contrast materials passing through the portal vein. An ultrasound-guided puncture can facilitate the technical procedure. Additionally, a direct portography via a percutaneous transhepatic puncture into the portal vein or a percutaneous transsplenic puncture into the splenic vein is another consideration. The second point is how the guidewire traverses the thrombus into the patent vessels. High technical experiences are warranted. The third point is how to maintain the blood flow after shunt placement, especially in the presence of extensive superior mesenteric vein thrombosis. If only very little blood returned into the portal vein or stent, the stent became rapidly occluded.

A systematic review identified a total of 424 PVT patients undergoing TIPS in 54 articles (Qi and Han 2012). The rate of successful TIPS

insertion was 67–100 % in 19 case series. Further, TIPS insertions were successful in 85 patients with portal cavernoma. TIPS procedure-related complications were reversible. The overall incidence of shunt dysfunction and hepatic encephalopathy was 8–33 % and 0–50 %, respectively.

5.5 Percutaneous Transhepatic/Transsplenic Balloon Angioplasty and Stent-Placement

Percutaneous transhepatic/transsplenic balloon angioplasty and stent-placement is an alternative choice for therapy of PVT. Cao et al. reported their experiences regarding the efficacy and safety of percutaneous transhepatic balloon angioplasty and/or stent placement alone in 14 patients with PVT (Cao et al. 2013). The main technical steps included: (1) percutaneous transhepatic puncture of the intrahepatic portal vein was performed under ultrasonic and fluoroscopic guidance; (2) portal venous system was observed by direct portography; (3) balloon angioplasty was used to push the thrombus to the vein walls; and (4) stents were placed. Overall, 93 % (13/14) of patients achieved a technical success, which was defined as a brisk portal inflow without significant residual thrombus; and 7 % (1/14) of patients had significant residual thrombus in the stents. Notably, during a median follow-up period of 16.3 months (range: 0.3–120), 43 % (6/14) of patients developed re-thrombosis in the stents. Among them, 2 patients reserved to the patency by stent replacement; 1 patient underwent liver transplantation; and 3 patients received conservative treatments. No procedure-related complications were reported.

More recently, Wang et al. also reported the outcomes of percutaneous transhepatic balloon angioplasty and stent-placement in 13 patients with portal vein occlusion after liver transplantation (Wang et al. 2015). Except for the above-mentioned technical procedures (Cao et al. 2013), transcatheter coil embolization of collaterals and thrombolysis were considered in selected cases. Overall, 84 % (11/13) of patients achieved a technical success. During a mean follow-up period of 28.5 ± 6.8 months, only 9 % (1/11) of patients developed suspected portal vein restenosis. Two patients were complicated with hemorrhagic pleural effusion, of whom one received conservative treatment and another underwent surgical local cauterization.

If a transhepatic approach was not feasible, percutaneous transsplenic portal vein catheterization would be considered. Zhu et al. reported their experiences regarding the feasibility and safety of percutaneous transsplenic portal vein catheterization in 46 patients with variceal bleeding and PVT (Zhu et al. 2013). The main technical steps included: (1) a vein within the splenic parenchyma was punctured under fluoroscopic guidance; (2) a transcatheter portography was performed to evaluate the varices; (3) gastroesophageal varices were embolized, if necessary; (4) a stent was placed to cover the thrombus; and (5) a TIPS was performed, if necessary. Overall, 44 patients achieved a technical success. Among them, 36 patients underwent gastroesophageal variceal embolization, 5 patients underwent stent-placement into the portal vein with variceal embolization, and 4 patients underwent TIPS with variceal embolization. Additionally, 2 patients did not successfully undergo a percutaneous transsplenic portal vein catheterization due to a very fine intra-splenic vein branch, but underwent gastroesophageal variceal embolization. Re-bleeding was rare (8/46). Notably, 3 patients developed procedure-related major bleeding, but were cured by conservative treatments with intravascular embolization.

5.6 Rex Shunt Surgery

In 1992, de Ville de Goyet and colleagues for the first time introduced the extrahilar mesenterico-left portal shunt surgery in a child with

extrahepatic portal hypertension after partial liver transplantation (de Ville de Goyet et al. 1992). In the same year, Chen and colleagues also developed the proximal splenic-left intrahepatic portal shunt surgery in a patient with extrahepatic portal vein obstruction (Chen et al. 1992). The primary principle of the two surgical approaches is to restore the physical portal flow. Currently, the former surgical approach by de Ville de Goyet, which is called as a meso-Rex shunt, is widely employed by experienced surgeons for the treatment of extrahepatic portal vein obstruction (di Francesco et al. 2014). In detail, a jugular vein or saphenous vein graft is employed to bypass from the superior mesenteric vein to the intrahepatic left portal vein within the Rex recessus of the liver.

Lautz and colleagues retrospectively compared the efficacy of the meso-Rex bypass with surgical portosystemic shunts in children with extrahepatic portal vein obstruction (Lautz et al. 2013). Variceal bleeding disappeared in nearly all patients after meso-Rex bypass and surgical portosystemic shunts (96 % versus 100 %). However, compared with those undergoing surgical portosystemic shunts, the patients undergoing meso-Rex bypass achieved a more significant improvement in the platelets count (+82.1 ± 60.0 versus +32.4 ± 56.3 thousand/ml, $P = 0.004$) and weight-for-age z-score (+0.84 ± 0.98 versus +0.17 ± 0.79, $P = 0.044$). Additionally, the serum ammonia level was elevated after surgical portosystemic shunts, but was decreased after meso-Rex bypass. Certainly, meso-Rex bypass is technically feasible in selected cases. Only if the junction of the umbilical remnant and left portal vein was patent, the surgery would be considered. Guerin and colleagues evaluated the outcomes of 69 patients with extrahepatic portal vein obstruction who were suitable for surgery to treat portal hypertension (Guerin et al. 2013). The success rate of meso-Rex bypass was 60 % (26/43), but that of surgical portosystemic shunt was 100 % (26/26). A previous history of neonatal umbilical catheter was associated with a higher rate of technical failure of meso-Rex bypass.

6 Prognosis

Regardless of the etiology of PVT, the major factors associated with reduced survival include advanced age, malignancy, cirrhosis, mesenteric vein thrombosis, and deteriorated liver function (Janssen et al. 2001). In the absence of liver cirrhosis and malignancy, the prognosis of PVT is relatively good. This is primarily because most of non-cirrhotic patients with PVT have preserved liver function. In a single-center retrospective study by Spaander and colleagues, ascites is identified as an independent prognostic factor of non-cirrhotic and non-malignant PVT (Spaander et al. 2010). In details, the 5- and 10-year survival rates were 83 % and 42 % in patients with ascites and 95 % and 87 % in patients without ascites. Qi and colleagues also confirmed the prognostic value of ascites in non-cirrhotic and non-malignant patients with portal cavernoma (HR = 10.729, 95 %CI: 1.2-95.2, $P = 0.033$) (Qi et al. 2013d). Based on these findings, an early decision of aggressive treatment modalities may be appropriate in patients with ascites.

In patients with liver cirrhosis, occlusive PVT is often regarded as an important factor associated with reduced survival (Qi et al. 2011). However, it should be noted that partial PVT may not significantly affect the prognosis of liver cirrhosis. Spontaneous recanalization of partial PVT has been frequently observed (Qi et al. 2014d), which is not associated with the survival (Girleanu et al. 2014; Luca et al. 2012). Certainly, if partial PVT progressed, the prognosis would be further deteriorated (Girleanu et al. 2014). Accordingly, we should avoid the progression of partial PVT and treat occlusive PVT as early as possible.

7 Conclusion

The current knowledge and treatment modalities of PVT are being gradually improved. Accordingly, a preliminary algorithm regarding the

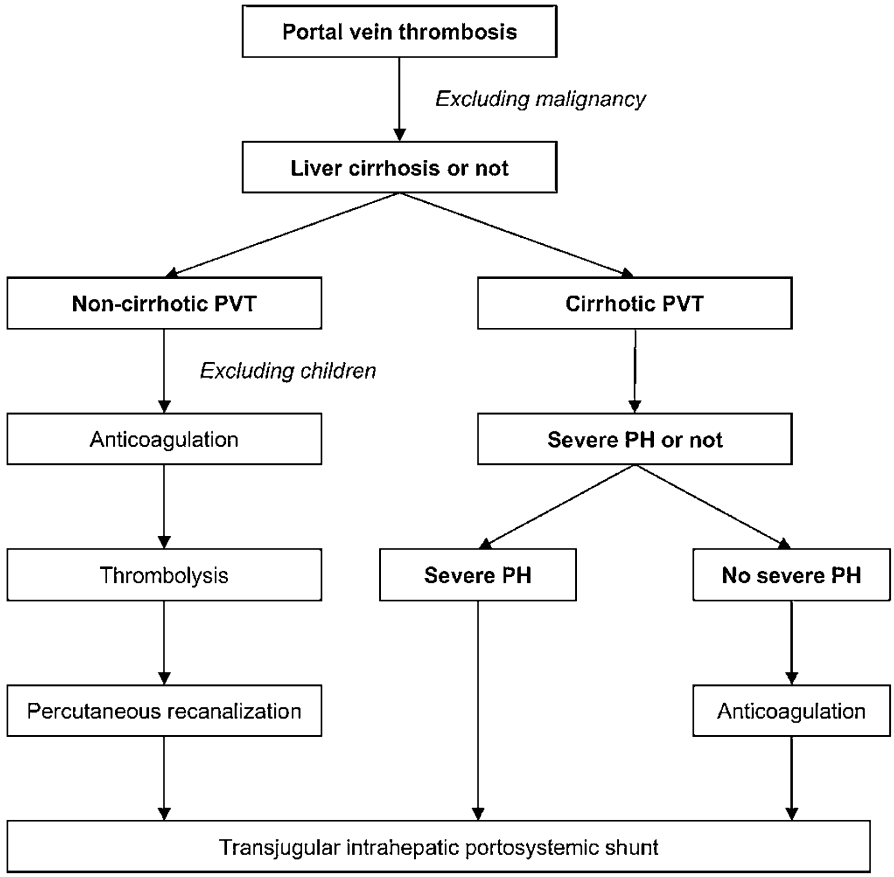

Fig. 1 Preliminary treatment algorithm of recanalizing portal vein thrombosis (Abbreviations: *PH* portal hypertension, *PVT* portal vein thrombosis)

recanalization of PVT can be established (Fig. 1). Certainly, future well-designed studies should provide high-level evidence to define the accurate timing of various treatment modalities of PVT.

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Portal Vein Thrombosis After Splenic and Pancreatic Surgery

Jaime Ruiz-Tovar and Pablo Priego

Abstract

The portal vein is formed by the confluence of the splenic and superior mesenteric veins, which drain the spleen and small intestine respectively. Occlusion of the portal vein by thrombus typically occurs in patients with cirrhosis and/or prothrombotic disorders. However, portal vein thrombosis (PVT) can also happen after determined surgeries. Moreover, PVT can have serious consequences depending on the location and extent of the thrombosis, including hepatic ischemia, intestinal ischemia, portal hypertension... In this chapter, we will review the incidence, management and prophylaxis of PVT after splenectomy, pancreas transplantation, pancreatic surgery and in the setting of acute and chronic pancreatitis.

Keywords

Portal vein thrombosis • Splenic surgery • Pancreatic surgery • Laparoscopy • Prophylaxis • Pancreatic neoplasms

1 Introduction

Portal vein thrombosis is a multifactorial disorder predisposed by certain risk factors, which can be broadly divided into acquired and inherited conditions [1]. Local intra-abdominal inflammatory processes (e.g., pancreatitis, inflammatory bowel disease), or trauma (e.g., splenectomy), increase the risk for portal vein thrombosis and tend to affect the larger veins. Heritable and acquired thrombophilias (e.g., prothrombin G 20210 mutation) and hypercoagulable states related to systemic disorders (e.g., nephrotic syndrome, malignancy) are more likely to affect the smaller veins [2]. However, this is not always the rule.

In this chapter we will review two of the main local causes of portal vein thrombosis, derived from surgical acts: splenic and pancreatic surgery.

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2 Portal Vein Thrombosis After Splenic Surgery

2.1 Epidemiology

Portal vein thrombosis is a complication of splenectomy less usual than bleeding or infection, but it can be potentially deadly. It is considered as an unfrequent event, although the recent increasing use of image techniques suggest that its appearance could be more frequent than previously suspected [3–6]. Several studies estimate its incidence in open surgery between 1.6 and 11 % after splenectomy [7–10].

In the last decade, laparoscopic splenectomy has become very popular for elective splenic surgery. Laparoscopic approach has shortened considerably the hospital stay and thrombosis may appear once the patient has left the hospital, conditioning a delayed diagnosis. Because symptoms are often mild and non-specific, being sometimes even an asymptomatic process, the diagnosis can be missed, achieving it when chronic complications appear, generally related with portal hypertension syndrome [11]. Therefore, the estimated incidence of portal vein thrombosis after laparoscopic splenectomy is completely different among the different published series, ranging between 8 and 54 % [3, 12–15]. Ikeda et al. [14] reported up to date the highest incidence of portal vein thrombosis after laparoscopic splenectomy. However, 67 % of their cases were asymptomatic and diagnosed after a screening with contrast enhanced CT scan. Since many patients remain asymptomatic, the real incidence of this complication is probably underestimated.

Moreover, some of the reported studies in literature are transversal studies, determining the prevalence of portal vein thrombosis rather than the real postoperative incidence. Some cases of thrombosis resolution without treatment have been reported: Loring et al. [16] describe two cases of complete resolution and one of partial one and Skarsgard et al. [17] two other of complete resolution. Thus, it cannot be discarded that in many transversal series there would have been more cases of portal vein thrombosis, that they were asymptomatic and that the thrombosis has completely disappeared along the time.

Anyway, though after open splenectomy it has not been investigated about the real incidence of portal vein thrombosis, as much as after laparoscopic approach, the incidence of portal vein thrombosis seems to be higher after a laparoscopic surgery.

2.2 Risk Factors

There are some factors described that increase the risk of developing portal vein thrombosis. Splenomegaly over 1 kg rises the risk of all post-splenectomy complications, but specially the risk of portal vein thrombosis, that is 14 times more frequent in those patients. A possible explanation of this phenomenon would be a sudden reduction of the splenic vein flow, originating a thrombus that migrates proximally towards portal vein. Apart from this, there is a bounce in the platelet number proportional to the extirpated splenic volume [3, 18].

Diverse works indicate that when the postoperative recount overcomes the million of platelets (1000×10^9/L), thrombosis risk also rises considerably [1]. However, Griesshammer et al. [19] point out that primary thrombocytosis is the one that increases thrombosis risk, not secondary thrombocytosis, concluding that thrombocytosis after splenectomy does not associate a higher risk of portal vein thrombosis. Other recent studies point out that only qualitative platelet disorders increase the risk of portal vein thrombosis [20]. Anyway, the use of antiplatelets is universally accepted when the recount overcomes the million of platelets [19].

Hypercoagulative disorders are also a risk factor for portal vein thrombosis. Qi et al. [21] supported that inherited antithrombin, protein C, and protein S deficiencies significantly increased the risk of portal vein thrombosis, although they were rarely observed in these patients. Similarly, the same authors also reported that the Factor V Leyden and prothrombin G20210A mutations are

associated with an increased risk of portal vein thrombosis without cirrhosis, although they were also rarely observed in such patients.

Regarding their results, Ikeda et al. [14] conclude that the laparoscopic approach implies a higher risk of portal vein thrombosis than the open procedure. Experimental studies [22] suggest that CO_2-pneumoperitoneum associated to anti-Trendelemburg position during laparoscopic surgery reduces the portal and splenic blood flow, being the flow reduction proportional to the intra-abdominal pressure [22]. The vessels clipage of the splenic hilium has also been involved to the blood flow reduction around the bounded area and to an increase venous ecstasy. These findings might suggest that laparoscopic approach could be the start-point of portal vein thrombosis, although its appearance weeks or months after surgery would indicate that it is a multifactorial process. Some cases of portal vein thrombosis have been described appearing up to 3 years after surgery [3].

2.3 Clinical Manifestations and Diagnosis

As previously mentioned, symptoms are often mild and non-specific, being sometimes even an asymptomatic process. Therefore, the diagnosis can be missed, achieving it when chronic complications appear, generally related with portal hypertension syndrome [11]. The progression of the thrombus, occluding portal and mesenteric veins, may cause acute hypertension in splacnic circulation and intestinal infarct, or develop long term portal extrahepatic hypertension, conditioning hepatic failure or the appearance of oesophageal varixes and portal cavernoma. Early diagnosis is therefore crucial, since the complete reabsorption of the thrombus can be achieved with adequate treatment [5, 6, 11].

Ultrasonography has been classically considered the gold standard for the diagnosis of portal vein thrombosis, because of its sensibility, accessibility, low costs and non-invasiveness [20]. However, at the moment it has been broadly overcome in terms of sensibility and specificity by contrast enhanced CT-scan, that allows the detection of portal segmentary and distal splenic vein thrombosis, difficult to observe at US-Doppler, because of the interference of intraabdominal gas [14]. Nowadays, contrast enhanced CT-scan should be maybe considered the test of choice to carry out when portal vein thrombosis is suspected [23].

2.4 Prophylaxis

Preventive measures to avoid portal vein thrombosis (**primary prophylaxis**) include perioperative use of anticoagulant, thrombolytic and antiplatelet treatments [20]. Prophylactic anticoagulation with low dosis of Low Molecular Weight Heparin perioperatively do not avoid completely the appearance of portal vein, but it probably reduces the risk of deep vein thrombosis or pulmonary thromboembolism [9, 23]. Ikeda et al. [14] do not use antithrombotic prophylaxis in their patients, what could probably have increased their thrombosis incidence; although Chaffanjon et al. [9] describe a thrombosis incidence of 6.7 % in spite of heparinic prophylaxis, while Skarsgard et al. [17] describe an incidence of 6.3 % without any anticoagulant treatment. Considering the proposed etiopathogenic way for portal vein thrombosis and valuing that most thrombotic cases appear in the first week after surgery, some authors think that it would be necessary to consider these patients as high risk subjects and anticoagulant prophylaxis should be prolonged up to 1 month after surgery. Probably, this would not avoid thrombosis, but could reduce the number of cases, always individualizing the risk of postoperative bleeding in each patient [10].

A recently conducted meta-analysis to explore the role of pharmacologic prophylaxis of PVST after splenectomy, concluded that pharmacologic prophylaxis might decrease the incidence of PVST after splenectomy in patients with portal hypertension and did not increase the risk of bleeding. However, the effect of pharmacologic prophylaxis of PVST in patients with

hematological diseases remained questioned. It has to be considered that the indication for splenectomy is different between Asiatic and Western countries. In Western countries, most of patients underwent splenectomy due to the hematological diseases, while in China and Japan most of patients underwent splenectomy due to the portal hypertension. Thus, the difference in the indications for splenectomy might lead to the discrepancy in the role of pharmacologic prophylaxis of PVST after splenectomy [23].

It has also been suggested that heparin combined with antiplatelet agents or Vitamin K antagonists could be indicated in high risk splenectomized patients, although their management appear to be difficult because of the risk of postoperative bleeding. Most published works do not recommend their employment with prophylactic aims [20].

Some authors recommend screening with US-Doppler or CT-scan as the best prevention method (**Secondary prophylaxis**), mainly in high risk patients (big spleen, mielodysplasic syndrome and thrombocytosis), that allow an early diagnosis [16, 24]. In our opinion, a contrast enhanced CT-scan should be performed when any suspicious clinical manifestation take place; US-Doppler can present numerous misdiagnosis. It is still unclear the value of a contrast enhanced CT-scan screening after laparoscopic splenectomy in high risk thromboembolic patients, considering the clinical importance of this entity and its consequences, but the variable incidence reported among the different studies reported in literature.

To avoid the appearance of complications secondary to portal vein thrombosis, anticoagulant treatment should be started (**Tertiary prophylaxis**). A complete disappearance of the thrombus after anticoagulant treatment between 2 and 6 months after its setting-up has been reported in around 75 % of the cases, with clinical improvement in the remaining 25 % [14]. In our experience, in those cases diagnosed diagnosed in acute phase and treated with Acenocumarol during 6 months, contrast-enhanced CT-scan carried out after having finished treatment, showed a complete disappearance of the thrombus. Agreeing with literature, we also defend that anticoagulation seems to be the most effective treatment, achieving resolution of the process in most cases [23].

3 Portal Vein Thrombosis After Pancreatic Surgery and Pancreatic Diseases

3.1 Pancreas Transplantation

Nowadays, results of Pancreas Transplantation (PT) have significantly improved [25]. More efficient immunosuppressive agents, better postoperative care and more refined surgical technique have improved overall survival and decreased postoperative complications after portal thrombosis (PT). Even so, surgical complications and technical failures keep on being a severe problem after PT, associated with increased morbidity and graft loss [26]. Most frequent events are vascular complications, pancreatitis, anastomotic leaks and intraabdominal infection.

Incidence of vascular complications after PT is around 10–20 %. These are divided in thrombosis, haemorrhagia, pseudo-aneurisms, anastomosis stricture and arteriovenous fistulas [27].

3.1.1 Thrombosis

Incidence of thrombosis is around 8.8–35 % (venous in 60 % of the cases and arterial in the rest 40 %) [28]. An early diagnosis is essential, but normally, and instead of an early surgical treatment, this complication is associated with a 50 % of graft loss [29]. There are two types of thrombosis:

(a) Early thrombosis: Most part of the cases (70 %). Normally during the first week after transplantation.
(b) Late thrombosis: More rare and associated to chronic failure of the graft. The mechanisms are not well-known.

Analysis of ***risk factors*** implicated in thrombosis of the graft is so much complex, with multiple variables in its pathophysiology. Nowadays,

Table 1 Risk factors for thrombosis

Risk factors	
Donor	Receptor
Older 45 years old and cardiovascular disease as cause of death	Pancreaticoduodenojejunal anastomosis
Asystolia donor	Acute failure of graft
Unstable haemodynamically	Peritoneal dialysis
Use of desmopressin	Hypercoagulability
Obesity with a BMI >30 kg/m^2	Re-transplantation
Traumatic extraction of pancreas with an excess of fluid preservation	Partial and segmentary pancreas transplantation
	Arterial reconstruction with Carrel "Patch"
Time of preservation >24 h	Excessive length of portal vein or use of an interposition of a portal venous graft
Preservation injury and pancreatitis of the graft	Implantation of the graft in left iliac fossa
	Post-transplant pancreatitis
	Immunosuppressive drugs (cyclosporine, tacrolimus)

it has been described multiple risk factors dependant on the donor and receptor, that are involved in this specific complication [30, 31] (Table 1).

Diagnosis

Clinical manifestations are variable [27], with acute abdominal pain in the location of the pancreatic graft (normally right iliac fossa), acute and not suspected hyperglycemia, haemoperitoneum (especially in venous thrombosis), thrombocytopenia, leucocytosis, gross haematuria (in venous thrombosis) and suddenly decreasing of the amylase levels in urine. Occasionally, a deep venous thrombosis of the ipsilateral iliofemoral system could be identified, due the retrograde progression of the portal venous thrombus.

However, in other cases, partial venous thrombosis can develop asymptomatically, and be detected in a routine Doppler ultrasound.

A Doppler ultrasound is mandatory in case of a suspected thrombosis to analyze arterial and venous flow. The absence of arterial or venous flow is suggested of vascular thrombosis; however there are episodes of graft loss and pancreatitis that could develop a diminution of the flow. A gammagraphy of the pancreatic graft and a CT angiography could be also performed. Anyway, and in cases of doubts, the definitive test is the arteriography.

Treatment of Venous Thrombosis

In cases of total venous thrombosis (TVT), urgent revascularization of the venous system is vital. This thrombolysis or thrombectomy can be performed by interventional radiologists, or by surgeons with an early re-laparotomy [32]. Total venous thrombosis has a poor prognosis, and in most part of the cases, a re-transplantation is required. In the series of Fernandez- Cruz et al. [33], reporting 20 cases of TVT, a transplantectomy was performed in 14 cases and a surgical thrombectomy with postoperative anticoagulation for 3–6 months in 6 cases. Four of these six cases could be recovered with a good posterior functional result.

In cases of partial venous thrombosis confirmed by Doppler, a thrombolysis or thrombectomy performed by interventional radiologists or high doses of anticoagulation could be used.

Most pancreas transplant centers utilize some form of anticoagulation following transplantation to prevent these complications. Moreover, aspirin is highly recommended. Unfractionated or low-molecular-weight heparin is often administered, but some centers use heparin selectively and typically at low dose to avoid postoperative bleeding. Warfarin is less frequently given and its use should probably be limited to patients with thrombophilia [28].

3.2 Pancreatoduodenectomy (Whipple Procedure)

Pancreatoduodenectomy (PD) is a complex procedure that brings a not insignificant number of postoperative complications. Of these, the most common complications can be divided in four groups: surgical site infections (SSI), delayed gastric emptying, bleeding and anastomotic leakage [34]. Nevertheless, other complications, much less frequent, exist. Their identification in early postoperative course is complicated and if left untreated, they may lead to the death of the patient.

Among such unfrequent complications, it must be included superior mesenteric vein (SMV) thrombosis with subsequent ischemia of the tributary area. Clinical symptoms of SMV thrombosis are untypical, obscure and characterized by slow progress, all this covered by early postoperative period [35]. Because of these obscure symptoms, it was not until 1935, that thrombosis of SMV was identified as a nosology entity [36, 37].

Although PD offers the only chance of cure for patients with adenocarcinoma of the pancreas, questions have arisen regarding the indication, safety and outcomes of patients undergoing extended resections for locally advanced disease [38]. While previous studies demonstrated an overall survival benefit after pancreatic resection without an increase of morbidity and mortality rates [39–41], high mortality rate was reported for patients with PVT after PD [42–45]. In the last years, venous resection and reconstruction is becoming more common during PD. There are multiple options for reconstruction of the mesenteric venous system ranging from primary repair to grafting with autologous or synthetic material [38]. Anyway, if *en bloc* resection with involved vein has been performed and the initial postoperative care of the patient was not uneventful, it must be kept in mind that a PVT could be established.

At this point, recommendations for anticoagulation following major venous reconstruction for malignancy are not clearly established, because it has been showed that the systematic administration of anticoagulation does not protect against venous thrombosis [46]. In a study of the durability of 64 PV reconstructions by Smoot et al. [38], no significant difference in thrombosis rate was observed between those who did and those did not receive anticoagulation. Most patients remained patent without the use of warfarin or aspirin, and that anticoagulation therapy did not seem to influence outcomes. A possible explanation is that, because of the high flow and the absence of valves in the portomesenteric vein, the risk for thrombosis seems to be low.

Diagnosis of this entity is hard by the fact that clinical symptoms are non-specific and covered by postoperative paralytic ileum and modified pain reaction secondary to analgesics [47]. Nausea, vomiting abdominal pain and distention with no other signs of obstruction appear to be the initial presentation in most patients. No plasma biomarkers for intestinal ischemia exist, and only D-dimers is used as a marker of [48]. This postoperative complication should be considered in a patient requiring unusually large amounts of fluids to maintain homeostasis.

Although angiography remains the standard diagnostic modality, CT scan of the abdomen may shows reduced contrast enhancement in the SMV with or without PV thrombosis, dilated intestinal loop with wall thickening and the presence of peritoneal fluid.

Therapy of thrombosis of SMV is divided into conservative, endovascular, and surgical. Basis of the *conservative management* was stated by Barrit and Jordan in 1960 [49]. Treatment of the thrombosis of SMV (heparinization) does not differ from the treatment of the thrombosis in any other localization.

The basis on the *endovascular treatment* is thrombolysis, either administered systemically or locally. First option is via transfemoral approach with the direct introduction of thrombolytic agents into the superior mesenteric artery (chemical thrombolysis); and the second alternative, is by direct aspiration thrombectomy from SMV without use of thrombolysis (mechanical thrombolysis) [50].

When the patient is clinically deteriorated, with a suspicious thrombosis of the SMV, with signs of peritonitis or bowel paralysis of unclear origin, a *laparotomy* is mandatory [51]. Goal of laparotomy is facilitation of venous outflow (usually by thrombectomy) and resection of the necrotic parts of the bowel. Considering complicated assessment of the bowel vitality in venous congestion, recommended practice is planned re-laparotomy 24–48 h after revision [52].

Mechanical injury to VSM during surgery can be considered as the most common cause of postoperative thrombosis of SMV, ant this occurred in patients with extreme inflammatory and fibrotic surrounding tissue around the pancreas (severe acute and/or chronic pancreatitis, huge tumors that involve PV...).

Prognosis of the patient depends on the clinical state, early identification and aggressive treatment. Management of the patient is multidisciplinary (surgeon, anesthesiologist, internal medicine specialist, radiologist...) but the mortality rate even after aggressive surgery is high. Due to the possibility of different surgical revisions, the use of open abdomen with negative pressure wound therapy could be indicated, not only to avoid the developing of a compartment syndrome, but also to evacuate fluids and contaminate collections [46].

3.3 Distal Pancreatectomy

Although incidence of PVT following pancreatic transplantation and pancreatoduodenectomy has been previously described [53] and it is well accepted, there is a paucity of data in the literature on PVT in patients undergoing distal pancreatectomy (DP) [54]. Recently, the Mayo Clinic [55] has published a study with nearly 1000 patients undergoing DP with or without splenectomy, and has showed an overall incidence of PVT of 2.1 % (21 patients). However, in this study, patients who had a portal venorrhaphy, portal venous reconstruction, pre-operative PVT or chronic pancreatitis were excluded.

Although, it is well-known that pancreatic cancer has a major risk of venous thromboembolism and that it is the most common indication for DP, surprisingly, PVT occurred infrequently in this population.

Clinical presentation of PVT was variable and depended on the extent and location of PVT. The median time from DP to diagnosis of PVT was 16 days. Non-specific abdominal pain was the most common symptom (52 %), clinical suspect for pancreatic leak or intraabdominal infection (24 %) and during the follow-up surveillance in the rest 24 %. Anyway, authors concluded that the true incidence of PVT after DP is difficult to assess, because some patients could develop asymptomatic PVT that was not diagnosed.

The diagnosis of PVT was confirmed by CT or ultrasonography in all the patients. Thrombus occurred in the main PV in 15 patients (71 %), right portal vein branch in 8 (38 %), left portal vein branch in 3 (14 %), and superior mesenteric vein in 7 (33 %) patients. In 8 patients (38 %) there were multiple segments of the PV involved, and a complete PV occlusion was seen in 9 patients.

The difference in frequency of PVT after DP in patients who underwent laparoscopic or open procedure was not statistically significant (6 % vs. 2.5 %).

Related to treatment, and although anticoagulation does not appear to influence the rate of PVT resolution, authors advice to use anticoagulation until larger and controlled studies define clear advantages and disadvantages. In their series, the duration of the treatment was 6 months, and there was no case of recurrence or progression of PVT. Over a median follow-up of 22 months, complete resolution, defined as recanalization of the portal vein, was observed in only a third of the patients, being these results similar to those obtained in other groups with the anticoagulation treatment for PVT from acute and chronic pancreatitis.

Risk factors for persistence of PVT were anesthesia time >180 min, DM type II, Body mass index (BMI) > 30 kg/m^2, thrombus in an intrahepatic segment of the PV, simultaneous

involvement of multiple segments, a complete occlusion of the PV and presence of thrombus in a sectorial branch of the right portal vein.

Duration of treatment has been largely discussed because of the risk of recurrence and progression of the thrombosis. Current literature on PVT does not support prolonged anticoagulation because of the low rate of recurrence and thrombus progression, and a substantial rate of gastrointestinal bleeding (10–26 %) [53–56].

Because most DP are performed for a malignant disease, and due to the operation itself (it is a pro-coagulant condition), in the absence of thrombus propagation or pro-coagulant condition (e.g., Factor V Leyden, Protein C/S deficiency), authors recommend that the decision for anticoagulation should be made individually, on basis of the extent of PVT and clinical manifestations. Anyway, they advise to provide at least a short-term anticoagulation treatment to patients with PVT followed by repeat imaging study to assess the response of the treatment and decide its duration.

3.4 Pancreatitis

Venous thrombosis (mesenteric, splenic and portal) is a frequent complication that occurs as a sequelae to pancreatitis [57]. All forms of pancreatitis have been implicated as risk factors for thrombosis. Targeted studies report its incidence in hereditary pancreatitis, autoimmune pancreatitis, acute pancreatitis (AP) and chronic pancreatitis (CP). It is considered that this entity is more commonly associated with CP, although a single attack of AP appears sufficient to cause this disorder. The physiopathology of this complication seems to be related to the compression of the vein following inflammation and fibrotic tissue of the pancreas, the injury of the intima secondary to the acute attack and the compression by pseudocysts. Anyway, venous thrombosis may be linked to inherited coagulation disorders, such as deficits of protein C or protein S, or acquired coagulopathies, such as antithrombin III deficiency. Clinical consequences of the venous thrombosis depend on the velocity of instauration, the grade of occlusion and the creation of collateral blood flow [58, 59].

3.4.1 Splenic Thrombosis

In either AP or CP, the incidence of splenic vein abnormalities has ranged from 0.9 to 54 % [60] in surgical series and up to 89 % in radiographic series [61]. Regardless of its etiology, splenic vein thrombosis (SVT) generates a localized form of portal hypertension commonly referred to as “sinistral”, “left-sided” or “linear”. Collateral blood flow develops through the splenoportal or gastroepiploic systems and the resulting localized venous hypertension may produce gastric, esophageal or colonic varices. Historically, patients with SVT most commonly presented clinically with an episode of gastrointestinal (GI) bleeding or abdominal pain. However, nowadays, with the improvement of availability and quality of CT scan, the majority of the patients are asymptomatic. Despite the heterogeneity of available data, the meta-analysis of Butler et al. [58] quantifies an overall SVT incidence of 14.1 % and a bleed rate of 19 %. In relation to operative management, it has been suggested that patients with SVT and a prior history of upper GI tract bleeding or symptomatic hypersplenism may represent a high-risk group and the splenectomy is mandatory. By contrast, asymptomatic patients without history of bleeding, in whom SVT was identified through imaging, were found to have an incidence of bleeding of only 3.8 % and a conservative management could be adopted.

3.4.2 Splenoportal Thrombosis

The real prevalence of splenoportal thrombosis (SPT) is not well-known. Sometimes it is an incidental finding on radiological imaging performed to assess the severity of an attack of AP. Some studies [62, 63] reported and incidence of 25 % in patients with AP, so this entity has to be ruled out in these cases. The problem is that its clinical manifestations may include signs and symptoms that overlap with those of the pancreatitis. Although the natural history of splenoportal vein thrombosis in pancreatitis is unclear; severe

haemorrhage, bowel ischemia, portal hypertension and liver failure have been reported.

Diagnosis of SPT is essential even in asymptomatic patients because this could lead and modify the surgical or endoscopic technique. Arteriography is mandatory, but a CT-angiography could also be performed, reporting changes in pancreatitis.

3.4.3 Mesenteric Thrombosis

Incidence of mesenteric thrombosis (MT) is difficult to assess, and normally it is an incidental radiological diagnosis without intestinal ischemia or in the necropsies series. Some authors describe an incidence higher than 10 % [62].

Subacute MT is characterized by large evolution abdominal pain without intestinal ischemia, meanwhile patients with chronic MT remains asymptomatic and develops signs and symptoms of portal hypertension. Treatment of choice in cases of ischemia is surgery but in absence of this complication, anticoagulation with heparin is useful.

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Genetic Risk Factors in Venous Thromboembolism

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Abstract

Genetic risk factors predispose to thrombophilia and play the most important etiopathogenic role in venous thromboembolism (VTE) in people younger than 50 years old. At least one inherited risk factor could be found in about half of the cases with a first episode of idiopathic VTE.

Roughly, genetic risk factors are classified into two main categories: loss of function mutations (such as deficiencies of antithrombin, protein C, protein S) and gain of function mutations, (such as prothrombin mutation G20210A, factor V Leiden). A revolutionary contribution to the genetic background of VTE was brought by the achievements of the genome-wide association studies which analyze the association of a huge number of polymorphisms in large sample size.

Hereditary thrombophilia testing should be done only in selected cases. The detection of hereditary thrombophilia has impact on the management of the anticoagulation in children with purpura fulminans, pregnant women at risk of VTE and may be useful in the assessment of the risk for recurrent thrombosis in patients presenting an episode of VTE at a young age (<40 years) and in cases with positive family history regarding thrombosis.

Keywords

Gene mutations • Thrombophilia • Inherited risk factors

1 Introduction

Venous thromboembolism (VTE) is a multifactorial disease, usually the result of the intervention of hereditary and acquired risk factors. Genetic risk factors predispose to hypercoagulability- inherited thrombophilia- and play the

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most important etiopathogenic role in VTE in people younger than 50 years old [1].

There is a complex relationship between genetic and acquired risk factors leading to the occurrence of VTE. The synergistic gene-gene and gene-environment interactions contribute to the increase of the risk of both incident and recurrent thrombosis more than the simple sum of the corresponding risk associated to each involved factor [1]. Thus, the concomitant presence of heterozygosity for factor V Leiden (associated with four to sevenfold increase in risk) and the use of oral contraception (associated with three-fold higher risk) leads to an increase by 34 times of the thrombotic risk [2]. The transitory intervention of some acquired risk factors (e.g. trauma, surgical interventions, pregnancy, the use of oral contraceptives or hormonal replacement therapy) may trigger the occurrence of VTE on a genetically predisposed thrombotic terrain [3]. The risk for recurrent VTE is not increased in the presence of hereditary thrombophilia [4]. According to the guidelines, the detection of hereditary thrombophilia should be done in selected cases [5].

Although considered idiopathic in many cases, at least one inherited risk factor could be found in about 50 % of patients presenting with a first episode of idiopathic VTE [2].

2 Historical Perspective

Although some risk factors for VTE were recognized from centuries (such as "milk leg" associated with deep vein thrombosis during postpartum period), others, especially genetic risk factors, were recently discovered.

The term "thrombophilia" was used by Jordan and Nandorff in 1956 and since then the interest for the detection of the genetic background of thrombosis has increased [6]. The first important step forward was done in 1965 by Olav Egeberg, who described first the antithrombin (AT) deficiency in a Scandinavian family, in which several members presented VTE; he also showed the autosomal dominant mechanism of transmission of this condition [7]. Later, in 1981, family studies detected the role of deficiencies of protein C and S in VTE, based upon the analysis of plasma levels of antigen or activity of the natural anticoagulant.

The DNA analysis using PCR (polymerase chain reaction) method represented the most important step forward in understanding the genetics of VTE, allowing the detection of hundreds mutations. In 1993, Dahlbäck et al. described a familial thrombophilia due to a poor anticoagulant response to activated protein C, which was later found to result from a single nucleotide polymorphisms (SNPs) in factor V gene, FV Leiden [8]. In 1996, Port at al. identified a nucleotide change at position 20210 of prothrombin gene associated with an increased risk of VTE [9]. The research shifted then progressively from family studies to case-control studies, such as LETS (the Leiden Thrombophilia Study, which included 474 patients with VTE, in 1997), MEGA (Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis, which enrolled 3220 patients, between 1999 and 2002), MARTHA (the Marseille Thrombosis Association study, which enrolled 1150 patients between 1994 and 2005) [6, 10]. Although the non O-blood groups were found to be associated with VTE since 1969, the underlying mechanism, supposing the increase of von Willebrand factor and factor VII levels, is not completely clarified [11].

Recently, several polymorphisms of coagulation factors genes were found to increase the susceptibility to thrombosis, such as: factor XII C46T polymorphism leading to decreased levels of factor XII, factor XIII Val34Leu polymorphism, protein Z-dependent protease inhibitor Arg67Stop nonsense polymorphism, fibrinogen gamma (FGG) C10034T polymorphism [10]. Some genetic factors involved in the occurrence of hyperhomocysteinemia (called "the cholesterol of nineties" because of the cardiovascular risk), were also recently studied in association with VTE. *MTHFR* (methylenetetrahydrofolate reductase) C677T polymorphism (also called the "thermolabile variant") in homozygous state and associated with

hyperhomocysteinemia, shows a modest increase of VTE risk as well as of recurrent pregnancy loss [12].

A revolutionary contribution to the genetic background of VTE was brought by the achievements of the genome-wide association studies (GWAS) which analyze the association of a huge number of polymorphisms in large sample size. The two-stage CHARGE VTE consortium investigation studied 2.5 million SNPs identified in the HapMap II sample of European ancestry and their associations with thrombotic risk among 9 epidemiologic studies. The discovery GWAS confirmed the already established associations of the FV Leiden and the ABO blood groups with VTE (similar with the results of two previous GWAS studies: Heit et al, in 2012 and Tregouet et al, in 2009). The combined data of both stages showed additional genome-wide significance of the variants in the *F11* (4q35, rs4253399) and *FGG* (4q28, rs6536024) loci, similar with the third previous GWAS study (Germain et al, in 2011) [12]. New candidate loci for VTE, showing borderline and novel associations with VTE were found at some regions: at or near *SUSD1*, *sushi domain containing 1; ovarian tumor domain containing 7A* (*OTUD7A)*; on chromosome 5q13.3, about 6.1 kb from *synaptic vesicle glycoprotein 2C (SV2C)*; about 90 kb from *contactin-6 (CNTN6)* on chromosome 3p26). However, future studies are required to replicate these new candidate associations and to establish the clinical implications. Some genetic risk scores (e.g. Thrombo inCode) were designed to improve the predictive capacity of clinical factors, including family history assessment [13].

3 Classification

Genetic risk factors could be roughly classified into two main categories: loss of function mutations and gain of function mutations.

Loss of function mutations involve the natural anticoagulants: antithrombin (AT), protein C (PC), protein S (PS). These deficiencies are due to numerous distinct mutations, present a low incidence and a high risk of VTE.

Gain of function mutations may result from three mechanisms: the synthesis of a hyper functional molecule (factor V Leiden), an impaired downregulation of a normal protein or an increased synthesis of a normal protein (prothrombin mutation G20210A). This category may also include the elevation of factor VIII, von Willebrand factor, and factors V, VII, IX and XI. The gain of function mutations are more common, but the risk of thrombosis may be weaker [2, 14, 15].

Beside these, there are also factors affecting fibrinolytic system genes leading to impaired fibrinolysis, such as 4G/5G polymorphism of the PAI-1 gene [11].

Since it appears that these factors are involved only in about half of the thrombotic risk attributed to genetic factors, new mutations are still studied or remain to be discovered [6].

4 Factor V Leiden

4.1 Gene Mutation (Gene Symbol/ Chromosome Locus: Factor V Leiden: F5; 1q23)

FV Leiden is the result of the guanine to adenine substitution at nucleotide 1691 in the FV gene with consecutive substitution of arginine by glutamine at position 506, leading to an impaired ability of activated Protein C (APC) to cleave FVa and thus to increased thrombin generation. Factor V is also a cofactor of APC-mediated factor VIII inactivation. FV Leiden induces thus a prothrombotic state manifested with elevated levels of D-dimer, prothrombin fragment F1 + 2, and other activated coagulation markers [8]. This mutation is called after the city Leiden, where it was first described by Bertina et al [16]. FV Leiden represents the main cause of APC resistance. Other mutations involving FV, such as FV Cambridge (VThr306), FV HR2 haplotype, are associated with a mild increase of APC resistance and a weak risk of VTE, which increases when FV Leiden is also present [8].

4.2 Prevalence in Healthy Population and VTE

FV Leiden presents an autosomal dominant pattern of inheritance. It could be detected in about half of the cases of inherited thrombophilia, being the most common cause of it. This mutation is found in about 1–15 % of healthy Caucasians (Europeans and non-Europeans: Jews, Israeli Arabs, Americans and Australians) whereas in Africans, Asians and races with Asian ancestry (Amerindians, Eskimos, Polynesians) has a very low prevalence; this suggests a single origin of this mutation in a common European Caucasian ancestor in the distant past. A high prevalence of FV Leiden was also found in Middle East and North Africa regions due to the location close to Europe and population dynamics [17]. The highest prevalence in Eastern Mediterranean countries suggests the origin of the mutation in this region, where possibly occurred 10,000 years ago. Some epidemiologic studies found an Eastern-to-Western gradient as well as a South-to-North gradient of the prevalence of FV Leiden in European countries, the last one when the southwestern populations were excluded [17, 18]. In USA, the following frequencies of FV Leiden were found: 5.2 % in white Americans, 2.2 % in Hispanic Americans, 1.25 % in native Americans, 1.2 % in African Americans and 0.45 % in Asian Americans [8].

The prevalence of FV Leiden in VTE varies also according to the same geographical and ethnic criteria, being high in Sweden (41.5–50 %), Germany (30 %), Serbia (29.9 %), Italy (9–42.8 %), Greece (16.2–31.9 %), Tunisia (20.3–24.6 %), Turkey (21–30.8 %), and low in Malaysia (0.5 %), Pakistan (1.25 %) [17].

The prevalence of FV Leiden in European countries in both healthy populations and VTE is shown in Fig. 1 [17, 19–21].

4.3 Clinical Implication

There is no specific clinical feature correlated with FV Leiden. The main effect of this mutation is the increase of thrombotic risk, by 10-fold in heterozygotes and by 30–140-fold in homozygotes. Heterozygous carriers have a 10 % lifetime probability of VTE. Homozygotes may experience one or more episodes of VTE over their lifetime and are prone to present VTE at a younger age [8]. FV Leiden could be found in about 25 % of patients presenting with a first idiopathic episode of VTE and up to 50 % of cases with recurrent VTE or concomitant use of estrogens [8].

Although the main manifestation of the thrombotic effect of FV Leiden is deep venous thrombosis (DVT) of the lower limbs, the mutation could be also found in the upper limb thrombosis (in 11.8–20 % of these cases) and less frequent in thrombosis with unusual location such as cerebral, retinal, hepatic, ovarian, and renal veins [8, 22]. This mutation may be associated with superficial thrombophlebitis, but the association is weak, showing that other factors should be taken in consideration in the etiopathogenic background [23].

Interestingly, considering DVT and pulmonary embolism (PE) as manifestations of the same disease- VTE-, FV Leiden is associated predominantly with DVT, with a relative risk of 4.5, whereas the relative risk of PE is 1.7; this is known in the literature as FV Leiden paradox [24]. Some studies show that other factors associated with a higher risk for DVT than for PE also act by increased APC resistance (oral contraceptives or hormonal replacement therapy, pregnancy, puerperium) [24, 25]. Several theoretical mechanisms proposed to explain FV Leiden paradox, such as the location of the thrombus (proximal *versus* distal veins) and the difference in the thrombus density were recently studied, but with inconsistent results. The hypothesis about the difference in the growth speed of the thrombus was also tested. The mouse models detected a faster growing thrombus in FV Leiden carriers and human studies showed a longer period of time between the occurrence of PE and the diagnosis. However, further studies are required to confirm these findings as pathogenetic background of FV Leiden paradox [26].

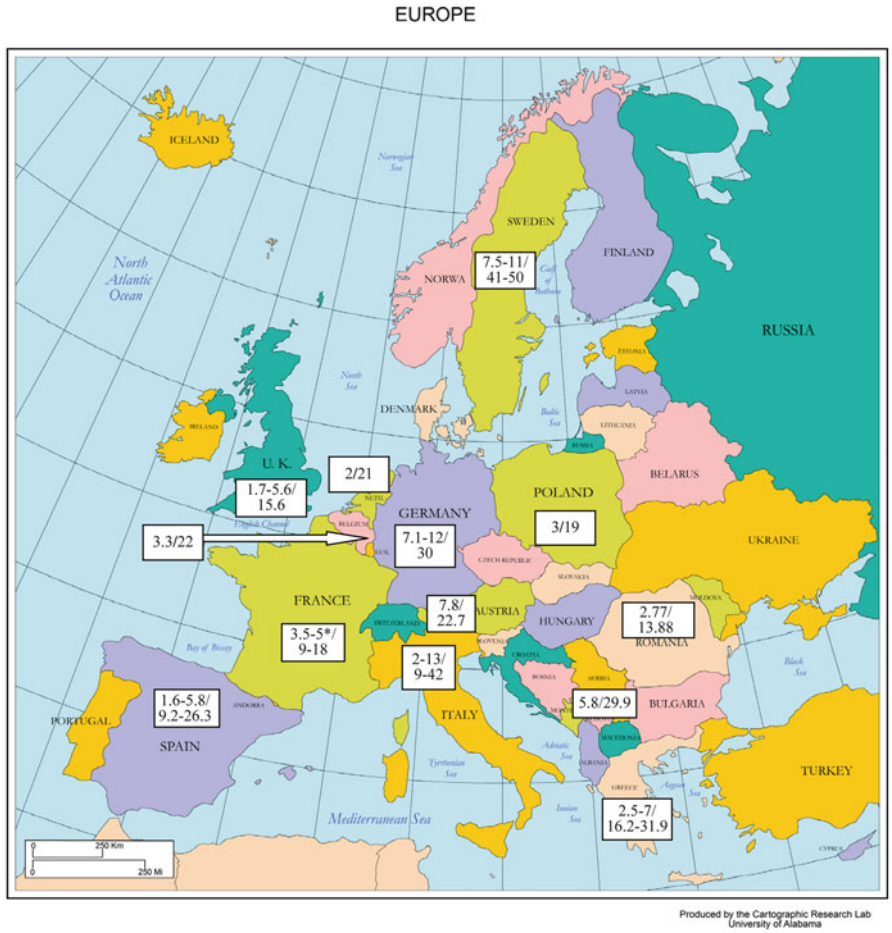

Fig. 1 The prevalence of FV Leiden in European normal population/ VTE (%) (Refs. [17, 19–21])
*In France the frequency ranges from 1.3 % in southwestern to 7.1 % in northeastern regions (Ref. [8])

The role of FV Leiden in arterial thrombosis (manifested with acute myocardial infarction, stroke, peripheral arterial disease) is less clarified; some studies have shown a weak association between FV Leiden and arterial ischemic events, which could be slightly increased in women and in patients younger than 55 years old [27, 28].

The risk of recurrent VTE is not well established in patients with this mutation: LETS showed a 5-year cumulative recurrence rate of 12.5 % in homozygotes not receiving long-term anticoagulation and a meta-analysis including 3104 patients with VTE found a slightly increased risk in heterozygotes; other studies showed no risk of recurrence in homozygotes as well as in double heterozygous carriers of FV Leiden and prothrombin G20210A mutation [29–31]. The concomitant association between heterozygosity for FV Leiden and other thrombophilic factors may influence the risk of recurrent thrombosis: thus, some studies show an increase of the risk by three to nine-fold when heterozygosity for prothrombin G20210A was also present (in contradiction with previously mentioned data) and, by four- to five-times when hyperhomocysteinemia was associated [8].

The impact of FV Leiden on VTE associated with cancer was recently shown by the results of CATS (Vienna Cancer And Thrombosis Study): the probability of the occurrence of VTE is 13 % in patients with cancer who are also carriers of

FV Leiden mutation *versus* 5.7 % in those with malignancy but without FV Leiden [32]. Previous studies offered contradictory results. This finding may be helpful in the assessment of the individual thrombotic risk in these cases.

Other pathological conditions associated with FV Leiden include the pregnancy complications, with a risk increased by two-to three-fold compared to non-carriers of the mutation: pregnancy loss, preeclampsia, intrauterine growth restriction and placental abruption. An episode of VTE during pregnancy may occur in almost half of the carriers of FV Leiden [33].

Usually, 50 % of VTE events in patients with FV Leiden are triggered by the intervention of an acquired risk factor, the most common being the pregnancy and the use of oral contraception in women [34]. The concomitant presence of another genetic thrombophilic factor will increase supplementary the thrombotic risk, acting synergistically: thus, the double heterozygosity for FV Leiden and prothrombin G20210A will lead to a 20-fold increase in relative risk, whereas the association between FV Leiden allele and hyperhomocysteinemia results in 21.8-fold increase, in a similar manner as for the recurrent thrombotic events previously presented [35, 36].

4.4 Practical Aspects

The American College of Medical Genetics Consensus Statement on Factor V Leiden recommends for detection a DNA-based genotyping test or a FV Leiden-specific functional assay. If the functional assay shows a positive result, a further DNA test is required to confirm it and to identify homozygosity or heterozygosity. The molecular test is recommended for the relatives of a carrier of FV Leiden as well as in cases on heparin therapy or with known lupus anticoagulant [37].

The APC resistance assay analyses the activated partial thromboplastin time (aPTT) in plasma in the presence and absence of a standardized amount of exogenous APC. In case of APC resistance, the response to APC will be a minimal prolongation of the aPTT. The test cannot be used in conditions associated with a prolonged aPTT, such as patients receiving oral anticoagulation or with a lupus anticoagulant. The test cannot distinguish well between heterozygotes and normal cases and measures only the resistance to APC no matter its cause. Thus, the modified assays were developed, which include a pre-dilution in FV-deficient plasma before the addition of APC and calcium, to reduce the confounding factors that might affect the aPTT. These tests could be used in patients receiving anticoagulation, but not in the presence of lupus anticoagulants which may offer false positive results. The chromogenic assay shows the APC resistance APC expressed as a ratio of the factor Xa amidolytic activity without APC to its factor Xa activity with the addition of APC. Russell Viper Venom Assay is another screening test based on the same principle and showing the ratio between dilute Russell Viper Venom Time with and without addition of the venom. For a better discrimination between FV Leiden mutation and protein C deficiency, samples could be pre-diluted with factor V deficient plasma [38].

PCR (Polymerase Chain Reaction) is the method used for the definitive diagnosis of FV Leiden, detecting wild-type or mutant allele (homozygous wild-type, homozygous mutant, heterozygous).

The Consensus Statement indicates the test in at least one of the following situations [37]:

- Age <50, any venous thrombosis.
- Venous thrombosis in unusual sites (such as hepatic, mesenteric, and cerebral veins).
- Recurrent venous thrombosis.
- Venous thrombosis and a strong family history of thrombotic disease.
- Venous thrombosis in pregnant women or women taking oral contraceptives.
- Relatives of individuals with venous thrombosis under age 50.
- Myocardial infarction in female smokers under age 50.

FV Leiden could be also tested in female relatives of a patient with this mutation, before

considering the pregnancy or the use of oral contraception as well as in women with recurrent pregnancy loss or unexplained pregnancy complications to manage better future pregnancies [37]. Otherwise, the prenatal testing and newborn screening are not recommended by routine. In young patients with acute arterial thrombosis in the absence of the classical risk factors, testing may be also worthwhile [37, 39].

The guidelines issued in 2011 are against FV Leiden and prothrombin G20210A routine testing in adults with idiopathic VTE (for the secondary prophylaxis of recurrent thrombosis) as well as in asymptomatic adult relatives of patients with VTE carrying one of these mutations (for the primary anticoagulation prophylaxis against the first VTE) [40].

The summary of recommendations for testing of inherited thrombophilia, including for FV Leiden, according to the grade [1–3] and quality of evidence (A,B,C) is presented at the final chapter "Guidelines".

5 Prothrombin G20210A

5.1 Gene Mutation (Gene Symbol/ Chromosome Locus: Factor II: F2; 11p11-q12)

Prothrombin is produced by the liver and is activated into thrombin by activated factor X. Thrombin plays a key role in coagulation: it activates platelets as well as factors V, VIII and XI, cleaves fibrinogen to fibrin, modulates fibrinolysis by binding to thrombomodulin. Prothrombin (FII) G20210A mutation, identified by Poort et al. in 1996, is the result of the substitution of guanine to adenine at position 20210, present at 3′ untranslated region of prothrombin gene, leading to an increase of mRNA accumulation and increased prothrombin levels by 133 %. As a consequence, the level of thrombin activatable fibrinolysis inhibitor may increase, contributing to the hypercoagulability state [41]. This mutation represents the second most common cause of inherited thrombophilia.

Recently, other mutations in prothrombin gene were described, such as the substitution of arginine to leucine at position 596 (p. Arg596Leu) (called prothrombin Yukuhashi) associated with an increased trombotic risk [42].

5.2 Prevalence in Healthy Populations and VTE

Similar to FV Leiden, the prothrombin G20210A mutation is found with the highest prevalence in Caucasians, suggesting a single event in a Caucasian ancestor occurring around 24 thousand years ago after the divergence of Africans from Non-Africans and Caucasoids from Mongoloids [41]. The prevalence in general population is 1–4 % with geographical differences: the prevalence in Southern Europe (3 %) is nearly twice as in Northern Europe (1.7 %) whereas in individuals from Asian and African descent, in native Americans and in Australians is very rare [43]. In Mediterranean region, the prevalence is between 1 and 12 % in general population, respective 3–24 % in VTE patients, suggesting the possibility that the mutation occurred here first and then spread to Europe [41]. The prevalence of prothrombin G20210A in VTE cases shows the same geographical differences: 6.5 % in North Europe, 2.7–17.2 % in South Europe, 3.2–9.7 % in Caucasians in USA, 0 in India [41].

The mutation was found in 4.3–11.3 % of unselected cases diagnosed with a first episode of DVT and in 7.9–24.1 % of patients with a personal or family history of VTE or thrombophilia [44].

5.3 Clinical Implication

The main manifestation of this mutation is correlated with the prothrombotic effect, the risk of VTE being increased by two to four-fold [41].

It was shown that children with prothrombin G20210A mutation present predominantly arterial thrombosis and the central nervous system involvement, unlike those with FV Leiden or

deficiencies of proteins C and S; when VTE occur, additional risk factors are usually present [45].

Although the carriers of prothrombin G20210A mutation may present a five-fold increase in the risk of a first episode of myocardial infarction, the arterial thrombotic risk is generally low and is manifested before the age of 50 [46].

The episodes of VTE in carriers of prothrombin G20210A mutation younger than 30 years old tend to occur with a higher annual incidence than in carriers of FV Leiden (0.44 % *versus* 0.25 %) [46]. The risk of VTE is more than double in carriers of prothrombin mutation with a positive family history and may be higher in homozygotes [46].

The risk for recurrent spontaneous VTE in individuals carrying this mutation is not significantly increased, no matter if the first episode was spontaneous or secondary [47].

The risk of VTE is increased in the presence of other acquired risk factors; thus, carriers of prothrombin G20210A mutation taking oral contraceptives may present a seven-fold increased risk, and, respective, 17-fold higher risk in case of concomitant heterozygosity for FV Leiden [35].

Prothrombin G20210A mutation could be found in about 17 % of pregnant women with VTE [48]. However, a family study showed that prothrombin mutation is not a risk factor for pregnancy adverse outcome in female relatives [46]. Although numerous case-control studies have shown adverse obstetric events associated with inherited thrombophilia, including prothrombin mutation, a recent prospective study conducted by Eunice Kennedy Shriver National Institute of Child Health and Human Development, which enrolled more than 4000 women in a low risk cohort, failed to prove a link between pregnancy loss, preeclampsia, placental abruption, intrauterine growth restriction and prothrombin mutation [48]. This study suggests the lack of benefit from thromboprophylaxis in women with thrombophilia, regardless the previous pregnancy complications, as shown by another nonrandomized cohort [49].

5.4 Practical Aspects

The indications for prothrombin mutation testing are the same as previously presented regarding FV Leiden [37, 39, 40].

The mutation is detected using PCR; the amplification of genomic DNA is followed by a number of methods to identify the mutation: the use of restriction enzymes (Mn/I), DNA microarrays, real-time PCR.

6 Protein C (PC) Deficiency

6.1 Gene Mutations

PC is a vitamin K-dependent glycoprotein produced in the liver. It circulates in the blood as an inactive form and combines with thrombomodulin producing activated PC (aPC). The aPC interacts with PS at the platelets level and degrades factor Va and VIIIa which are required for factor X activation and thrombin generation [50]. The deficiency of aPC will create a prothrombotic state, manifested especially in venous circulation. This may occur due to genetic and acquired causes.

The PC gene, located on the long arm of chromosome 2, present numerous mutations leading to a quantitative (type I) or functional (type II) deficiency of PC [50]. The mechanism of inheritance is usually autosomal dominant. Heterozygotes with type I deficiency present half levels of aPC comparatively to normal individuals. Type II deficiency occurs less common than type I and could be involved in about 15 % of symptomatic deficiencies [51]. PC deficiency was first described in 1981 by Griffin et al. who detected heterozygosity in a family with a history of recurrent thrombosis. Few years later, in 1984, homozygous PC deficiency was found to be associated with severe neonatal purpura fulminans and disseminated intravascular coagulation within hours of birth [50].

6.2 Prevalence in General Population and VTE

PC deficiency is found in 0.2 % of the general population. It was initially considered as a rare but strong risk factor for thrombosis; however, it was identified in 1:250 blood donors, who were not found to present a higher incidence of thrombosis as well as their relatives carrying the deficiency [50]. Homozygous or compound heterozygous PC deficiency occurs in approximately 1 in 500,000 to 1 in 750,000 live births [52]. There are no apparent racial or ethnic differences regarding the prevalence of PC deficiency in general populations.

The prevalence of PC deficiency in VTE is about 2–5 % [53].

6.3 Clinical Implication

Clinical manifestations in PC deficiency depend upon the underlying mutation and the levels of PC. Many affected individuals may be asymptomatic.

Homozygosity and compound heterozygosity for PC deficiency are manifested either with disseminated intravascular coagulation either with massive thrombosis. Homozygotes with absent levels of PC in plasma present neonatal purpura fulminans shortly after birth. This is a life threatening condition, manifested with extensive thrombosis of capillaries and venules, necrosis of the tissues and massive bleeding into the skin [54]. Homozygotes may also present milder manifestations. The clinical phenotype of heterozygosity for PC deficiency can range from asymptomatic to warfarin-induced skin necrosis and recurrent VTE with consecutive chronic venous insufficiency. The thrombotic risk is usually increased by seven-fold. The first episode of VTE occurs by the age of 45 in half of the cases [51, 55].

In symptomatic families, PC deficiency is associated with an adjusted relative risk of 11.3 for VTE [56]. Family studies showed the importance of the interaction between PC deficiency and other genetic risk factors. The study of each individual's plasma composition revealed no direct correlation of thrombin generation with PC levels. Recent data shows the cell adhesion molecule 1 as a possible interacting gene, whereas the role of prostaglandin H synthase 1 gene and alpha2 subunit of platelet-activating factor acetyl-hydrolase Ib has not been confirmed [55].

Although it has not been proved an increased risk for arterial thrombosis, several case reports found an association with stroke and myocardial infarction, suggesting that PC deficiency could be tested in young patients, in the absence of the classical cardiovascular risk factors [57].

PC deficiency does not appear to be associated with adverse pregnancy outcome [58].

6.4 Practical Aspects

PC deficiency is detected using immunologic and functional assays. Immunological assays include ELISA (enzyme-linked immunosorbent assay), RIA (radioimmunoassay) and electroimmunoassays [59]. The levels of PC are age-dependent, with lower values in neonates and infants than in adults; the levels may persist lower than in adults until the age of 16. The functional assays use the venom of the southern copperhead snake which activates the PC that will be measured by clot-based or chromogenic methods. Patients with levels less than 50 % are likely to have a deficiency, whereas levels between 55 % and 65 % may be due to heterozygosity or represent the lower limit of the normal values [56].

The functional test is used for the screening of PC deficiency. If PC deficiency is detected, a PC antigen assay should be considered to detect the type I or II of deficiencies [56, 58]. Since there are numerous mutations (almost 200) involved in PC deficiency, no confirmatory DNA test is readily available at the present.

To confirm hereditary PC deficiency, the test should be performed in the absence of an acquired cause of deficiency, such as: oral

anticoagulants, vitamin K deficiency, liver diseases. It is recommended to stop oral anticoagulation 10 days before testing [56]. It is commonly believed that acute phase of VTE produces a decrease of PC and PS. However, a recent study found a false positive rate of only 2.2 % of the tests done within 24 h of the diagnosis of VTE, before the administration of oral anticoagulation. This shows that PC testing during the acute VTE event is a valid approach and a normal result is enough to rule out deficiency [60].

Prophylactic therapy for VTE in PC deficiency could be administrated in cases with a positive family history for VTE, in the presence of an acquired risk factor for VTE such as: pregnancy and puerperium, surgery, trauma. Long-term anticoagulation is often recommended in patients with a first episode of VTE, considering the risk for recurrent VTE of about 60 %. Warfarin- induced necrosis is a medical emergency, requiring the immediate discontinuation of warfarin, the administration of vitamin K, heparin and exogenous PC, in the form of fresh frozen plasma or purified concentrate. Neonatal purpura fulminans is a very severe condition, requiring the normalization of PC levels immediately with PC concentrate and then administration of anticoagulant indefinitely [61].

7 PS Deficiency

7.1 Gene Mutations

PS, a vitamin K–dependent glycoprotein, circulates in plasma in two forms: a form bound to protein (60 % of total PS) and a free form (40 %). The free form serves as cofactor in the inactivation of factor Va and VIIIa by PC, enhancing the cleavage of FVa approximately ten-fold [62].

PS deficiency was first described in 1984 by Schwarz who reported the association with VTE in a family. There are three types of PS deficiency: type I (characterized by a decreased amount of both bound and free forms of PS), type II or type IIb (with normal levels of PS, but with an altered function, unable to interact normally with PC) and type III also called IIa (with a low level of free PS, but a normal amount of total PS). Type I and type III deficiencies have been found concomitantly in many families, suggesting the same genetic disease with phenotypic variants [63].

The inherited PS deficiency is an autosomal dominant condition. Molecular studies identified two genes encoding PS, linked closely on chromosome 3p11.1-3q11.2: the active gene, PROS-b (PROS1) and the other, the pseudogene PROS-a, a nonfunctional gene, similar with the active gene, but without the exon 1. Almost 200 mutations of PROS1 gene have been described, such as: the PS Heerlen mutation (due to the substitution of Ser460 by Pro, consecutive to T→C transition in exon 13) resulting in type III deficiency, the PS Tokushima due to K196E substitution, located in the epidermal growth factor-2 domain and causing type II deficiency [62].

7.2 Prevalence in Healthy Populations and VTE

PS deficiency is a rare disorder; a study including 3788 healthy Scottish blood donors showed a prevalence of hereditary PS deficiency of 0.03–0.13 % [62]. The higher prevalence of PS deficiency in Japanese than in Caucasians (1.12 % in men, 1.6 % in women), especially in case of PS Tokushima, may be explained by racial differences or the use of different assay methods [63].

PS deficiency may be found in about 5 % of VTE patients and 1–2 % of patients with a first episode of VTE [63].

However, the incidence of PS deficiency is not well known, since the inter- and intra-individual variation in plasma levels of PS, making the diagnosis of PS deficiency difficult [63].

7.3 Clinical Implications

The main result of PS deficiency is the increase in thrombotic risk. The risk ratio is 8.5 compared

to normal individuals and is also higher than in carriers of FV Leiden mutation. Studies of thrombophilic families revealed that individuals with PS deficiency have a five to ten-fold higher risk for VTE than healthy relatives [63]. The annual incidence of recurrent VTE in patients with positive family history is about 6–10 %. However, the risk of VTE associated with PS deficiency in general population is controversial: LETS has shown that only very low levels of free PS are associated with 5.44 higher risk of VTE and not the low levels of total PS. MEGA study found that decreased free PS (and not total PS) leads to a double risk of unprovoked thrombosis. Previous family studies revealed that the cutoff level of free PS to detect PS deficiency should be very low compared to the range that is commonly used [64]. Thus, the free PS levels appear to be a better indicator for the risk of VTE than total PS. Recent data concluded that low free PS and low total PS levels could rarely identify individuals at risk for VTE in population-based studies and should not be considered for testing in unselected cases [64].

It has been shown that about half of PS deficient patients present VTE till the age of 55 and half of VTE events are unprovoked [62]. The use of oral contraceptives by PS deficient women may increase the risk of VTE by 600-fold compared to healthy subjects. Pregnancy or puerperium represents the trigger factor for VTE in women with PS deficiency in about 20 % of cases; the risk of pregnancy loss is triple in PS deficient patients [62]. Possibly linked to these findings, data showed that PS deficient young women present a higher risk of VTE than young men carrying the deficiency [65].

Homozygous or compound heterozygous deficiency is manifested with massive VTE or neonatal purpura fulminans, which could be life-threatening in the absence of medication. Retinopathy may be the initial manifestation in some cases [62].

In spite of several reports about the association between PS deficiency and arterial thrombosis, the results of the large studies are conflicting.

7.4 Practical Aspects

PS deficiency is detected using tests for PS antigen (total antigen or free PS antigen) measured by ELISA methods and functional tests for PS activity, which are indirect and based on prolongation of blood clotting. Since a false PS deficiency could be found in patients with FV Leiden, the dilution of plasma is required for a more accurate determination [66]. Decreased levels of PS are found in inherited deficiency of PS as well as in some acquired conditions, such as liver diseases, vitamin K deficiency, therapy with vitamin K antagonists, pregnancy, HIV infection, varicella, sickle cell disease, malignancy, nephrotic syndrome [67]. The free PS level is not influenced by age, whereas total PS increases with age. Since from practical point of view the distinction between type I and type III of deficiency is not important (no clinical impact on the management of the case), the free protein S antigen testing should be done in any suspected case of PS deficiency.

The total PS antigen in healthy adults is in average 23 mcg/mL, which corresponds to a value of 100 %, or 1 unit/mL, whereas in individuals treated with warfarin is decreased by half [68].

VTE associated with PS deficiency requires anticoagulation according to the protocols. Warfarin could be administrated lifelong in case of life- threatening VTE, located at multiple and unusual sites and in cases with repetitive episodes of VTE. In asymptomatic individuals with PS deficiency, the prophylaxis of VTE should be done in the presence of a major acquired risk factor for thrombosis: (e.g. surgery, pregnancy and postpartum) [69].

Neonatal purpura associated with severe PS deficiency should be promptly treated with vitamin K antagonists. However, despite maintaining the international normalized ratio of the prothrombin time within the therapeutic range for VTE, warfarin-induced skin necrosis may occur. New anticoagulants targeting FII or FX (dabigatran, rivaroxaban) have been proved to be a valid therapy in cases with severe PS deficiency and warfarin- induced skin necrosis [70].

8 Antithrombin Deficiency (or AT III Deficiency)

8.1 Gene Mutations

Antithrombin (AT), a vitamin K-independent glycoprotein, plays a central role in coagulation system, by the inhibition of thrombin and other serine proteases of the coagulation cascade (serpin) including FXa and FIXa. Its inhibitory function is increased by heparin. AT is found in plasma as two main forms: an active monomer and a latent, inactive form. AT undergoes a slow spontaneous conversion to its latent conformation and a more rapid conversion at higher temperature, when a heterodimer of active and latent antithrombin also appears. Heterozygotes with conformationally unstable antithrombins may present severe episodes of thrombosis [71].

AT deficiency is transmitted in an autosomal dominant pattern, in case the patient inherits one copy of the SERPINC1 gene on chromosome 1q25.1, or could be transmitted in an recessive manner, in case two defective genes are inherited, leading to massive thrombosis in neonates [72]. Beside the genetic causes, there are some acquired conditions associated with AT deficiency: liver diseases, nephrotic syndrome, severe trauma, chemotherapy, disseminated intravascular coagulation. There are two main types of AT deficiency: type I, the most common, due to a decreased level of AT and type II, the result of a decreased AT function with possible normal levels of AT antigen. Type II is subdivided into type IIb deficiency, more common, but less thrombogenic, caused by a defect in the heparin-binding region of AT and type IIa deficiency, less common, but more thrombophilic, caused by mutations in the thrombin-binding site. Type IIc deficiency has been also described, as a combination between the previous two subdivisions. Numerous mutations leading to AT deficiency have been reported (e.g. wibble and wobble, mutation of the shutter region of the gene) [73].

8.2 Prevalence in Healthy Populations and VTE

AT deficiency occurs with a rate of 1 in 500 or 1 in 5000 in general population, without a predilection according to gender, ethnicity or race [73]. The prevalence of AT deficiency in patients with a history of VTE is about 2 % [74].

8.3 Clinical Implications

AT deficiency is associated with a high risk of thrombosis, especially VTE, which occurs spontaneously in about 60 % of cases. The thrombotic risk increases after the age of 20 and by the age of 50, about half of the carriers of this condition present a thrombotic episode. The lowest risk of VTE is associated with type IIb of AT deficiency [73]. DVT involves especially the lower limbs, but it may also occur at unusual location. AT deficiency is associated with a three to sevenfold higher risk of VTE compared to other thrombophilias [75]. The risk of recurrent episodes of VTE is about 2.7 %/year, despite anticoagulation [73].

Pregnant women with AT deficiency may present VTE in a proportion of 31 %, which increases up to 50 %, if they have a history of VTE [76]. Although pregnancy in women with AT deficiency presents an adverse outcome, several reports have shown a lower incidence of the complications when antithrombotic therapy was administrated [77].

8.4 Practical Aspects

AT activity should be tested first and, if low, the antithrombin antigen should be measured. Thus, a low antigenic assay may detect a type I or IIc of AT deficiency. The functional test is influenced by heparin (AT levels will be lower) and vitamin K antagonists (AT levels will be increased and a possible deficiency could not be detected) [73].

Although the identification of the type of AT deficiency may be useful for the assessment of the thrombotic risk, this is not done by routine.

Genetic analysis as well as the prenatal testing are not indicated, since there are numerous mutations leading to AT deficiency [74].

Guidelines show that long- term anticoagulant thromboprophylaxis is not recommended in asymptomatic patients with AT deficiency, but recommend short-term prophylaxis in high-risk situations such as surgery, trauma, partum and postpartum. The treatment of the acute episode of VTE in AT deficient patients may be difficult, since the response at even high doses of heparin, including low molecular weight heparins, may be variable. In case of inefficient response, AT concentrate should be administrated, aiming to increase initially the AT activity to at least 120 % of normal levels, followed by the maintenance of AT activity at minimum 80 % of normal levels. The agents used include: plasma-derived AT, fresh frozen plasma, and human recombinant AT [75]. The risk of recurrent VTE is high in AT deficient patients (10–17 % per year) in the absence of long- term anticoagulation following a thrombotic episode. New agents, acting as direct thrombin inhibitors, such as argatroban, may represent an alternative at heparin coagulation.

9 *MTHFR* Polymorphisms

9.1 Gene Mutations

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in homocysteine metabolism, regulating the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the substrate for homocysteine remethylation to methionine. *MTHFR* gene, located on the short (p) arm of chromosome 1 at position 36.3, presents two common polymorphisms: *MTHFR* C677T, characterized by the substitution of alanine to valine at codon 222, and *MTHFR* A1298C, due to the substitution of glutamine to alanine at codon 429. *MTHFR* C677T polymorphism, especially in homozygous state and in the presence of low folate levels, is associated to a decrease of the enzyme activity, resulting in hyperhomocysteinemia, whereas the *MTHFR* A1298C polymorphism presents a milder effect on homocysteine levels [78]. There are controversies regarding the direct or indirect role (*via* hyperhomocysteinemia) of *MTHFR* polymorphisms in VTE. Hyperhomocysteinemia is an independent risk factor for cardiovascular diseases, including VTE, by promoting the endothelial dysfunction, the inhibition of fibrinolysis resulting in a prothrombotic state and the increase of platelet reactivity [79].

9.2 Prevalence in Healthy Population and VTE

The prevalence of *MTHFR* C677T polymorphism varies among the populations. There is a latitudinal-dependent gradient of the T allele frequency in Europe, in the native American population and in the Eastern Asia. The highest T allele frequency (about 50 %) is found in the Apennine peninsula in Europe and the Bohai Bay Rim in China, whereas the populations near the equator and from polar area of North America present the lowest T allele frequency (less than 10 %). In Europe, the lowest T allele frequency is found in northern countries and the highest in Mediterranean region [80].

The prevalence of homozygous genotype *MTHFR* C677T in VTE varies also according to geographical factors, with a high prevalence in Italy, 25.6 %, and a low frequency in Germany, 10.6 % [78].

The *MTHFR* A1298C polymorphism was less studied in association with VTE. A high prevalence of the heterozygous form was found in the healthy Irish population (46.7 %). Heterozygous *MTHFR* A1298C polymorphism presents a prevalence of about 35–44 % in VTE [78].

9.3 Clinical Implication

The role of *MTHFR* polymorphisms in VTE is controversial. Some data show an association

between homozygous *MTHFR* C677T polymorphism and a mild increase of the risk of VTE (OR between 1.2- 3.26), whereas other studies failed to prove any relationship. No association with recurrent VTE was found. *MTHFR* A1298C polymorphism is not significantly associated with the risk of venous thrombosis [78].

MTHFR C677T polymorphism may be associated with other conditions, such as: arterial thrombosis (stroke, peripheral artery disease), migraine, hypertension, recurrent pregnancy loss, male infertility, some types of cancers, neuropsychiatric diseases and chemotherapy toxicity. There is no evidence of a higher cardiovascular mortality in homozygotes for *MTHFR* C677T polymorphism [81].

9.4 Practical Aspects

The professional guidelines do not recommend testing for *MTHFR* polymorphisms for the etiology of VTE (College of American Pathologists, American College of Medical Genetics, The British Committee for Standards in Haematology and the British Society for Haematology). However, it is recommended to measure homocysteinemia rather than the detection of *MTHFR* polymorphisms in cases carrying FV Leiden, because of the increase of the risk [78, 81]. Patients with *MTHFR* polymorphisms and hyperhomocysteinemia can be treated with folic acid and B vitamins. However, despite of the lowering of homocysteine levels, there is no evidence of the reduction of the risks associated with these conditions [81].

10 Antiphospholipidic Syndrome

10.1 Gene Mutations

Antiphospholipid syndrome (APS) is an autoimmune disease manifested with both arterial and venous thrombosis and/or recurrent pregnancy loss, associated with persistent elevated levels of antiphospholipid antibodies (aPL). Although considered as an acquired condition, various studies suggest a familial occurrence of anticardiolipin antibodies and lupus anticoagulant. The underlying genetic background is not completely clarified; some of Human Leukocyte Antigens (HLA) molecules are associated to the presence of aPL in primary APS: HLA-DR4, -DR7, -DRw53 [82]. Several polymorphisms, affecting proteins related to aPL or influencing hemostasis and inflammatory pathways, have been described in APS. These polymorphisms are associated with the thrombotic manifestations in APS: beta2-glycoprotein I gene polymorphisms (substitution of Val for Leu at amino acid 247), polymorphisms within the tissue factor pathway inhibitor (−33C /T and −399C/T), polymorphisms in platelet glycoproteins (glycoprotein Ia/IIa: ITGA2 C807T polymorphism), polymorphisms in platelet Fcγ receptor IIA (Arg131His FcγRIIA), TNF-alpha gene polymorphisms [82, 83].

10.2 Prevalence in Healthy Populations and VTE

The exact prevalence of APS is unknown. The prevalence of aPL in general population is low (1–4.5 %) and increases with age. The incidence of aPL is higher in patients with lupus, 30–60 % [82, 84].

The prevalence of anticardiolipin antibodies and lupus anticoagulant in VTE is 3–17 %, respective 3–14 % [84]. APS may be the cause for up to 1 % of all thromboses [82].

10.3 Clinical Implications

The history of arterial or venous thromboses and/or pregnancy morbidity represents criteria for the diagnosis of APS.

Patients with APS usually present VTE at a young age, the first thrombotic episode occurring between 32 and 45 years old [84]. Some studies showed that lupus anticoagulant may be the most important risk factor for the occurrence of VTE in patients with APS.

The presence of IgM anti beta2glycoproteinI (β2GPI) is significantly associated with a history of thrombosis in cases with APS. The modulation of β2GPI tissue distribution by inflammation may contribute to the induction of the vascular manifestations of APS [85]. A Japanese study detected anti-prothrombin antibody as a significant marker for VTE in APS [84]. Recently it has been validated a scoring system to quantify the thrombotic or obstetric risk depending on aPL profiles [85]. Each 10-unit increase in IgM or IgG anticardiolipin antibodies was associated with a 5–7 % increase of the risk of VTE [86].

VTE is usually manifested with DVT of the lower limbs and PE. In the catastrophic form of APS, multiple small-vessel thromboses, occurring at different sites, are associated with systemic inflammatory response and result in a life-threatening multi-organ failure.

Arterial thrombosis in APS is commonly manifested with cerebral ischemia.

10.4 Practical Aspects

The presence of aPL may be detected directly by ELISA testing in the case of anticardiolipin and antiβ2GPI antibodies or by a clotting assay for lupus anticoagulant, which assess the dilute Russell viper venom time and activated partial thromboplastin time; in case of a positive initial test, the test should be repeated after at least 12 weeks to rule out a condition associated with a transient elevation of aPL [87].

Recent guidelines recommend testing for aPL in patients with unprovoked VTE (after stopping anticoagulation for at least 7 days), in young adults with ischemic stroke, in women with recurrent pregnancy loss before 10 weeks gestation. Primary thromboprophylaxis should not be used in those incidentally found to have aPL. Long term anticoagulation is recommended in patients with APS and an unprovoked episode of VTE. The target of oral anticoagulation in APS should be an INR of 3–5. Women with aPL should be considered for post-partum thromboprophylaxis [88].

11 Guidelines Regarding Thrombophilia

Hereditary thrombophilia testing should be done only in selected cases, since no benefit has been shown in the decrease of the thrombotic recurrence. MEGA study, a large case-control study, showed an unchanged risk for recurrent VTE even after correction for age, sex, family history, geographic region, presence of clinical risk factors, and year of first episode of venous thrombosis [4]. The detection of hereditary thrombophilia presents impact on the correct administration of anticoagulation in children with purpura fulminans, pregnant women at risk of VTE and may be useful in the assessment of the recurrent thrombosis risk in patients with an episode of VTE at an young age (<40 years) and in cases with positive family history regarding thrombosis (at least two other symptomatic family members) [5].

Before testing, patients should be told that being a genetic test, there are implications for the other members of the family regarding the risk. The informed consent of the patient is required in some states [40].

The guidelines regarding thrombophilia issued in 2010, including strong grade 1 recommendations and weaker grade 2 recommendations, with a quality of evidence graded as A (high quality randomized clinical trials), moderate (B) or low (C), show the followings [5]:

- Heritable thrombophilia does not influence the initiation and the intensity of anticoagulant therapy following the diagnosis of acute DVT (1B).
- Indiscriminate testing for heritable thrombophilias in unselected cases with a first episode of DVT is not indicated (1B).
- The duration of anticoagulation (lifelong or not) in unselected patients should be decided according to the occurrence of the episode of DVT (provoked or spontaneous), the presence or not of other risk factors, and the risk of anticoagulant therapy-related bleeding,

regardless of whether a heritable thrombophilia is known (1B).
- Testing for heritable thrombophilias in selected patients, such as those with a strong family history of unprovoked recurrent thrombosis, may influence decisions regarding duration of anticoagulation (C).
- Testing is not recommended in unselected patients with upper limb venous thrombosis or in patients with retinal vein occlusion (1B).
- Testing is not recommended in patients with central venous catheter related thrombosis (1C).
- Testing for heritable thrombophilia after a first episode of cerebral vein thrombosis or of intra-abdominal vein thrombosis has uncertain predictive value for recurrence (C).
- Neonates and children with purpura fulminans should be tested urgently for protein C and S deficiency (1B).
- A variety of functional methods may be required to identify specific severe type 2 functional defects when levels of PC or PS are not <5 % (1B).
- It is suggested that adults who develop skin necrosis in association with oral vitamin K antagonists are tested for protein C and S deficiency after this treatment is withdrawn (2B).
- Case finding of asymptomatic relatives with low risk thrombophilia, such as factor FV Leiden or prothrombin G21210A is not indicated (1B).
- Case finding of asymptomatic relatives with high risk thrombophilia, such as deficiency of AT, PC or PS, should only be considered in selected thrombosis-prone families (1B). It is not possible to give a validated recommendation as to how such patients and families should be selected.
- Case finding for very rare homozygosity or compound heterozygous heritable thrombophilia is not indicated as these defects are so rare, they are not predicted by family history, and the risk of unprovoked thrombosis is low (2C).
- If a first-degree relative with DVT has not been tested then suggest that women consider an alternative contraceptive or transdermal hormone replacement therapy (HRT). Testing for heritable thrombophilia will provide an uncertain estimate of risk and is not recommended (1C).
- If a first-degree relative with DVT has been tested and the result is negative then suggest that a woman considers an alternative contraceptive or transdermal HRT. Testing for heritable thrombophilia will provide an uncertain estimate of risk and is not recommended (1C).
- If a first-degree relative with DVT has been tested and the result is positive then suggest that women consider an alternative contraceptive or transdermal HRT before offering testing as a negative test result does not exclude an increased risk of venous thrombosis. Testing for heritable thrombophilia may assist counselling of selected women particularly if a high risk thrombophilia has been identified in the symptomatic relative (C).
- Women should be assessed for risk of pregnancy-associated venous thrombosis primarily in relation to clinical risk factors (1B).
- Most pregnant women with a previous unprovoked venous thrombosis (1B) or pregnancy or combined oral contraceptive- related thrombosis (2C) will qualify for thrombophylaxis on clinical risk alone and so testing for heritable thrombophilia is not required.
- Pregnant women with a previous event due to a major provoking factor, e.g. surgery or major trauma, would not usually require prophylaxis or testing (2B).
- Pregnant women with a previous event due to a minor provoking factor, e.g. travel, should be tested and considered for prophylaxis if a thrombophilia is found (2C).
- In the asymptomatic pregnant woman with a family history of venous thrombosis, testing is not required if the clinical risks alone are sufficient to result in thromboprophylaxis (2C).

- It is suggested that asymptomatic pregnant women with a family history of venous thrombosis be tested if an event in a first-degree relative was unprovoked, or provoked by pregnancy or a minor risk factor (2C). The result will be more informative if the first-degree relative presents a known thrombophilia.
- Testing asymptomatic women before assisted conception and those with ovarian hyperstimulation syndrome is not indicated (1B).
- Thrombophilia screening of hospitalized patients to identify patients at risk is not indicated (1A).
- All hospitalized patients should be assessed for the risk of DVT, regardless the heritable thrombophilia (1B). The presence of a previously known heritable thrombophilia may influence the clinical assessment of risk.
- Testing for heritable thrombophilia is not indicated in patients with arterial thrombosis (1B).
- It is suggested that testing for heritable thrombophilia is not indicated in children with stroke (2C).

Similar recommendations regarding thrombophilia could be found in other guidelines, according to: the European Genetics Foundation, Cardiovascular Disease Educational and Research Trust, International Union of Angiology, Mediterranean League on Thromboembolism, French Group on Hemostasis and Thrombosis, French Society of Vascular Medicine.

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Venous and Arterial Thrombosis: Is There a Link?

Paolo Prandoni

Abstract

An increasing body of evidence suggests the likelihood of a link between venous and arterial thrombosis. The two vascular complications share several risk factors, such as age, obesity, smoking, diabetes mellitus, blood hypertension, hypertriglyceridemia, and metabolic syndrome. Moreover, there are many examples of conditions accounting for both venous and arterial thrombosis, such as the antiphospholipid antibody syndrome, hyperhomocysteinemia, malignancies, infections, and the use of hormonal treatment. Finally, several recent studies have consistently shown that patients with venous thromboembolism are at a higher risk of arterial thrombotic complications than matched control individuals. We, therefore, speculate the two vascular complications are simultaneously triggered by biological stimuli responsible for activating coagulation and inflammatory pathways in both the arterial and the venous system. Future studies are needed to clarify the nature of this association, to assess its extent, and to evaluate its implications for clinical practice.

Keywords

Venous thromboembolism • Deep vein thrombosis • Pulmonary embolism • Myocardial infarction • Ischemic stroke • Atherosclerosis

1 Introduction

Venous and arterial thrombotic disorders have long been viewed as separate pathophysiological entities, partly because of the obvious anatomical differences, as well as their distinct clinical presentations. In particular, arterial thrombosis has long been held to be largely a phenomenon of platelet activation, whereas venous thrombosis is largely a matter of activation of the clotting system. However, there is evidence that this dichotomy is likely to be an oversimplification. Fibrin-rich thrombi form in the left atrial

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appendage of patients with atrial fibrillation and in the coronary artery system of patients with myocardial infarction. Accordingly, anticoagulant drugs are highly effective for prevention of arterial embolism related to atrial fibrillation [1], and for prevention and treatment of coronary artery disease [2]. Likewise, platelets play an inevitable role in the formation of thrombi in the venous system, and antiplatelet agents have been shown to be effective for prevention of venous thromboembolic (VTE) disorders, although to a smaller extent than anticoagulant drugs [3, 4]. As another example, subjects who sustain a retinal vein thrombosis commonly have associated cardiovascular risk factors [5], and the causes of mortality on follow-up are usually arterial vascular events [6].

2 Generation of the Hypothesis

In the second half of the 1990s, we published the results of a prospective cohort study dealing with the long-term follow-up of a wide cohort of patients after their first episode of both unprovoked and secondary acute deep vein thrombosis (DVT) of the lower extremities [7]. While the predominant interest of this observation focused on the development of recurrent VTE and late post-thrombotic sequelae, we were surprised by the unexpectedly high proportion of patients who died of acute myocardial infarction, ischemic stroke or experienced a sudden otherwise inexplicable death. Although this observation was not controlled, we had the distinct perception that this proportion would be higher than that expected in matched individual subjects free from thromboembolic disorders.

3 Association Between VTE and Atherosclerosis

In order to assess whether an association exists between VTE and atherosclerosis, in 1996, a prospective case-control study was initiated and its results were published in 2003 [8]. Ultrasonography of the carotid arteries was performed in 299 unselected patients with DVT without symptomatic atherosclerosis and in 150 control subjects. In a multivariate analysis taking into account risk factors for atherosclerosis, the odds ratio (OR) for carotid plaques in patients with unprovoked as compared to secondary DVT (i.e., DVT associated with active cancer, recent puerperium, trauma or fracture, prolonged immobilization or current estrogens use) and controls was found to be 2.4 (95 % CI, 1.4–4.0) (Fig. 1).

Subsequently, three studies have provided further evidence in support of the association

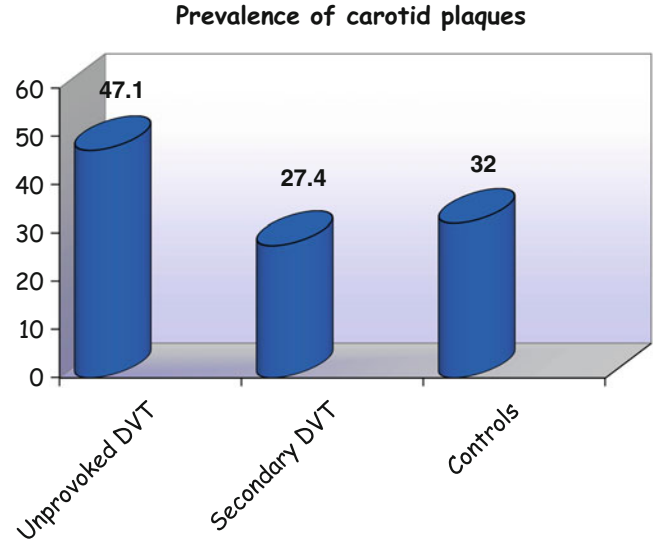

Fig. 1 Prevalence of carotid plaques in patients with unprovoked and secondary DVT and in the control subjects [8]

between VTE and atherosclerosis. In a case-control study, Hong et al. found a higher prevalence of coronary artery calcium, as assessed by chest CT scan, in patients with unprovoked VTE than in matched control individuals [9]. In a series of almost 24,000 consecutive autopsies, Eliasson et al. found an increased prevalence of VTE in patients with arterial thrombosis, except for those with coronary artery thrombosis [10]. Finally, in a recent a case-control study conducted on subjects older than 50, we assessed the prevalence of symptomatic or subclinical atherosclerosis in 100 unselected patients with unprovoked VTE, and compared it with that of 100 patients with secondary VTE and of 100 matched control individuals free from VTE disorders [11]. In patients with unprovoked VTE, the adjusted OR for symptomatic or subclinical atherosclerosis was 5.1 (95 % CI, 2.0–13.1) in comparison to patients with secondary VTE, and 14.5 (95 % CI, 5.8–36.3) in comparison to controls. The prevalence of atherosclerosis was higher in patients with secondary VTE than in controls (OR, 3.1; 95 % CI, 1.6–6.1).

4 Risk Factors of Atherosclerosis and Venous Thromboembolism

Ageno et al. reviewed the evidence favouring the association of the most important risk factors for atherosclerosis and VTE [12]. After reviewing 21 case-control and cohort studies dealing with a total of 63,552 patients meeting the inclusion criteria, factors that were found to be significantly associated with an increased risk of VTE were obesity, blood hypertension, diabetes mellitus, and hypertriglyceridemia, According to the results of subsequent population-based study, abdominal obesity appears to be the pivotal risk factor among the individual components of the metabolic syndrome [13–15].

While the review by Ageno et al. failed to identify smoking as an additional potential risk factor for VTE, the findings from two more recent population-based studies provided strong evidence that this is the case [16, 17]. Interestingly enough, in a cross-sectional study a few markers of atherosclerosis (namely, male sex and arterial hypertension) were found to be independently associated also with an increased risk of recurrent VTE after a period of 3–6 months of vitamin K antagonist therapy for the first VTE event [18].

5 Nature of the Association

Although information coming from the above reported investigations suggests the existence of an association between VTE and atherosclerosis, it does not clarify the nature of this association. On the one hand, atherosclerosis has the potential to promote the development of thrombotic disorders in the venous system. Atherosclerosis is associated with a detectable activation of both platelets and blood coagulation as well as an increased fibrin turnover, which can lead to thrombotic complications [19–28]. The role of this prothrombotic state in favouring venous thrombotic events is plausible given the assumption that activated platelets and coagulation factors appear in the slow-flowing venous system.

On the other hand, the two clinical conditions may share common mechanisms or risk factors. In nature, there are many examples of conditions accounting for both arterial and venous thromboembolic disorders, such as hyperhomocysteinemia, antiphospholipid antibodies, malignancies, paroxysmal nocturnal haemoglobinuria, infectious states, inflammatory bowel disease, and the use of hormonal therapy [29] (Fig. 2).

Interestingly enough, a few markers of endothelial dysfunction have been found to be significantly higher in patients with unprovoked DVT than in matched control individuals [30, 31]. In a case-control investigation enrolling patients with previous unprovoked DVT and matched control individuals, flow-mediated vasodilatation was found to be significantly lower in cases than in controls; accordingly, a few parameters of endothelial function (von Willebrand factor and

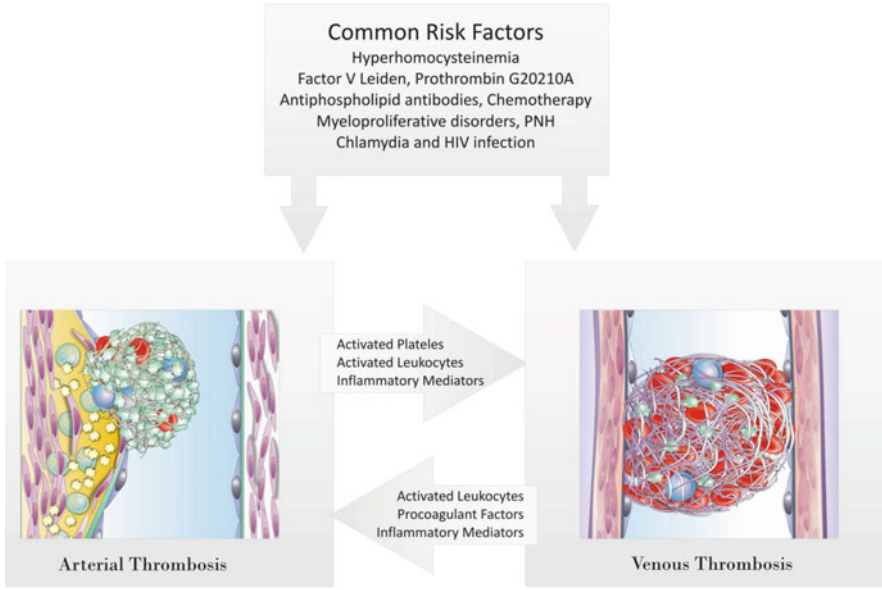

Fig. 2 Potential links between venous and arterial thrombosis

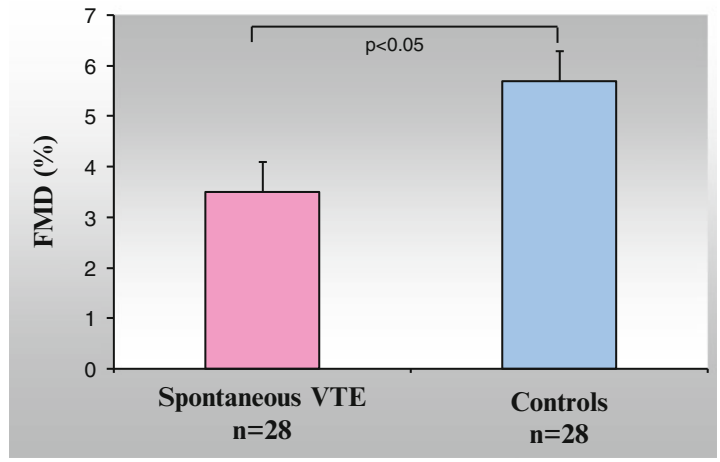

Fig. 3 Flow-mediated vasodilation of the brachial artery in patients with previous unprovoked DVT and in controls [30]

soluble P-selectin) were significantly higher. Interestingly enough, a few markers of platelet activation (plasma soluble CD40 ligand and urinary 11-dehydro-TxB2 levels) did not differ between the two groups (Figs. 3 and 4). Microalbuminuria, a well know marker of endothelial dysfunction whose and of arterial cardiovascular events, was found to be independently associated with an increased risk for VTE as well [32].

6 Is Atherosclerosis Predictive of VTE?

In an attempt to assess whether atherosclerotic disease predisposes to VTE, the authors of two similar population-based cohort studies carried out in the U.S.A., the Atherosclerosis Risk in Communities and the Cardiovascular Health Study, evaluated the rate of VTE development

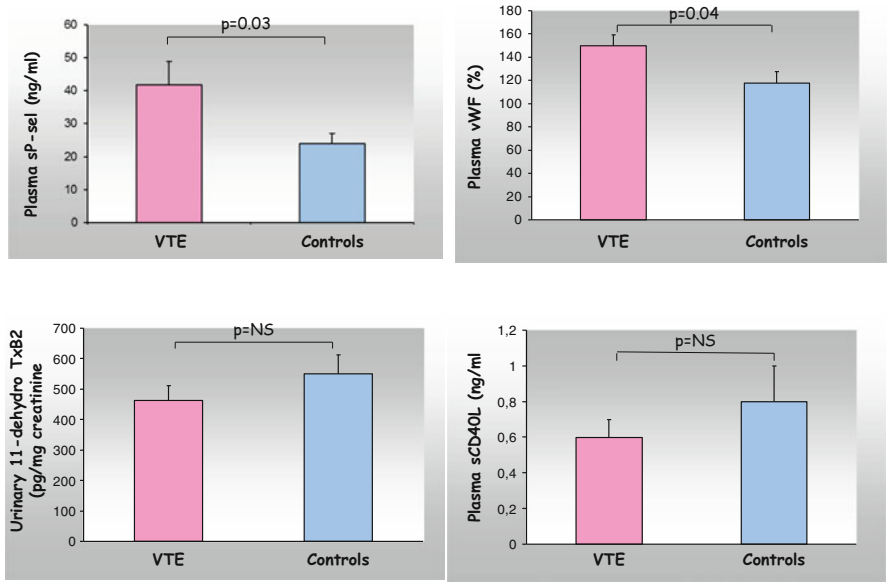

Fig. 4 Endothelium and platelets activation markers in patients with previous unprovoked DVT and in controls [30]

in subjects younger and older than 65, respectively, who had carotid ultrasound and the assessment of other subclinical parameters of atherosclerosis, and were then followed-up prospectively for several years [33, 34].

In the former study, 13,081 adults aged 45–64 years underwent carotid ultrasonography to assess the intima-media thickness and the presence of atherosclerotic plaques [33]. After adjustment for age, sex, ethnicity, body mass index and diabetes, no association was found between ultrasound parameters of subclinical atherosclerosis and VTE development after a mean follow-up of 12.5 years (adjusted hazard ratio [HR] of VTE for presence of carotid plaques, 0.97; 95 % CI, 0.72–1.29).

In the latter study, 4108 individuals aged at least 65 years underwent non-invasive assessment of subclinical atherosclerosis using carotid ultrasound (intima-media thickness and presence of plaques), ankle-brachial blood pressure index and electrocardiogram, and then were followed-up for a median of 11.7 years [34]. Surprisingly enough, the adjusted RR of overall and unprovoked VTE for presence of any type of subclinical atherosclerosis was 0.60 (95 % CI, 0.39 to 0.91) and 0.32 (95 % CI, 0.18 to 0.59), respectively. These unexpected findings were mostly explained by an inverse association of high-risk carotid plaques and arterial events during follow-up.

While in the former of the two above reported studies, the occurrence of cardiovascular and cerebrovascular events was significantly associated with the development of VTE [33], in the latter the opposite was seen [34].

In an attempt to determine the impact of cardiovascular risk factors, including family history of myocardial infarction, on the incidence of VTE, a few investigators from Norway extracted data from more than 21,000 subjects, aged 25–96 years, who had been enrolled in a prospective, population-based study (the Tromsø Study) [35, 36]. In multivariable analysis, family history of myocardial infarction was significantly associated not only with an increased risk of infarction but also of total VTE (HR, 1.27; 95 % CI 1.01–1.60) and unprovoked VTE (HR, 1.46; 95 % CI: 1.03–2.07. The risk was found to increase with increasing number of affected individuals. The association was not explained by modifiable atherosclerotic risk factors. In another population-based study, having first degree relatives with myocardial infarction

before the age of 60 years was positively associated with VTE compared to participants not having a positive family history (OR 1.3; 95 % CI 1.1–1.6) [37]. Finally, in a more recent population-based study conducted in Denmark patients with a history of arterial cardiovascular events had a clearly increased relative risk of VTE events in the first 3 months following the index event, then the risk decreased yet remained statistically significant [38].

Based on these findings, asymptomatic atherosclerosis is unlikely to constitute a risk factor of venous thromboembolic disorders. Whether patients developing symptomatic complications of atherosclerosis such as myocardial infarction or stroke are at a higher risk of VTE complications is controversial.

7 Is VTE Predictive of Arterial Cardiovascular Events?

Another scenario assumes that the same biological trigger is responsible for activating coagulation and inflammatory pathways in both arterial and venous thromboembolism, in such a way determining a simultaneous risk of arterial and venous thrombotic complications. This assumption is supported by the results of a cohort study. Indeed, in an attempt to evaluate whether elevated clotting factors, which have been linked to chronic sub-clinical inflammation and arterial thromboembolic disease, have a high prevalence in patients with VTE as well, Luxembourg et al. measured the plasma level of fibrinogen, factor VIII, and high-sensitivity C-reactive protein in a cohort of sex- and age-matched patients with unprovoked VTE, patients with secondary VTE and controls [39]. They found that these markers of inflammation were significantly higher in patients with unprovoked compared to secondary VTE and controls, in such a way providing evidence in support of the hypothesis that VTE and arterial thromboembolism may share common risk factors.

If this is true, subjects with VTE may be at a higher risk of subsequent arterial cardiovascular events than matched control individuals. This hypothesis was tested in 11 studies [40–50] (Table 1) and summarized in a meta-analysis [51]. All together, the results of these studies are in keeping with the observation of a higher prevalence of carotid atherosclerosis in patients with unprovoked DVT than in matched control individuals [8, 11], and strongly suggest that patients with VTE have also an increased risk of subsequent symptomatic arterial cardiovascular events. Of particular relevance is a population-based cohort study carried out in Denmark. Using nationwide Danish medical databases, Sorensen et al. assessed the risk of hospitalization due to myocardial infarction, stroke and transient ischemic attack among 25,199 patients with DVT, 16,925 patients with PE and 163,566 population controls discharged from the Danish hospitals in a 25-year period [45]. Patients with both DVT and PE were found to have a substantially increased risk of myocardial infarction and stroke during the first year after the thrombotic event. For patients with DVT, the RRs varied from 1.60 for myocardial infarction (95 % CI 1.35–1.91) to 2.19 (95 % CI 1.85–2.60) for stroke. For patients with PE, the RRs were 2.60 (95 % CI 2.14–3.14) for myocardial infarction and 2.93 (95 % CI 2.34–3.66) for stroke. The RRs were also elevated, though less markedly, during the subsequent 20 years of follow-up, with 20–40 % increases in risk for arterial cardiovascular events. RRs were similar for those with provoked and unprovoked DVT and PE (Figs. 5 and 6).

Whether the risk of subsequent arterial thrombotic disorders applies to all VTE patients or to the only patients with unprovoked disease is uncertain. According to the results of a meta-analysis of six studies, the risk appears higher in patients with unprovoked VTE compared to those with provoked VTE (IRR 1.86, 95 % CI 1.19–2.89) [51]. Of interest, based on recent findings the persistence of residual thrombosis, as assessed with ultrasonography 3 months after an episode of proximal DVT, predicts the development of arterial thrombotic disorders both in patients with unprovoked and in those with secondary DVT [52].

Table 1 Main studies addressing the risk of arterial cardiovascular events in patients with VTE

Ref	Study design	Study population	Number	Findings
[40]	Prospective cohort	Idiopathic PE	209	Idiopathic PE risk factor of arterial cardiovascular events
		Secondary PE	151	
[41]	Prospective cohort	Idiopathic VTE	1063	Idiopathic VTE risk factor of arterial cardiovascular events
		Secondary VTE	856	
[42]	Extended follow-up of the DURAC study	VTE patients	897	Higher mortality from myocardial infarction or stroke in VTE patients
		General Swedish population		
[43]	Retrospective cohort	DVT patients	151	Idiopathic VTE risk factor of arterial cardiovascular events
		Controls	151	
[44]	Prospective cohort	DVT with residual thrombosis	173	Residual thrombosis risk factor of vascular death
		DVT with recanalized veins	143	
[45]	Population-based	VTE patients	42,124	VTE risk factor of myocardial infarction or stroke
		Controls	163,566	
[46]	Population-based	Idiopathic VTE	6065	Idiopathic VTE in patients aged < 40 risk factor of myocardial infarction
		Controls	12,040	
[47]	Prospective cohort	PE patients	364	Idiopathic PE risk factor of subsequent arterial cardiovascular events
		Suspected PE (not confirmed)	334	
[48]	Population-based	VTE patients	1311	VTE not a predictor of myocardial infarction
		Controls	1511	
[49]	International RIETE registry	VTE patients	23,370	PE-related mortality lower than mortality due to ischemic events
[50]	Prospective cohort	DVT patients	244	Idiopathic DVT risk factor of subsequent arterial cardiovascular events
		Suspected DVT (not confirmed)	991	

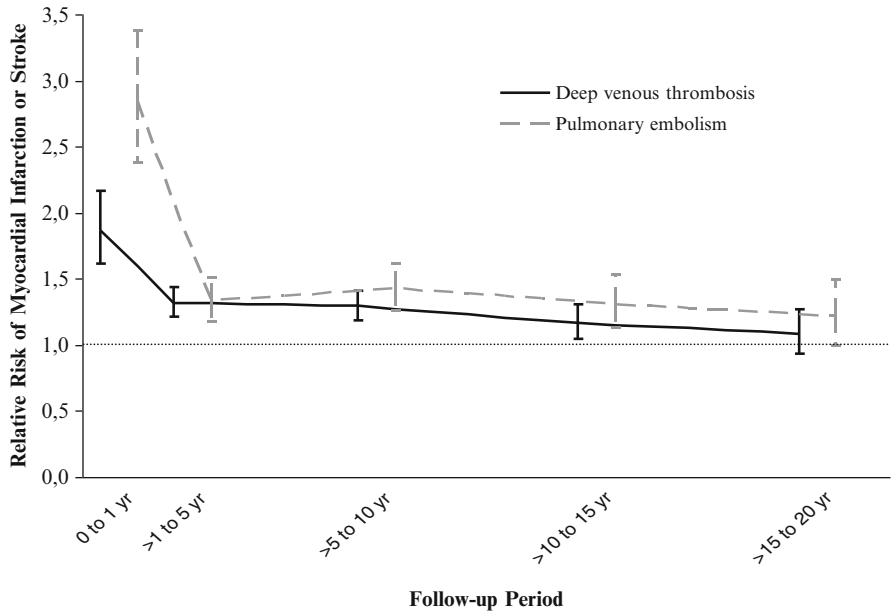

Fig. 5 Risk of acute myocardial infarction and stroke in patients with unprovoked VTE in relation to the length of the follow-up period [45]

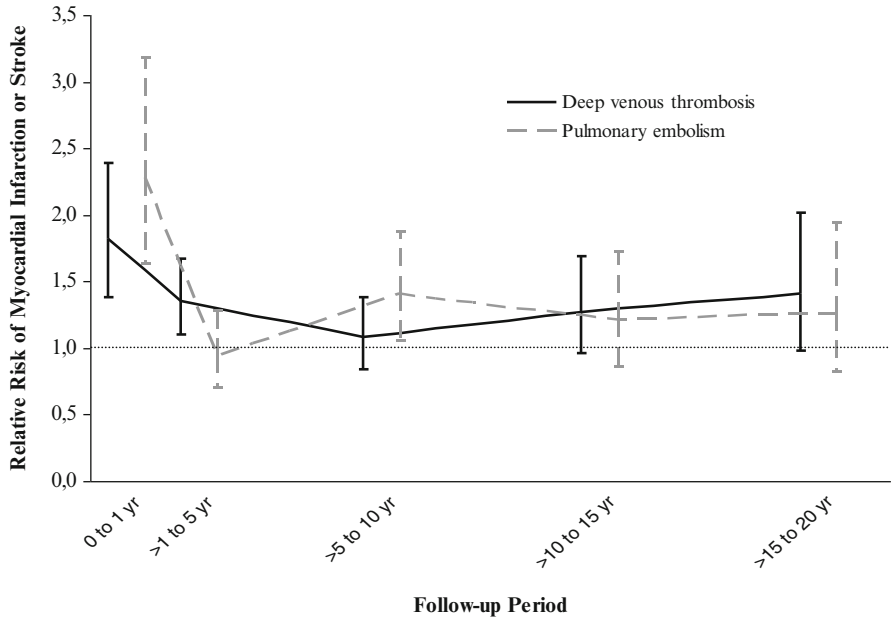

Fig. 6 Risk of acute myocardial infarction and stroke in patients with secondary VTE in relation to the length of the follow-up period [45]

8 Implications of the Association

We speculate that venous and arterial thrombosis are two aspects of the same disease (i.e., thrombosis), and that this disease may electively affect genetically predisposed individuals resulting in clinically manifestations that are, in turn, depending on a variety of elements including the age of patients, their lifestyle, and the occurrence of co-morbidities and circumstantial factors: the venous thrombotic events being more frequent, for example, after triggering risk factors such as surgery or trauma, and the arterial thrombotic events being more frequent in subjects who have developed atherosclerosis.

These findings have several implications for both research and medical practice. Patients with VTE of unknown origin could be examined for asymptomatic atherosclerosis, in order to modify aggressively the risk profile in those with abnormal test results. Measures could include appropriate counselling about lifestyle changes and control of risk factors for atherosclerosis. Interestingly enough, lifestyle factors are likely to have a major impact on the risk of VTE. A diet including more plant food and fish and less red and processed meat [53] and more in general the Mediterranean diet [54], the supplementation of vitamin E [55], and alcohol consumption [56, 57] have recently been found to be associated with a lower incidence of venous thrombosis. Whether regular sport activity decreases this risk as well is controversial, as there data in favour [58] and against [59] this association. Consistent with these findings are the results of a prospective cohort study conducted in Sweden on 40 000 Swedish women who were followed-up for a mean of 11 years: women non-smokers who were physically active and who consumed alcohol in moderation were found to have a lower risk of VTE [60]. Conversely, sedentary life was recently found to increase the risk of unprovoked PE in women [61].

In addition, a potential role for prophylaxis of both recurrent VTE and arterial cardiovascular events with antiplatelet therapy or statins may be explored. Interest in statins has increased, given recent data that consistently suggest an

unexpected role in lowering the risk of venous thromboembolism [62–67]. As far as the role of aspirin is concerned, according to the results of recent studies, aspirin in low doses when administered for the long-term management of patients with unprovoked VTE reduces by approximately 35 % the risk of recurrent VTE while offering a considerable protection against the development of arterial cardiovascular events [68–70].

In conclusion, the separate nature of arterial and venous thrombotic disorders has been challenged. Future studies are needed to clarify the nature of this association, to assess its extent, and to evaluate its implications for clinical practice.

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Thrombosis and von Willebrand Factor

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Abstract

One of the key players in both hemostasis and thrombosis is von Willebrand factor (vWF), which demonstrates a duality between these two processes. Thrombus is structured by numerous elements, including endothelial cells, platelets, plasma proteins and shear stress alteration. In circulation, once a vessel wall is injured, collagen is exposed and platelets attach to the site of injury. Accordingly, vWF mediates adherence of platelets to the damaged vessel wall by binding both to the collagen and platelet receptor. A growing body of data also indicates a role for neutrophil extracellular traps (NETs) in human thrombosis as scaffolds for vWF, promoting thrombosis. VWF also mediates the protection of factor VIII, a main cofactor of the intrinsic clotting pathway. Since vWF plays a critical role in both thrombotic and bleeding events, a decreased plasma level of this factor may point to a bleeding disorder, while an elevated plasma level may predict occurrence of thrombosis. Since thrombotic events are the foremost cause of death, inhibiting the vWF activity would be a novel prophylaxis to reduce these events. Though, accumulated data have made vWF a promising focus for research on cardiovascular diseases (CVD). This chapter, however, aims to clarify the role of vWF in thrombus formation and pathogenesis of thrombosis.

Keywords

Von Willebrand factor • Thrombosis • Endothelial cell • Platelet • Shear stress • Thrombotic thrombocytopenic purpura (TTP) • A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) • Neutrophil extracellular traps (NETs)

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1 Introduction

There is accumulated evidence that vWF has a pivotal role in thrombosis. This factor is present in plasma as a mixture of disulfide-bonded multimers of different sizes [1, 2] and therefore, may be considered as a marker for thrombus and/or endothelial activation. VWF was first recognized in 1924 when a 5-year-old girl referred to Dr. Erik von Willebrand for treatment of a severe bleeding disorder. Primarily, it was thought that the cause of bleeding was platelet defect, but it was found to be a defect in homeostasis afterward, which was originated from the patient's plasma. Finally, von Willebrand factor (vWF) was identified in 1971 as it is known today [3]. This factor has been reported to support the progression of an occlusive thrombus by numerous studies [4–6]. Deactivation of vWF in pigs via monoclonal antibody prevented the induction of occlusive thrombosis, indicating the strong thrombotic effect of this protein [7]. Regarding these data, von Willebrand factor has been suggested to be a target for inhibition of thrombosis [8]. VWF also mediates the protection of factor VIII (hemophilic factor), a main cofactor of the intrinsic clotting pathway, which is inactive in circulation (Fig. 1). Hemophilic factor, therefore, degrades rapidly when it is not bound to vWF. Afterward, thrombin causes factor VIII release from vWF, which is required for procoagulant activity [9]. An abnormality, either quantitative or qualitative, of von Willebrand factor can consequently cause a set of bleeding disorders that are called von Willebrand disease. Several studies have shown the relationship between high vWF levels in plasma and thromboembolic cardiovascular events [10]. Our *in vitro* findings also showed that C-reactive protein (at the levels that have been claimed to be a risk factor for the development of cardiovascular diseases) increases vWF and decreases the production of tissue plasminogen activator concomitantly [11].

Moreover, vWF has been proposed as a novel marker for the increased risk of re-infarction and mortality in survivors of myocardial infarction [12–14]. vWF has also been associated with thromboembolism, metastasis and angiogenesis [15]. In addition, a marked increase in vWF levels was found in HIV patients with a history of thrombosis [17]. The above studies, however, have made vWF a remarkable target for research on CVD, atherosclerosis and the rest of thrombotic events.

2 VWF Gene

VWF is encoded on the short arm of chromosome 12 at position 13.3 and comprises 180 kb length and 52 exons [18]. The VWF gene belongs to a family of genes named endogenous ligands. Twin studies have revealed that 66 % of

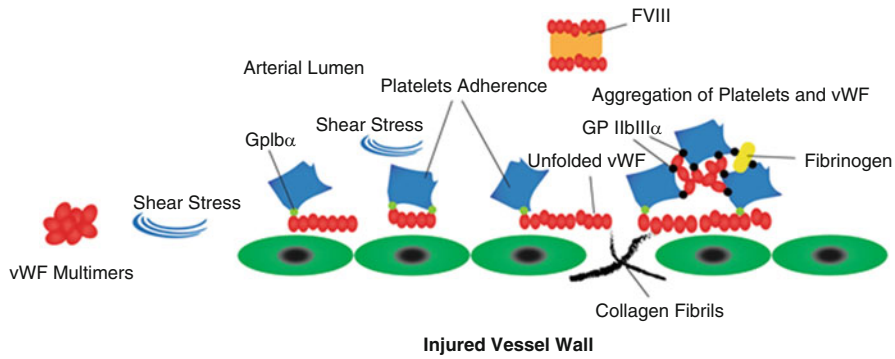

Fig. 1 VWF functions: After the platelets detect any defect in vascular wall, shear rate leads to the initial arrest and attachment of platelet at the site of injury. Shear-induced conformational changes in vWF may contribute to the regulation of vWF binding to platelet GPIbα. Excess of the large vWF multimers in circulation results in platelet clumping afterwards

the discrepancy of vWF level underlies a genetic influence and 30 % of the genetic variance is because of the effect of ABO blood group. Naturally occurring genetic differences among individuals in the VWF gene are linked with vWF levels. These includes polymorphic variations in the 5′-regulatory region of hemostatic factors, which can contribute to the level of vWF presence in plasma and eventually the risk of thrombotic events. In addition, the presence of three single nucleotide polymorphisms (SNPs) within the regulatory region of vWF gene at nucleotides −1234C/T, −1185A/G and −1051G/A demonstrated a significant association with plasma levels of vWF:Ag in a population of normal group O blood donors [19]. The 1793C/G polymorphism is in the promoter region of the gene and the G allele is linked with greater levels of vWF antigen, which is more noticeable after the age of 40. In addition, endothelial cell-derived nuclear proteins preferred to bind to certain alleles at these sites [20]. The association of 1793C/G polymorphism with the incidence of ischemic stroke has also been reported in a number of studies [21, 22].

3 VWF Biosynthesis

The location of vWF biosynthesis and secretion is consistent with its biological function, which is in a close association with that of platelet. It is primarily synthesized and stored in endothelial cells, megakaryocytes and platelet precursors in the bone marrow. vWF as a large multimeric glycoprotein is present in blood plasma, platelet α-granules, sub-endothelial connective tissue and endothelium with a plasma concentration of approximately 5–10 μg/ml [23]. The plasma form of smaller size is corresponding to the dimer, with an approximate size of 500,000 Da.

3.1 Synthesis of vWF in Endothelial Cells

Normally, vWF is synthesized as pre-pro-vWF in endothelial cells. This immature form of protein encompasses the signal peptide, pro-peptide and mature subunit. The protein goes through a process during which the signal peptide is removed, and dimerization and multimerization occur, respectively [24]. The pro-peptide, a tag for the protein, is stored in the storage granules and can be detached before releasing into blood, where it is known as von Willebrand antigen II (vWAgII). In the endothelial cells, vWF is stored in specialized rode-like granules identified as Weibel–Palade bodies (WPB), which are assumed to be a derivative of Golgi apparatus. It is worth noting that vWF multimerization itself is confirmed to trigger WPB formation. VWF, therefore, is responsible for the cigarette shape of WPBs [25]. These constructions are able to rapidly respond to alteration in the integrity of the cells covering the vessel walls. VWF, however, is synthesized in the vascular endothelial cell through both constitutive and stimulated release (Fig. 2). This major part of vWF (85 % of all vWF) may either constitutively be secreted in plasma or deposited in the WPBs. Moreover, circulating plasma vWF mostly originates from endothelial cells, while platelet vWF might be released through platelet activation. The role of plasma vWF in the hemostatic process is more dominant than platelet vWF (Figs. 2 and 3). The modification is a vital occasion that may affect different steps from biosynthesis to function and finally to degradation of a protein. VWF glycosylation as a posttranslational modification results in the covalent attachment of carbohydrate structures to the protein backbone.

Thus vWF goes through several modifications, including N-linked and O-linked glycosylation (Fig. 3). O-glycosylation proceeds in the Golgi following N-linked glycosylation, protein folding, and oligomerization. The process is initiated by transferring of N-acetylgalactosamine (GalNAc) from UDP-αGalNAc to a serine or threonine, followed by addition of monosaccharides via specific transferases [26]. In addition, the cellular origin of protein and the variability of enzymes mediating glycosylation in different cell types are the important elements of glycosylation.

The differences, however, between the vWF secreted constitutively by human endothelial

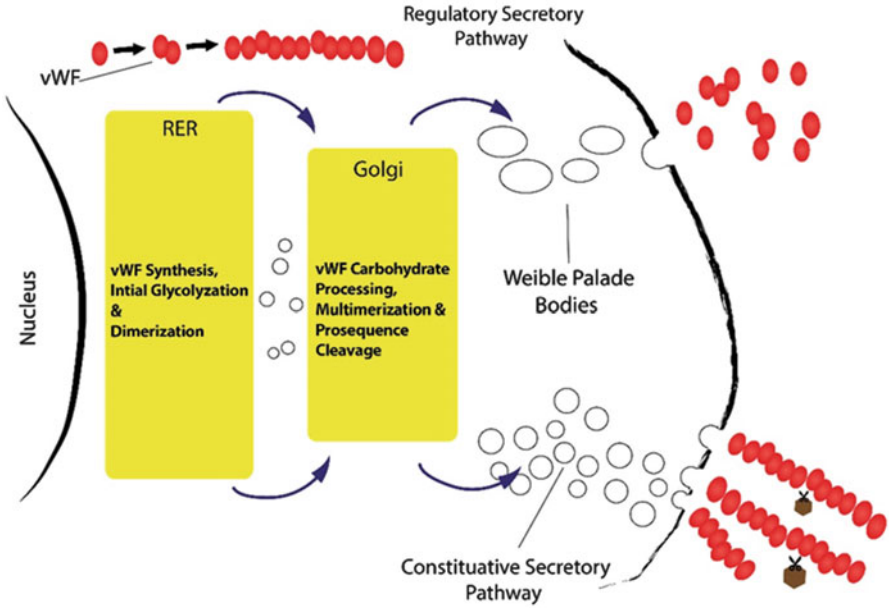

Fig. 2 VWF from biosynthesis to release: Glycosylation is a posttranslational modification that results in the attachment of carbohydrate to the protein backbone. VWF may be either constitutively secreted in plasma or regulated & deposited in the Weibel-Palade bodies

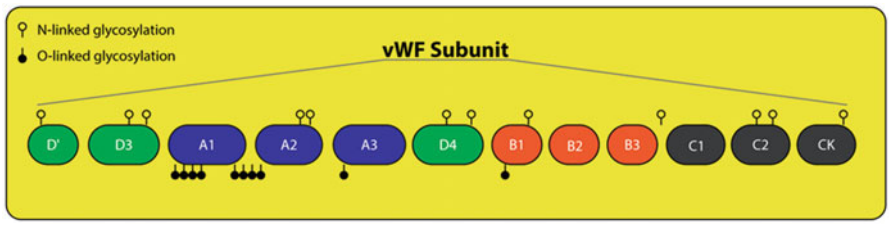

Fig. 3 VWF glycosylation: The location of N-linked and O-linked glycosylation on a vWF subunit

cells and that released from Weibel-Palade bodies after stimulation was explained by Sporn et al. The majority of constitutively secreted molecules were dimeric and contained both pro-vWF and mature subunits as they described. In contrast the vWF released by the calcium ionophore A23187 or thrombin consisted of mature subunits of very large multimers. These large subunits have been recognized to play a very important task. They are more active in platelet binding assays in vitro, and their absence in vivo results in a bleeding disorder. Weibel-Palade bodies though contain a special concentrated subclass of very large and biologically potent vWF multimers [27].

3.2 Synthesis of vWF in Platelet

VWF is also synthesized by the megakaryocyte, which includes 10–25 % of the total amount of vWF antigen present in plasma. However, analysis of reduced vWF purified from human megakaryocytes has demonstrated a subunit composition comparable to that of endothelial cell-derived vWF. Studies have also shown that platelet vWF is placed within the α-granules, as detected by immune-fluorescence study [28], which can be released upon platelet activation. Nevertheless the storage of α-granules may be provided via both biosynthesis at the megakaryocyte and uptake of plasma proteins. This may

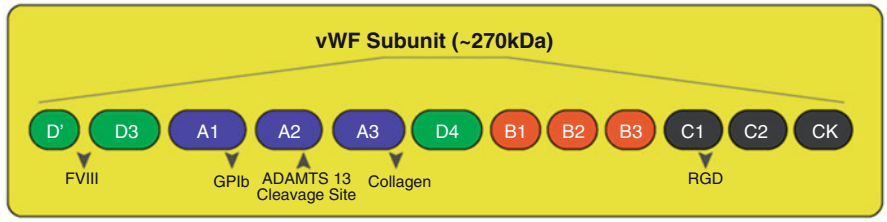

Fig. 4 The main functional domains of vWF subunit: As it is shown, A1 domain binds to the platelet receptor GPIbα & heparin, A2 domain is the cleavage site for ADAMTS13, A3 domain attaches to collagen, C1 domain has RGD sequence and is recognized by integrins (αIIbβ3 and αvβ3), and D′–D3 contains the binding site for FVIII

occur at the megakaryocyte and/or platelet stage [29]. Release of platelet vWF is prompted by a variety of agonists, including ADP, collagen and thrombin [30].

4 VWF Structure

VWF, a long multimeric protein, contains several distinct domains, each with specialized functions. This long polypeptide chain has a molecular mass of ~270 kDa and encompasses the identical repeated domains, whose rearrangement looks like a mosaic protein. VWF monomers are dimerized via disulfide bonds [31]. These bonds subsequently turn these 500 kD dimmers into multimers of different sizes, may be more than 10, 000 kD. VWF monomer, is composed of repeated domains (as seen in Fig. 4) of cDNA, which are responsible for the various binding functions of the molecule [32]. The main functional domains are A1 through which vWF binds to the platelet receptor GPIbα and heparin, A3 for attaching to collagen, C1 that has RGD sequence and is recognized by integrins (αIIbβ3 and αvβ3), and D′–D3, which contains the binding site for FVIII [33].

5 VWF Function

It has been established that active vWF is present only in partial amounts within normal plasma, whereas pathological conditions are usually associated with increased levels of active vWF. Immediately after the platelets detect any defect in vascular wall, a rapid diversion in the blood flow and shear rate leads to the initial arrest and attachment of platelet at the site of injury. This is known as primary homeostasis after which, permanent platelet adhesion and aggregation are formed in the line of vessel endothelium. VWF and platelet vessel-wall interaction promotes GPIbα binding to the halted vWF multimers. This binding promotes the recruitment of circulating platelets to the site of injury, where subendothelium is exposed [34]. Shear rate rising causes the immediate interaction of platelet GPIbα with A1 domain of vWF; an essential adhesive interaction that can tether platelets on the endothelial surface. However, this initial adhesion is an unstable phase in which, vWF plays a key role. The temporary binding may promote a stronger and prolonged adhesion, which is mainly mediated by vWF [35].

Using vWF-A1 knock-in mice, mutations that increase (I1309V) or interrupt (R1326H) platelet receptor glycoprotein Ibα binding were investigated. R1326H mutation into the major site, however, shortened the bond lifetime and resulted in hemostatic and thrombotic defects. In contrast, the I1309V mutation near the minor site prolonged the bond lifetime and developed a type 2B-like vWD phenotype. Nevertheless, combination of these two mutations normalized both bond kinetics and thrombotic properties of vWF. Increased levels of active vWF have been associated with thrombotic complications in several inflammatory conditions, suggesting the role of active vWF in this regard. Additionally, miR-24 has been found to control vWF levels in diabetic patients [36]. These findings highlight the importance of combined biophysical and genetic approaches in identifying potential

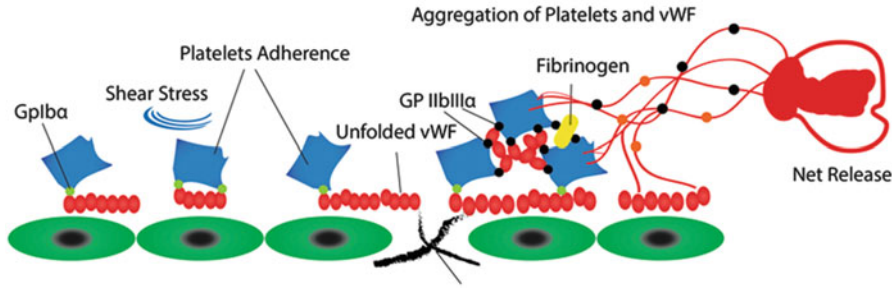

Fig. 5 Involvement of NETs in thrombus formation: in addition to fibrin and von Willebrand factor, NETs characterize a third thrombus scaffold. VWF can bind and immobilize extracellular DNA released from leukocytes at the site of injury

therapeutic protocols for treatment of bleeding and thrombotic disorders [37].

5.1 VWF and Neutrophil Extracellular Traps (NETs)

NETosis, an innate immune response mediated by neutrophils, has recently been recognized to immobilize microorganisms inside the vasculature in infectious and non-infectious diseases. In fact, NETs are extracellular DNA fibers comprising histones and neutrophil antimicrobial proteins, which might be detected by some markers. Since the markers of extracellular DNA traps were abundantly found in deep vein thrombosis (DVT) [38, 39], NETs were introduced as an exceptional link between inflammation and thrombosis, providing a stimulus and scaffold for thrombus formation. Further investigations have shown co-localization of the DNA network and vWF, indicating the involvement of NETosis mechanism in thrombus formation [40, 41]. A recent study revealed that vWF can bind and immobilize extracellular DNA released from leukocytes. Therefore, vWF might act as a linker for leukocyte adhesion to endothelial cells, but DNA–vWF binding does not affect vWF degradation by ADAMTS13. In contrast, DNA–vWF complexes diminish platelet binding to vWF [42]. These findings, however, have revealed a new feature of vWF biology, introducing vWF and NETs as prospective targets for the development of novel therapeutics for the treatment of venous thrombosis (Fig. 5).

6 Factors Influencing vWF Levels and Activity

The clinical signs of thrombosis perhaps result from the coincidence of multiple adverse genetic and environmental elements. However, a number of parameters may affect vWF levels and activity, such as blood group, genetic variability, acute-phase response, and proteolysis by a disintegrin and metalloprotease with thrombospondin motifs (ADAMTS13, Fig. 6).

6.1 VWF and Blood Group

Plasma vWF levels were determined in more than a thousand blood donors. The results showed that ABO blood group had a significant influence on vWF values, as investigated by quantitative immunoelectrophoresis. The findings also showed that the individuals with blood group O had the lowest mean vWF level than those of non O [43]. VWF antigen levels also showed significant differences between O heterozygotes and non-OO homozygotes [22, 44]. VWF and blood group, however, were related to thrombosis risk, which could be mediated through factor VIII [45].

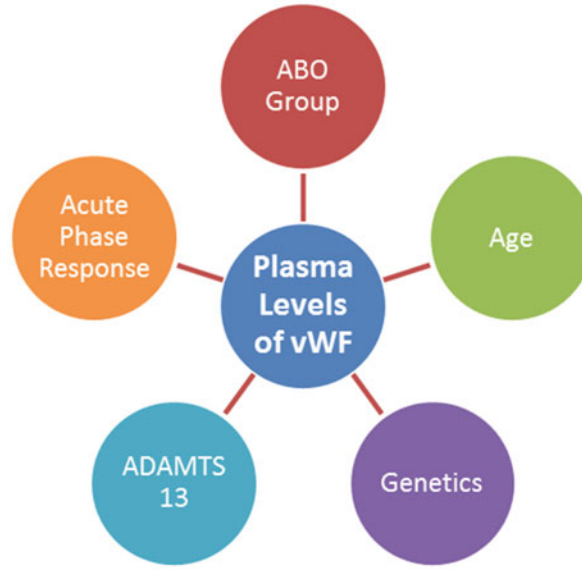

Fig. 6 Factors influence vWF antigen levels and activity: the most important elements affect vWF antigen levels and activity, containing blood group, genetic variability, proteolysis by ADAMTS13 and acute-phase response

6.1.1 Updated and Theoretical Rationale for vWF and ABO Interaction

It was though that ABO blood group might modify the synthesis and secretion rate of vWF within endothelial cells. In addition, ABO group may affect vWF plasma clearance rates, which might vary by different types of ABO group [46]. VWF multimers are built up from vWF monomers that contain 12 N-linked and 10 O-linked glycosylation sites. Even though the functions of these glycosylation sites are not fully elucidated, there is some evidence showing that they may protect vWF from proteolytic degradation. This glycosylation may also be essential for dimerization, polymerization and secretion, respectively. The reduced number of terminal sugars on N-linked glycan increases susceptibility of globular vWF to ADAMTS13 proteolysis, thereby reducing plasma vWF levels. ABO antigens have been shown to present on vWF-derived N-linked carbohydrates [41]. Nevertheless, the existence of blood group antigens on vWF O-linked carbohydrates has not been reported. VWF level has, therefore, been demonstrated to be slightly higher for homozygotes (AA or BB) than heterozygotes (AO or BO) [46, 47]. Expectedly, Bombay phenotype showed a lower plasma-vWF levels and an increased proneness to ADAMTS13 proteolysis [48]. In addition, individuals with homozygous secretor genotype (SeSe) showed a higher level of plasma vWF in comparison with non-secretors [49]. Another study, however, demonstrated that the risk of venous thrombosis was not associated with the secretor status [50]. As a result, ABO blood group influences the expression of the vWF involved in hemostasis and accordingly can be linked to various thrombotic events [22, 51–53].

6.2 VWF and Aging

The results of multiple regression analysis revealed that age was significantly correlated with vWF levels in each blood group [43]. In addition, G allele, which is linked with higher levels of vWF antigen, is more marked after the age of 40, as previously mentioned. Later studies also confirmed that vWF was increased with age increase [54]. In contrast, plasma levels of ADAMTS13 were reduced by aging in humans. This might indicate an increasing chance of thrombotic events, although the mechanism responsible for this is not accurately clarified [22, 55].

6.3 The Role of a Disintegrin-Like and Metalloprotease with ThromboSpondin Type I Repeats-13 (ADAMTS13)

Since the active large vWF multimers were found to be degraded to smaller forms with less activity, Furlen et al. could reveal a proteolytic activity associated with a high molecular weight protein [56]. The weight of this protein, however, was about 300 kD. Purified vWF was treated with protease. Subsequently, the size, amino acid composition, and amino terminal sequence of the smaller fragments indicated that the cleavage of vWF by the plasma protease was dependent on its conformation and needed calcium ion [57, 58]. Eventually, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) was defined to mediate the breakdown of vWF. This takes place by the cleavage between tyrosine at position 842 and methionine at position 843 [56, 59]. Decreased vWF-cleaving activity has been reported in a wide range of conditions, including thrombotic thrombocytopenic purpura (TTP), idiopathic thrombocytopenic purpura (ITP), liver cirrhosis, chronic uremia, disseminated intravascular coagulation (DIC), systemic lupus erythematosus (SLE), leukemia, pregnancy, postoperative state, neonatal period, and ageing. Unconjugated bilirubin also inhibited proteolytic cleavage of vWF by ADAMTS13, as it was reported by a recent study [60]. This metalloprotease stretches the vWF A2 domain so that the cleavage site becomes available to hydrolyze the peptide bond within the A2 domain of vWF. Cleavage by ADAMTS13 facilitates vWF release into blood circulation [61]. Next cleavage by ADAMTS13 takes place after vWF release into the blood stream [62], where the elongated conformation occurs. This conformation not only exposes the binding site for platelets in the vWF A1 domain but also expands the vWF A2 domain. Consequently the cleavage site becomes accessible for ADAMTS13. The cleavage site, however, is bordered by the regions of vWF that bind platelet glycoprotein 1b in the A1 domain and collagen [63–65], resulting in two fragments of 176 and 140 kDa. ADAMTS13 cleavage site in vWF is enclosed by two N-linked glycosylation sites (asparagine 752 and asparagine 811) and five O-linked glycosylation sites (threonine 705, 714, 724 and 916, and serine 723). The presence of O, A or B blood groups bordering the site might be the reason for altered values of vWF in various ABO blood groups. It is suggested that this neighboring may influence proteolysis. However, individuals with the lowest levels of ADAMTS13 have shown twice the risk of ischemic stroke compared with individuals with the highest levels of ADAMTS13 [21]. In addition, reduced ADAMTS13 activity significantly exacerbates ischemic brain injury in murine stroke models [66]. Temporary appearance of ultra-large vWF (ULvWF) multimers is evident in the normal plasma of patients after therapeutic agent desmopressin (1-desamino-8-D-arginine vasopressin or DDAVP). ULvWF multimers are also present in the pathological state of diseases such as thrombotic thrombocytopenic purpura (TTP) in which the deficient ADAMTS-13 is a hallmark for the disease [67]. However, the relationship of both vWF and ADAMTS13 with arterial thrombosis has been reviewed. The most studies, however, have shown an association between high vWF levels and arterial thrombosis. Furthermore, a hydrophobic pocket in the Cys-rich domain of ADAMTS13 was recognized, which may interact with hydrophobic pocket in the A2 domain of vWF for its cleavage [68]. Although the infusion of recombinant human ADAMTS13 reduced the infarct size in mice [69], whether ADAMTS13 is a pivotal independent risk factor or not remains unclear.

7 Plasma vWF Versus Platelet vWF

Since von Willebrand factor (vWF) is stored within both the Weibel-Palade bodies and the platelet alpha-granules, it was thought that these two storages should be replaced with each other. The pool of platelet vWF, however, is distinct from plasma-vWF and consists of hemostatically-active high molecular weight multimers. In addition, the glycosylation profile of platelet vWF significantly differs from that of

Table 1 The differences between platelet vWF and plasma vWF

Platelet vWF	Plasma vWF
Higher molecular weight	Lower molecular weight
Less sialic acid & galactose	More sialic acid & galactose
Lack of ABO BG carbohydrate	Presence of ABO BG carbohydrate
Lower affinity to platelet GpIbα	Higher affinity to platelet GpIbα
Higher affinity to GpIIbIIIα and heparin	Lower affinity to GpIIbIIIα and heparin
Specific resistance to ADAMTS13 proteolysis	No specific resistance to ADAMTS13 proteolysis

plasma vWF. Furthermore, total sialic acid and galactose expression are little on platelet vWF. ABO blood group carbohydrate determinants do not also exist on the N-linked glycans of platelet vWF. Accordingly, the critical role of vWF glycans is modulating its activity, and functional properties of platelet vWF vary markedly from those of plasma-vWF (Table 1). It has been reported that platelet-vWF could be bound to both GpIIbIIIa and heparin. Nevertheless platelet-vWF binding to platelet GpIbα occurs with a higher affinity in comparison with plasma-vWF [70].

In addition, both platelet-vWF antigen levels and activity differ significantly between patients with different types of von Willebrand disease (vWD). However, animal model studies have suggested that both types of vWF play important roles in obtaining the primary hemostasis [71]. There was a correlation between the bleeding time and platelet-vWF activity and platelet-vWF Ag. The length of bleeding time though was inversely correlated with the level of platelet vWF activity. The plasma-vWF Ag and activity, however, did not significantly correlate with the bleeding time, indicating that the platelet-vWF plays a greater role in the early stages of hemostasis [72]. Further investigations have demonstrated that plasma vWF and subendothelium support thrombosis, whereas plasma FVIII and platelet vWF are not essential for thrombosis in dogs [73]. Recent findings demonstrated that platelet-vWF with a particularly marked reduction in N-linked sialic acid expression displayed resistance to ADAMTS13 proteolysis. Accordingly, high local concentrations of this type of vWF at the site of injury may further enhance a platelet plug formation that is resistant to ADAMTS13 [74]. The molecular mechanisms responsible for the variances between these two types of vWF are likely to be associated with the differences in the posttranslational modification.

8 VWF and Shear Stress

Platelet adhesion to a thrombogenic surface is highly dependent on the velocity of blood flowing around the site of injury. Since blood consists of concentric layers, the flow rate markedly differs through the lumen. Shear stress is the force per unit area between such layers, which varies through the artery lumen from minimum level at the center-line to maximum level near the wall. In contrast with arterioles, shear rates are generally low in the venous part of the circulation. At a shear rate of $>500\ s-1$, the initial binding of platelets to the vessel wall is mainly mediated by glycoprotein (GP) Ib-V-IX and the von Willebrand factor (vWF). Studies have indicated that vWF principally stimulates platelet activation through an adenosine diphosphate (ADP) release. The investigations have also shown that activation of vWF-GPIbα interacting platelets is triggered by transmembrane Ca^{2+} [75]. It is reported that under higher shear stress ADP signaling may cause platelet adhesion and activation through P2Y12, a chemoreceptor for ADP, facilitated by immobilized vWF to persistent thrombus formation [76]. The marked shear gradients around stenotic sites such as arteries with advanced atherosclerosis stimulate the endothelial release of vWF and initiate thrombus formation [77]. A recent study identified a role for vWF in transducing hemodynamic forces, indicating that amplified platelet aggregation in stenotic channel is associated with plasma and endothelial vWF. It is thought that vWF goes through a conformational change from a

Fig. 7 vWF and Shear stress: vWF undertakes a conformational change from a compacted globular to a prolonged form at high shear stress

compacted spherical to a prolonged form at high shear stress. It was also suggested that the size of vWF fractions may be varying concomitantly with the shear stress rate [78]. A recent study, moreover, showed that removal of O-linked glycan structures of vWF elevates the flexibility of hinge linker region between the D3 and A1 domains. This assisted vWF unfolding by shear stress and improving its ability to bind collagen and to arrest platelets. The result indicates the important functional role of vWF O-linked glycan structures under shear stress conditions [79]. Furthermore, a recent study showed that in a higher shear stress, the loss of ULvWF multimers was greater and the functional activity of vWF for platelet aggregation was lower [80]. The above results may support the theory of conformational extension for vWF in shear flow (Fig. 7).

9 Von Willebrand Factor and Thrombosis

Thrombosis, as the pathological characteristic of hemostatic process, is the foremost cause of death, particularly in the Western society. There are several therapeutic approaches that have been developed to treat this severe clinical complication. Thrombus is structured by numerous elements, including endothelial cells, plasma proteins and shear stress alteration [24]. As vWF plays a critical role in both thrombotic and bleeding events, an elevated plasma level of this factor may predict a thrombotic occurrence but a decreased plasma level may point to a bleeding condition. We investigated the effect of C-reactive protein at moderate levels (the concentrations which are related to atherosclerosis *in vivo*) on the endothelial cells *in vitro*. The results exhibited an increased level of vWF, signifying an association between enhancement of vWF levels and risk of thrombosis [12]. Up to now, enoxaparin and Polyethylene glycol (PEG)-hirudin have been used to control vWF rise in cases with unstable angina pectoris [81]. This has been linked with a progressive clinical outcome. Nevertheless, a recent study showed that p-selectin, as an inhibitor of vWF, promoted the resolution of thrombus better than its enoxaparin [82]. Besides, one group identified plasma sodium concentration to increase blood coagulability by affecting the vWF production. They reported that severe hypernatremia reversibly increased both vWF mRNA and vWF secretion in cultured endothelial cells. This was conducted via transcription factor NFAT5, suggesting the involvement of hypertonic signaling in vWF up-regulation. The result however indicated that extracellular sodium enhancement might increase coagulability and risk of thrombosis [83]. Testing the compounds targeting vWF-mediated platelet adhesion points to a favorable bleeding risk profile and higher efficacy compared with traditional antithrombotic drugs. Antibody to vWF, however, inhibited thrombosis in arterioles and venules. Blockade of GPIb-vWF leads to the inhibition of thrombus formation in the stenosed coronary arteries [84, 85]. In contrast, some autoantibodies to vWF have been shown to increase vWF binding to platelets and activated platelet via binding to the Fc gamma RII receptor. Thus, these autoantibodies may be responsible for a new form of antibody-mediated thrombosis [86].

9.1 Von Willebrand Factor and Thrombotic Thrombocytopenic Purpura (TTP)

Thrombotic thrombocytopenic purpura (TTP) is a disorder of systemic platelet aggregation and a life-threatening microangiopathic syndrome. The underlying pathophysiology of TTP is an extensive presence of platelet and vWF-rich microthrombi. However in hemolytic uremic

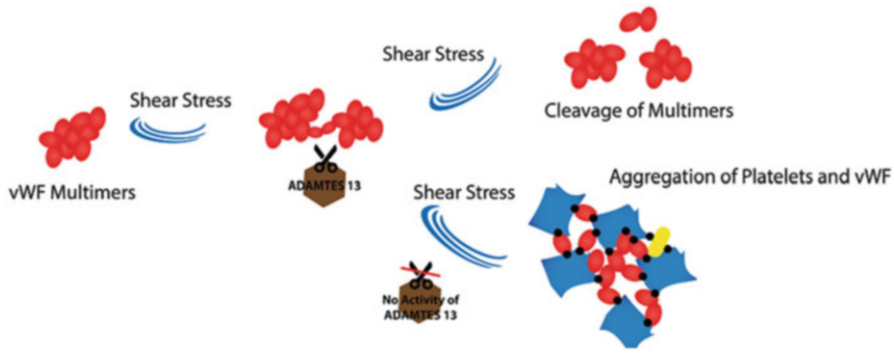

Fig. 8 The role of ADAMTS13 in maintaining intravascular homeostasis: In regular state, when von Willebrand factor multimers are secreted from stimulated endothelial cells, ADAMTS13 enzyme molecules attach to them and then cleave the multimers, but in thrombotic thrombocytopenic purpura (TTP) disease, the absence of ADAMTS13 causes the arrest of multimers cleavage. Thus platelets adhere to the unusually large vWF multimers and cause the risk of developing thrombosis

syndrome (HUS) pathophysiology, microthrombi consist of platelet and fibrin, while in other thrombotic micro-angiopathies (TMAs), varying amounts of infiltrated lymphocytic or neutrophil are interconnected to the microthrombi [87]. Familial TTP/HUS is not common and usually occurs in the immediate postnatal period or infancy, but there are reported cases of delayed onset from the second to third decade of life, too. Nevertheless, more frequently TTP is either idiopathic or secondary to a variety of conditions.

9.1.1 TTP Pathological Mechanisms and Recent Insights

A defect in the protease activity of ADAMTS13 causes the remaining vWF multimers uncleaved in the blood stream, which consequently leads to intravascular thrombosis (Fig. 8).

Evidence has indicated that the aggregating agonist in TTP of all categories might be von Willebrand factor. The data have also shown that uncommon large vWF multimers derived from endothelial cells are the main form of vWF in this process. ULvWF multimers function as the sites for platelet adhesion and aggregation and activate surfaces for the alternative complement pathway. Additionally, activation of complement pathway for generation of terminal complement complexes (C5b-9) occurs in TTP and HUS [88]. Metalloproteinase (ADAMTS13), therefore, plays a vital role in maintaining intravascular homeostasis. It is suggested that a defect in the processing of ULvWFMs after synthesis and secretion by endothelial cells makes patients prone to repeated relapses (Fig. 8). Existing evidence also demonstrated that the metalloproteinase involved in vWF breakdown is not appropriate in children with chronic relapsing TTP. Enzyme deficiency, therefore, might be responsible for congenital chronic relapsing TTP. In contrast autoantibodies might be the main inhibitor for neutralizing vWF metalloproteinase in adults with intermittent or single episode types of TTP. The inhibitors are more frequently IgG subclass in patients with acquired TTP [89], although rare production of IgA and IgM antibodies has been reported. Surprisingly, the rising level of ADAMTS13 inhibitor may be associated with switching the IgG subclasses. This may suggest that cytokine dysregulation may be responsible for the rising inhibitor levels observed in some cases of TTP. However, these types of TTP in adults are likely to be short-term or recurrent autoimmune processes, respectively [89]. Almost one to two-thirds of patients with autoimmune TTP have been reported to show ADAMTS13-specific circulating immune complexes. This may be a pathophysiologic mechanism in this type of TTP, although it has not been methodically investigated [91].

9.1.2 TTP Subgroups

Thrombotic thrombocytopenic purpura (TTP) can be divided into different sub-types; therefore the diagnosis is based on the patient's history and relevant parameters.

Congenital TTP

The first type of TTP is usually found in neonates with severe jaundice, while the second type is associated with unexplained thrombocytopenia in children and adults. Eventually, the congenital TTP is diagnosed through ADAMTS13 activity <5 %, lack of antibody and the homozygous or heterozygous defects of ADAMTS13 gene.

Drug-Related TTP

Some drugs like quinine and oestrogen-containing medications are associated with TTP. Therefore to prevent relapse, these medications should be avoided and women with a history of TTP should take non-oestrogen containing drugs.

TTP and Pregnancy

TTP may occur frequently in women and therefore can be linked with pregnancy. The greatest risk for development of TTP is around the term and during the post-partum period. Henceforward, the successful outcome of pregnancy in a woman with TTP in early first trimester was achieved after treatment with therapeutic plasma exchange [92].

9.1.3 TTP Diagnosis Based on the Patient's History and Following Parameters

1. Clinical examination and routine laboratory factors, including blood film review
2. Considering human immunodeficiency virus (HIV), hepatitis B and C viruses and autoantibody screen
3. Detection of ADAMTS13 activity ranks and evaluation of anti-ADAMTS13 antibodies
4. Detection of ADAMTS 13 antigen levels in cases with congenital type of TTP

Management and Treatment

1. Plasma exchange using (PEX) solvent/detergent-treated plasma
2. Exaggeration in frequency and/or volume of PEX procedures in life-threatening cases
3. When two cases of myocardial infarction occur shortly after platelet transfusion, transfusion is contraindicated unless platelet count is low ($<20 \times 109$/L) [93]
4. Intermediate purity Factor VIII infusion
5. Avoiding quinine and oestrogen-containing medications in drug-associated TTP
6. Individualized treatment regimens for congenital TTP according to the patient's phenotype
7. Treatment considerations for TTP in pregnancy
8. Treatment considerations for TTP in patients with HIV infection
   - PEX in conjunction with highly active antiretroviral therapy (HAART) (triple or quadruple therapy)
   - Rituximab in resistant HIV-related TTP
9. Treatment considerations for malignancy-associated thrombotic microangiopathy (PEX should not be used)
10. Additional treatment
    - Intravenous methylprednisolone or high-dose oral prednisolone
    - Rituximab
    - Ciclosporin A and tacrolimus
    - Splenectomy
    - Anti-platelet agents
11. Supportive treatment
    - Red cell transfusion
    - Folate supplementation
    - Thromboprophylaxis with low molecular weight heparin (LMWH)
    - Increased frequency of PEX and addition of rituximab in refractory and relapsing TTP

A functional assay was developed based on the preferential binding of high-molecular-weight forms of vWF to collagen. To run the assay, the diluted sample plasma was added to

normal plasma in which protease activity had been eliminated. VWF-cleaving protease in the test plasma can digest the vWF present in the protease-depleted plasma. Low-molecular-weight forms of vWF consequently show impaired binding to microtiter plates coated with human collagen type III. This collagen-bound vWF was calculated using an antibody against human vWF, which was conjugated with peroxidase. Evaluation of TTP patient's plasma and HUS showed that the test could be used to discriminate these two syndromes.

To differentiate the patients with familial TTP from those with non-familial TTP, the presence of an inhibitor can be detected by carrying out the test after incubation of normal human plasma with the patient's plasma sample [94].

10 Von Willebrand Disease (vWD)

Blood coagulation is essential to repair an injury to a blood vessel. When a blood vessel is injured, vWF enables platelets to bind to the injured site and form a transitory plug to stop the bleeding. A qualitative or quantitative deficiency of vWF can interfere with the formation of the temporary platelet plug and affect the normal survival of factor VIII, which can indirectly interfere with the production of permanent clot. The disorder, however, affects males and females in almost equal proportions. Von Willebrand disease was described by the Finnish hematologist Erik von Willebrand for the first time in 1926. When he found that several male and female members of a family showed increased bruising and prolonged occurrences of bleeding, he called these disorders "Hereditary Pseudohemophilia". The disorders were differentiated from classical hemophilia by lack of muscle and joint bleeding and the effect exerted on people of either sex. In addition, this disease occurs when the body is not able to produce enough vWF, or produces the abnormal type of this factor. Three major types of vWD were introduced (Table 2). The most common form or type is described by low levels of vWF, which may also be associated with a low level of factor VIII, but the signs are usually mild.

In type 2, which has several subtypes (Fig. 9), vWF does not function properly, thus the symptoms tend to be more significant. In type 2A, because of the wrong size vWF multimers, which could be the result of defective multimer assembly or increased cleavage of multimers by ADAMTS-13, platelets are not able to make a proper plug, whereas in type 2B, the wrong size vWF multimers become too active, thereby causing the deficiency of both platelets and vWF in the blood flow. Type 2N is recognized by lack of vWF function for carrying factor VIII. In type 2M, the secretion and assembly of multimers is not quite normal, therefore the vWF adhesion to platelets does not occur appropriately (Fig. 9). Ultimately, type 3 might be identified by the absence of vWF, which is associated with decreased levels of factor VIII [95]. Consequently, the symptoms will be severe, as bleeding into the joints and muscles. Acquired vWD, however, may develop later in life possibly due to such underlying conditions as systemic lupus erythematosus, hypothyroidism and multiple myeloma.

Table 2 Characteristics of different types of vWD

vWF type	Type of deficiency	% People affected	Inheritance	Common symptom
Type 1	Quantitative (low vWF production)	~75 %	Autosomal dominants	The mildest type
Type 2	Qualitative (abnormal vWF)	~15–25 %	Autosomal dominants	More severe than type 1
Type 3	Absent vWF production	Rare	Autosomal recessive	The most severe form
Pseudo, or platelet type	Qualitative		Autosomal dominants	More severe than type 1

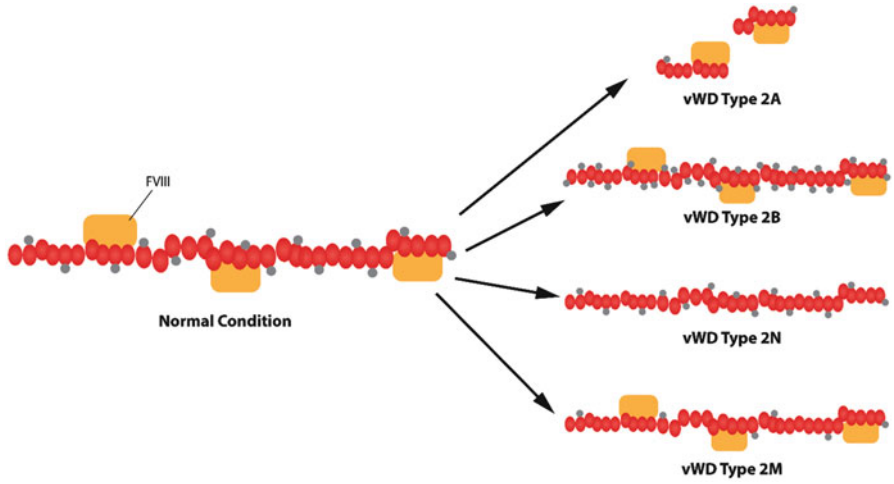

Fig. 9 Different subtypes of vWD Type 2: as it is shown, the wrong size vWF multimers in type 2A make them not to perform a proper platelet plug, whereas in type 2B, the wrong size vWF multimers become too active and cause the deficiency of both platelets and vWF. Type 2N is characterized by lack of vWF function for carrying factor VIII, and in type 2M, the vWF adhesion platelets does not take place properly

10.1 Von Willebrand Disease and Thrombosis

In spite of lack of vWF or presence of vWF in vWD, some patients with an arterial or venous thrombosis were reported in the literature. From a total of 30 cases, 11 patients showed arterial thrombosis and 19 of them demonstrated venous thrombosis. Numerous risk factors though were linked, including infusion of FVIII or FVIII plus vWF concentrates, surgery, pregnancy, desmopressin infusion and variable coagulation defects or polymorphisms. Most of the vWD patients who showed thrombotic phenomena were type I and type 3 patients, respectively. In general, both arterial and venous thrombosis occur infrequently in vWD, while they take place more frequently in hemophilia A and B [33].

10.2 History, Signs, and Symptoms

According to NIH (National Heart, Lung and blood institute) guidelines, clinical evaluation of vWD should be focused on the personal or family history of excessive hemorrhage during life. This history should categorize the severity, locations and length of hemorrhage, type of injury associated with hemorrhage and the medications. This includes the medications, which were taken at the onset of hemorrhage such as aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), clopidogrel, warfarin, or heparin. The patient should be asked for any history of blood or bone marrow disease, liver or kidney disease or abnormal platelet counts, especially in the case of invasive procedure. Further evaluation or referral would be mandatory for cases with the above history.

10.3 The Laboratory Diagnosis of vWD

It is not very simple to diagnose vWD in the lab, hence a panel of different laboratory tests and a proper quality control process is required. To this end, the European Thrombosis and Disabilities Foundation has established an external quality control program for various laboratory tests for diagnosis of vWD since 2003. At present, numerous laboratories are participating in this program and most of them perform vWF antigen and activity tests. The closest between-laboratory variation has been found for the vWF antigen assay, with a preference for the latex

Table 3 Laboratory guidelines for diagnosing vWD

Initial tests	More recommended tests	Additional studies
vWF:RCo, vWF:Ag and Factor VIII activity	Estimation of the ratio of vWF activity (vWF:RCo and/or vWF:CB) to vWF antigen	Gene sequencing, assays for antibodies to vWF and Platelet binding
	vWF multimer study, Ristocetin induced platelet aggregation and vWF collagen binding activity (vWF:CB)	

immunoassay than the enzyme immunoassay. However the ristocetin cofactor activity assay (RCo) and the collagen-binding assay have shown a higher between-laboratory variation. Further, development in the laboratory diagnosis of vWD is mandatory [96–98]. According to NIH guidelines, the initial tests for diagnosing or excluding vWD include the following three tests: vWF:RCo, vWF:Ag and Factor VIII activity. An abnormal finding revealed by the above tests may recommend more studies including: estimation of the ratio of vWF activity (vWF:RCo and/or vWF:CB) to vWF antigen and vWF multimer study, ristocetin induced platelet aggregation and vWF collagen binding activity (vWF:CB). Additional studies among the selected patients may include: gene sequencing, assays for antibodies to vWF and platelet binding (Table 3).

It is suggested that FVIII measurement is the best interpreter of soft tissue or surgical bleeding, while bleeding time (BT) level is considered a reliable indicator for an effective treatment of mucosal bleeding.

10.4 VWD Treatment

Individuals with the minor form of the disease have no major bleeding symptoms during their lives; thus it is not easy for a clinician to decide whether any treatment is really necessary. In contrast, patients with moderate to severe form who demonstrate factor VIII and vWF deficiency should regularly be treated to stop or prevent bleeding. Decompression (DDAVP) administration increases autologous FVIII/vWF. This medication is administered by injection or through a nasal spray. In addition, infusion of plasma-derived concentrates can compensate FVIII and vWF deficiencies and shorten BT. Recombinant FVIII is not recommended unless there is alloantibody against exogenous vWF, which may deactivate vWF function as a stabilizer of factor VIII. Recently, a new concentrate of vWF has been produced [99]. The best approach to select an appropriate treatment is desmopressin infusion in subjects with clinical features of vWD, providing no contraindication to the compound.

11 VWF Multimers and Thrombotic Events

VWF demonstrates a thin line between the normal hemostatic process and an overactive state that develops thrombosis. It is, therefore, quite challenging to determine the regular levels of this protein, as these values are changeable and overlap. VWF levels, however, are advocated to be very important in the diagnosis and intensive care of post-transplant thrombosis. Further extensive epidemiologic studies are needed to establish this level. Thrombus is structured by numerous elements, including endothelial cells, plasma proteins and shear stress alteration [100]. Existing evidence demonstrates that interactions between the cerebral blood vessels and platelets via vWF cause ischemic brain disease [101]. In 1986, the relationship between cardiac disorders and the decreased high molecular weight vWF multimers was also reported. It was determined that loss of high molecular weight multimers caused bleeding complications in some patients with aortic stenosis. Pareti et al. (2003) argued that shear forces could trigger the binding of higher vWF multimers to platelets, which could explain the reduced hemostatic potential of vWF. In addition, they discovered that the loss of vWF multimers

corresponded with an enhancement of vWF degradation products, demonstrating that vWF is more prone to degradation in this clinical condition [102]. Eventually, it was reported that proteolysis of vWF by its protease ADAMTS13 occurs powerfully upon the unfolding of vWF under a high shear stress [103].

12 How to Manage vWF Fluctuations

Since vWF levels are important in both thrombotic and bleeding events, elevation of this factor in plasma may predict thrombotic events, while its decrease may forecast a bleeding circumstance. Increased plasma vWF levels, however, were associated with an adverse prognosis in patients with atrial fibrillation [104]. In addition, vWF was recognized as a biomarker in transient ischemic attack and minor ischemic stroke, as reported recently [105]. Also, a potential effect of high vWF and low ADAMTS13 on venous thromboembolism was discovered, indicating an unbalance between the two interconnected proteins. ADAMTS13 and vWF, thus might play a role in the pathophysiology of venous thromboembolism [106]. Marked association of thrombosis with ADAMTS13 and vWF levels suggests that checking these proteins may be potentially useful to predict thrombotic events after arthroplasty. Thus, inhibiting the vWF activity has been suggested to be a novel prophylaxis to reduce these events [107]. Prospective clinical trials on the effectiveness of protease replacement in vivo seem to be coherent [108]. In addition, amino acid regions 572–579 and 657–666 of the spacer domain were introduced as a common antigenic core required for binding of anti-ADAMTS13 antibodies in patients with acquired TTP [109]. However, the problem with various present anti-coagulants is that they may lead to uncontrolled bleeding or other complications. Therefore, there is a perpetual need to identify new and improved antithrombotic drugs. Replacement therapy, however, has been the main treatment for the bleeding phenotype [81].

12.1 Effectors and Inhibitors of vWF

Testing the compounds targeting vWF-mediated platelet adhesion points to a favorable bleeding risk profile and higher efficacy compared with traditional antithrombotic drugs. Antibody to vWF, however, inhibited thrombosis in arterioles and venules. Blockade of GPIb-vWF leads to the inhibition of thrombus formation in the stenosed coronary arteries [85]. In contrast, some autoantibodies to vWF have been shown to increase vWF binding to platelets and to activate platelet via binding to the Fc gamma RII receptor. Thus, these autoantibodies may be responsible for a new form of antibody-mediated thrombosis [86]. Besides, we discovered an *in vitro* inhibitory effect of sodium salicylate on vWF secretion by endothelial cells, indicating an additional reason for the effects of sodium salicylate on atherothrombotic events [110].

12.1.1 Inhibiting the vWF Activity as a Novel Treatment

There are several therapeutic approaches that have been developed to treat thrombosis as the pathological characteristic of hemostatic process including inhibitors of vWF. As thrombolytic therapy was the underlying treatment of acute atherothrombotic events, vWF degradation was revealed after therapy with plasmin, which was more predominant by addition of streptokinase [111]. The interaction between the N-terminal ligand-binding domain of GpIbα and the vWF-A1 domain is markedly enhanced as hydrodynamic shear increases. Vascular injury and enhanced shear rates, however, lead to inappropriate conformational activation of vWF or GpIbα, and both results in thrombus formation [112]. Therefore, it is not unforeseen that vWF is currently considered an attractive drug target [27]. Antibodies have also demonstrated promising results and appear to exert their effects in GpIbα-vWF interaction. These inhibitors reduce the side effects of bleeding, when compared with currently available anticoagulants. Monoclonal antibodies against GPIbα (6B4 and its humanized form h6B4) are fab-fragments of a

Table 4 A number of GpIbα-vWF binding inhibitors

Monoclonal antibodies against GPIbα, as a Fab-fragment of a monoclonal antibody against platelet GPIbα, inhibit the binding of vWF to GPIbα (6B4)
Monoclonal antibody against vWF A3 domain inhibits the binding of vWF to collagen
ARC1779, as an aptamer against vWF A1 domain, inhibits the binding of vWF to GPIbα
ALX-0081 and ALX-0681 nanobody against vWF A1 domain that inhibits binding of vWF to GPIbα
rADAMTS13 as a recombinant protein cleaves vWF multimers in the Y1605-M1606 bond in the vWF A2 domain
The recombinant GPIbα fragment GPG-290
The OS1 inhibitor isolated from a cysteine-constrained phage is capable of disrupting the GpIbα–vWF interaction with a subnanomolar potency
Anfibatide, a snake venom-derived GPIbα antagonist, bound to GPIbα and blocked the binding of both vWF A1 and thrombin with no bleeding tendency and detectable anti-Anfibatide antibodies

monoclonal antibody against platelet GPIbα, which inhibit the binding of vWF to GPIbα in a high shear arterial thrombosis model in baboons [113]. Another monoclonal antibody against vWF A3 domain inhibits the binding of vWF to collagen [114]. In addition to antibodies, short single-stranded oligonucleotides such as ARC1779, an aptamer against vWF A1 domain, inhibit the binding of vWF to GPIbα [115]. Recent studies, nevertheless, have shown the effect of ALX-0081 nanobody against the A1 domain of von Willebrand factor in a thrombosis model in guinea pigs. ALX-0081 prevented thrombosis and induced reperfusion, indicating that the inhibition of GPIb-VWF axis avoided cerebral artery thrombosis without provoking intracerebral bleeding [22]. Besides, rADAMTS13, a recombinant protein, cleaved vWF multimers at Y1605-M1606 bond in the vWF A2 domain. In addition, Meyer et al. examined GPG-290 with 2 gain-of-function mutations (G233V/M239V), which enhanced its affinity for the vWF A1 domain, in preclinical murine and canine models of arterial and venous thrombosis [116]. The OS1 inhibitor was also isolated from a cysteine-constrained phage, which is capable of disrupting the GpIbα–vWF interaction with a subnanomolar potency [117]. Moreover, a recent study showed that anfibatide, a snake venom-derived GPIbα antagonist, bound to GPIbα and blocked the binding of both vWF A1 domain and thrombin. Anfibatide incubation with human blood did not affect coagulation parameters. Finally, treating the volunteers with anfibatide did not show serious adverse events. Although anfibatide bound to GPIb and inhibited 90 % of platelet aggregation, the activated partial thromboplastin time, prothrombin time, thrombin time, bleeding time and platelet count were not affected by this treatment. In addition, bleeding tendency and detectable anti-anfibatide antibodies were not reported in volunteers [118], representing anfibatide as a safe and effective anti-platelet reagent (Table 4).

13 Summary

Recently, dramatic progress has been made in the information regarding the role of vWF in hemostasis and thrombosis. To the best of our knowledge, synthesized vWF by endothelial cells and megakaryocytes circulate in plasma as multimers with varying size. Binding of vWF (A3 domain) to exposed collagen type I and III, however, immobilizes vWF at vascular injury sites. This binding which is associated with high shear stress leads to conformational alterations and bearing the glycoprotein (GP)Ibα in the vWF A1 domain as a specific binding site for platelet GPIbα. This permits platelets to roll and results in platelet adhesion at the site of injury. The primary adhesion may trigger the involvement of platelet collagen receptors (GPVI and integrin α2β1). The platelet activation, however, together with soluble platelet agonists, including adenosine 5′-diphosphate, adenosine 5′-triphosphate, thromboxane A2 and platelet GPIIb/IIIa receptor convert into a high-affinity state. Platelet GPIIb/IIIa binding to fibrinogen and Arg-Gly-Asp

sequence in the C1 domain of vWF promotes platelet aggregation. Recruitment of an additional number of platelets to the site of injury, which is mediated by GPIbα receptors, is essential for both initial platelet adhesion to injury sites and enrolment of new platelets. ADAMTS13 cleaves the Y1605-M1606 bond in the vWF A2 domain in normal conditions to convert ULvWF into smaller molecules, thereby preventing the existence of extra reactive vWF. These ultra-large vWF fibers also bind to and immobilize extracellular DNA released from leukocytes (NETs) during the process of the newly discovered cell death program NETosis. This binding promote thrombus formation consequently. Hence ADAMTS13 deficiency is associated with thrombotic occlusion of microvessels as seen in thrombotic thrombocytopenic purpura. Marked association of thrombosis risk with both ADAMTS13 and vWF levels suggest that the ADAMTS13 and vWF levels may be potentially useful for predicting thrombotic events. Thus, inhibiting the vWF activity can be a novel prophylaxis to reduce these events. In addition, prospective clinical trials on the efficiency of protease replacement seem to be rational.

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Role of $P2Y_{12}$ Receptor in Thrombosis

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Abstract

$P2Y_{12}$ receptor is a 342 amino acid Gi-coupled receptor predominantly expressed on platelets. $P2Y_{12}$ receptor is physiologically activated by ADP and inhibits adenyl cyclase (AC) to decrease cyclic AMP (cAMP) level, resulting in platelet aggregation. It also activates PI3 kinase (PI3K) pathway leading to fibrinogen receptor activation, and may protect platelets from apoptosis. Abnormalities of $P2Y_{12}$ receptor include congenital deficiencies or high activity in diseases like diabetes mellitus (DM) and chronic kidney disease (CKD), exposing such patients to a prothrombotic condition. A series of clinical antiplatelet drugs, such as clopidogrel and ticagrelor, are designed as indirect or direct antagonists of $P2Y_{12}$ receptor to reduce incidence of thrombosis mainly for patients of acute coronary syndrome (ACS) who are at high risk of thrombotic events. Studies on novel dual-/multi-target antiplatelet agents consider $P2Y_{12}$ receptor as a promising part in combined targets. However, the clinical practical phenomena, such as "clopidogrel resistance" due to gene variations of cytochrome P450 or $P2Y_{12}$ receptor constitutive activation, call for better antiplatelet agents. Researches also showed inverse agonist of $P2Y_{12}$ receptor could play a better role over neutral antagonists. Personalized antiplatelet therapy is the most ideal destination for antiplatelet therapy in ACS patients with or without other underlying diseases like DM or CKD, however, there is still a long way to go.

Keywords

Platelet • $P2Y_{12}$ receptor • Signal transductions • Abnormalities • Antagonists

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1 Introduction of Platelet P2Y Receptors: $P2Y_1$ & $P2Y_{12}$

The potent activities of purines were first reported in 1929 [1] and purinoceptors were defined in 1978 [2, 3]. Then a distinction between P1 for adenosine and P2 for ATP/ADP was recognized; later P2X (ligand-gated) and P2Y (G-protein-coupled) subclasses of P2 purinoceptors were established [2]. In the 1990s, $P2Y_1$ was set to represent the cloned P2Y receptor (clone 803) from chicken brain; later it was found on platelets and megakaryoblastic cells [4] playing a role in ADP-induced platelet shape change through calcium mobilization by Gq signal transduction [5]. In 2001, Hollopeter et al. first cloned the elusive $P2Y_{12}$, the second ADP receptor required for platelet aggregation through Gi that inhibits adenyl cyclase (AC) [6].

Although $P2Y_{12}$ receptor was identified later than $P2Y_1$, its characteristics make it a much more potent target in medical research. $P2Y_1$ receptor only induces a transient and unstable platelet aggregation without the coactivation of $P2Y_{12}$ [7]. Therefore, $P2Y_{12}$ receptor is a more important target in clinical practice when thrombotic events are not desirable. $P2Y_{12}$ receptor is mainly expressed on platelets and neuronal tissues while $P2Y_1$ is expressed ubiquitously [7]; thus drugs targeting $P2Y_{12}$ receptor could limit side effects in other tissues. $P2Y_{12}$ receptor abnormalities are found in patients of coagulation disorders, which call for attention to the coding-genes, structures and up/down-stream regulation of the receptor.

Main characteristics of $P2Y_1$ and $P2Y_{12}$ receptors are summarized in Table 1.

In this chapter, we focus on the molecular mechanisms and abnormalities of $P2Y_{12}$ receptor in thrombosis aspects. Antiplatelet agents and therapies targeted on $P2Y_{12}$ receptor are illustrated according to the latest clinical trial or animal experiments. Other roles of $P2Y_{12}$ receptor in platelet apoptosis and inflammation are mentioned to give readers a comprehensive view.

Table 1 Main characteristic comparison between receptor $P2Y_1$ and $P2Y_{12}$

Receptor	$P2Y_1$	$P2Y_{12}$
Distribution [6–10]	Platelets, heart, blood vessels, smooth muscle cells, connective and neural tissues, testis	Platelets, some neural tissues, nasal mucosa, lymphocytes, endothelium
G-coupled protein [11, 12]	G_q	G_{i2}
Downstream mechanism [12–15]	Activation of PLC	Inhibition of AC, Activation of PI3K
Functions in thrombosis [16–19]	Mobilization of calcium from intracellular stores	Platelet sustained aggregation
	Platelet shape change	Potentiation of platelet secretion
	Platelet transient aggregation	
Platelet phenotypes of receptor knockout mice [20–22]	Impaired response to ADP	Greatly diminished aggregation in response to ADP
	Absent increase in cytosolic Ca^{2+} and shape change in response to ADP	Absent inhibition of AC by ADP
	Normal inhibition of cAMP formation by ADP	Increased bleeding time
Antagonists [14, 23–27]	A2P5P, A3P5P, MRS2179, MRS2279, MRS2500	AZD1283, MRS2395, AR-C69931MX, ticlopidine, clopidogrel, prasugrel, ticagrelor
Involvement in procoagulant activity [28, 29]	Interactions between platelets and leukocytes mediated by platelet P-selectin exposure	Interactions between platelets and leukocytes mediated by platelet P-selectin exposure, Thrombin-induced exposure of PS, TF-induced thrombin formation

2 Molecular Mechanisms and Effects of $P2Y_{12}$ Receptor Signaling

2.1 Biochemistry Structure

$P2Y_{12}$, as a G protein-coupled receptor, has the typical features of 7 hydrophobic transmembrane (TM) regions connected by 3 extracellular loops (EL) and 3 intracellular loops [14]. Human $P2Y_{12}$ receptor consists of 342 amino acid residues [30]. Like most G protein-coupled receptors, $P2Y_{12}$ receptor also possesses 4 extracellular cysteine residues at extracellular N-terminus (Cys17), 1st extracellular loop (Cys97), 2nd extracellular loop (Cys175), and 3rd extracellular loop (Cys270) [6]. Unlike $P2Y_1$ receptor, which forms 2 disulfide bridges among the 4 extracellular cysteines essential for ADP-induced $P2Y_1$ receptor activation [31], $P2Y_{12}$ receptor extracellular cysteines Cys17 and Cys270 are not essential for ADP-induced $P2Y_{12}$ receptor activation, and it seems that only one disulfide bridge is formed between Cys97 and Cys 175 [11, 32]. Thienopyridine antiplatelet drugs are believed to exert their antiplatelet roles by targeting Cys17 and Cys270 through their thiol group-containing active metabolites [32–34].

2.2 Agonists and Antagonists

ADP, released by ruptured red blood cells or platelets, is the natural agonist of $P2Y_{12}$ and $P2Y_1$ receptor [14]. The ADP analog 2-methylthio-ADP (2-MeSADP), frequently used in research, is a more potent and stable $P2Y_{12}$ and $P2Y_1$ agonist [11, 14, 25, 35].

Selective $P2Y_{12}$ receptor antagonists include MRS1283 [23], MRS2395 [36], AR-C69931MX (Cangrelor) [37–39], nucleotide analog AZD6140 (Ticagrelor) [40–42]. and active metabolites of the thienopyridine compounds (Ticlopidine, Clopidogrel, Prasugrel) [14, 34, 43]. ATP and its triphosphate analogs like 2MeSATP and 2ClATP are selective $P2Y_{12}$ receptor antagonists [44].

2.3 Signal Transductions

The network of $P2Y_{12}$ receptor signal transduction is complicated and contradictory reports exist. Here, we categorize the pathways by basic G protein subunits and emphasize commonly reported functions of each pathway mentioned, focusing on the importance of $P2Y_{12}$ receptor in multiple platelet functions.

2.3.1 Major Pathways

The $P2Y_{12}$ receptor couples to $G\alpha_{i2}$ subunit [6]. Upon stimulation, Gα and Gβγ subunits dissociate to activate various signal transduction pathways [12].

(a) $G\alpha_{i2}$ subunit inhibits production of adenyl cyclase (AC), resulting in decrease of cAMP levels [45], which reduces the activation of cAMP-dependent protein kinase (PKA) [6]. PKA has a wide range of substrates in human platelets, including actin binding protein, caldesmon, $G\alpha_{13}$, GPIbβ, IP_3 receptors, phosphodiesterase 3, -vasodilator-stimulated phosphoprotein (VASP), which all play important role in platelet functions [46].

(b) Gβγ subunit stimulates phosphatidylinositol-3 kinase (PI3K) activity, which results in late accumulation of phosphatidylinositol 3,4-bisphosphate [PtdIns(3,4)P_2] and rapid transient accumulation of phosphatidylinositol 3,4,5-triphosphate [PtdIns(3,4,5)P_3] [47–49]. PI3K pathway also activates Rap1b [13] and Akt [50]. Gβγ dimers can activate the G-protein-gated inwardly rectifying potassium channels (GIRKs) mediating Src tyrosine kinases [51].

2.3.2 Pathways in Platelet Activation

Platelet activation is a complex process in thrombosis and hemostasis induced by a variety of stimuli such as ADP, thrombin, collagen and thromboxane A_2 (TxA_2), which act cooperatively to ensure the rapid formation of a platelet thrombus at sites of vascular injury [45, 52]. The

process mainly contains platelet shape change, adhesion, aggregation and secretion.

Platelet Aggregation

Platelet aggregation requires engagement of integrin $\alpha_{IIb}\beta_3$ by soluble fibrinogen [53]. The process starts by agonists that stimulate calcium release within platelets to activate the integrin $\alpha_{IIb}\beta_3$ on the platelet surface to bind soluble fibrinogen [13]. The activation of Gi-coupled receptors provides another independent signal to achieve full activation of platelet and stable aggregates [13]. $P2Y_{12}$ receptor, connected to G_{i2}, participates in the process through following downstream signal pathways to activate integrin $\alpha_{IIb}\beta_3$.

(a) **Inhibition of adenyl cyclase**. Upon phosphorylation by PKA, actin binding protein and caldesmon may stabilize cytoskeleton of the resting platelets; IP_3 receptors may down regulate the release of calcium from intracellular platelet stores; GPIbβ may prevent collagen-induced actin polymerization; and so on [46]. The decrease of cAMP level blocks the phosphorylation, so platelets tend to activate and aggregate. PKA is also responsible for inhibiting VASP by phosphorylation, which is an actin cytoskeleton regulatory protein that inhibits the integrin $\alpha_{IIb}\beta_3$ activation [54].

(b) **Activation of PI3K**. PI3K is directly activated by Gβγ subunit. In murine blood, absence of PI3Kγ led to formation of unstable thrombi, resulting in dissociation of multi-platelet aggregates; in addition, inhibiting PI3Kβ delayed initial thrombus formation and decreased individual platelet-platelet contact [55]. Persistent signaling from $P2Y_{12}$ receptor to PI3Kβ and PI3Kγ isoforms is needed to sustain $\alpha_{IIb}\beta_3$ activation and maintain platelet aggregates [55].

(c) **Activation of Rap1b**. Rap1b can be stimulated by $G\alpha_{i2}$ – and PI3K-dependent as well as Gq- and Ca^{2+}-dependent mechanisms [13, 56]. Active form of Rap1 is required to convert integrin αIIbβ3 into a high-affinity conformation to bind fibrinogen, and to stimulate TXA_2 synthesis.

(d) **Phosphorylation of Akt**. It could be dependent on signaling through the $P2Y_{12}$ receptor – PI3K pathway to activate integrin $\alpha_{IIb}\beta_3$ [50].

(e) **Activation of ERK**. A coordinated pathway through both G_q from TxA_2 and G_i from ADP was necessary for activation of ERK2, involving in collagen-induced platelet aggregation and secretion [57, 58]. Activation of PLC and subsequent intracellular calcium increases occurring downstream of $P2Y_1$ and Src activation occurring downstream of the $P2Y_{12}$ receptor activation are both necessary for ADP-induced ERK2 activation [59]. PI3Kβ, mediating ADP-induced TxA_2 generation by regulating ERK phosphorylation, also plays an important role in platelet aggregation [60].

(f) **Activation of GIRK channels**. Gβγ subunit activates the GIRK channels by binding to their cytosolic regions [51]. Co-stimulation of $P2Y_{12}$ and $P2Y_1$ receptors, through activation of both GIRK channels and Src family of tyrosine kinases, is essential for ADP-induced $cPLA_2$ phosphorylation and TxA_2 generation [51].

(g) **Interaction with PAR**. Protease activated receptor (PAR) 1 and PAR4 are thrombin receptors that have differential roles in platelet activation [61]. Thrombin activates the rapamycin complex-1 (mTORC1) pathway in human platelets through PAR-activated PKC-mediated ADP secretion and subsequent activation of $P2Y_{12}$, in a manner largely independent of the canonical PI3K/Akt pathway [62]. PAR4, a low-affinity thrombin receptor in human platelets, participates in sustained platelet activation in a $P2Y_{12}$-dependent manner [63]. Using bioluminescent resonance energy transfer technology, Khan et al. found that PAR4 and $P2Y_{12}$ directly interacted to regulate Akt signaling after PAR4 activation in human embryonic kidney 293 T cells coexpressing PAR4 and $P2Y_{12}$ receptors [61]. PAR4-$P2Y_{12}$ association supports arrestin-mediated sustained signaling to Akt to stabilize platelet thrombi [61].

Platelet Shape Change

Platelet shape change (PSC) is an initiating process of platelet activation that leads to platelet aggregation. The $P2Y_1$ receptor plays the major role in PSC but the $P2Y_{12}$ receptor appears to be involved in ADP-induced PSC since this process was significantly inhibited by AR-C69931MX [18]. Research shows that $P2Y_{12}$ receptor plays a potential role in ADP-induced PSC through regulation of the Rho kinase pathway, potentiating both myosin phosphorylation and actin polymerization [64].

Platelet Granule Release

Research shows that ADP-induced α granule release in aspirin-treated platelets occurs through co-stimulation of $G\alpha_q$ and $G\alpha_i$ signaling pathways and $P2Y_{12}$ receptor plays an important role in TxA_2-mediated α granule release [65]. Phosphorylation of Ephrin-receptor family members is mediated by $P2Y_1$ and $P2Y_{12}$ receptors, among which EphA4 is an intermediate in $P2Y_{12}$ signaling to secretion thereby facilitating later stages of secondary aggregation and thrombus growth [19].

Thrombus Growth and Stability

Animal experiments demonstrate that ADP and its $P2Y_{12}$ receptor participates in thrombus growth, especially in the formation of downstream part of the emboli from the initial thrombus [66]. This may explain the beneficial effects of $P2Y_{12}$ receptor antagonists in secondary prevention of ischemic events in patients with arterial thrombosis [66]. Experiments on $P2Y_{12}$-null mice demonstrated that $P2Y_{12}$ receptor is involved in thrombus growth and stability [17].

2.3.3 Pathways in Platelet Apoptosis

Platelet apoptosis is the physiological way of platelet death if not forming thrombus. It is reported that the activation of $P2Y_{12}$ receptor could protect platelets from apoptosis. Relative signaling pathways are hypothesized that the activation of $P2Y_{12}$ receptor induces Akt and Bad phosphorylation and the phosphorylated Bad is sequestered in the cytoplasm by the adapter protein 14-3-3, which prevents a Bad association with Bcl-xL; therefore, free Bcl-xL heterodimerizes with Bak proteins to prevent Bak dimerization in mitochondria, thus antagonizing its proapoptotic activity [39, 67]. In an indirect way, Bcl-xL inactivates Bax by inhibiting its translocation into mitochondria [39]. From the view of preventing platelet apoptosis, we can see that the platelet lifespan could be shortened if $P2Y_{12}$ receptor is antagonized, thus reducing thrombosis.

2.3.4 Pathways in Inflammation and Immunity

In recent decades, the role of platelets in inflammation emerges as a new research hotspot [68]. Taking thrombosis events in atherosclerosis as an example, platelets initiate the thrombus formation if the atherosclerotic plaque is ruptured and large numbers of inflammation factors are released from the ruptured site to the circulating blood [69]. Most studies demonstrate that platelets function as proinflammatory cells through granular release of inflammatory mediators or cytokines, and platelet-leukocyte interaction [70, 71]. In myocardial infarction mouse model, clopidogrel inhibited P-selectin expression, platelet-leukocyte aggregation and myocardial inflammation [69]. Therefore, $P2Y_{12}$ receptor may contribute to cardiac inflammation after myocardial infarction.

Other disease models also demonstrate the importance of $P2Y_{12}$ receptor in inflammation, but pro- or anti-inflammation varies in different studies. Paruchuri et al. found that leukotriene E4-induced murine pulmonary inflammation is mediated by $P2Y_{12}$ receptor, suggesting that $P2Y_{12}$ receptor may be a potential therapeutic target for asthma [72]. Platelet microparticles were identified from joint fluid of patients with rheumatoid arthritis or other forms of inflammatory arthritis, and were proved proinflammatory for stimulating cytokine responses from synovial fibroblasts through IL-1 [73]. However, using rat model of peptidoglycan polysaccharide (PG-PS)-induced arthritis, Garcia et al. found that clopidogrel, the widely-used antiplatelet drug targeting $P2Y_{12}$ receptor, exaggerated the inflammatory response [74], supporting the anti-inflammatory role of $P2Y_{12}$ receptor in arthritis.

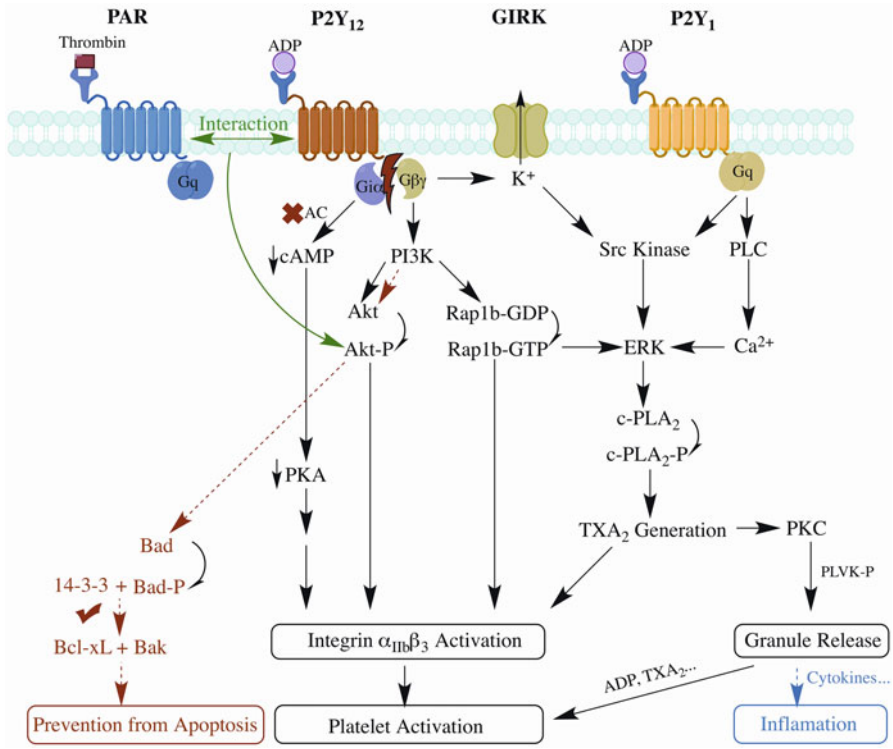

Fig. 1 A simplified overview of $P2Y_{12}$ receptor signaling pathways and its co-transduction pathways with $P2Y_1$ receptor and PAR receptor [39, 79]. $P2Y_{12}$ and $P2Y_1$ receptors are activated by ADP while PAR receptor by thrombin. Once $P2Y_{12}$ activated, $G_i\alpha$ inhibits adenyl cyclase to reduce cAMP level; $G_i\beta\gamma$ activates PI3K and GIRK to induce downstream activation of Akt, Rap1b and Src kinase. $P2Y_1$ receptor costimulates Src kinase or ERK through Gq signaling. PAR receptor costimulates Akt by interaction with $P2Y_{12}$ receptor. Effects include $\alpha_{IIb}\beta_3$ integrin activation, resulting in platelet activation and aggregates stabilization. Generation of TxA_2 induces both integrin activation and granule release, in which small molecules like ADP continues to activate platelets and cytokines may induce inflammation. The anti-apoptotic pathway of $P2Y_{12}$ receptor is mainly through Akt pathway to phosphorylate Bad to enable the binding of Bcl-xL with Bak thus achieving antiapoptotic effects

Consistently, using an LPS-induced systemic inflammation mouse model, the same group shows that $P2Y_{12}$ knockout aggravates inflammatory injury, showing the protective role of $P2Y_{12}$ receptor against inflammatory injury [75]. In contrast, in a LPS-induced systemic inflammation rat model, clopidogrel pretreatment reduces inflammatory damage of lung and liver [76]. The discrepancy cannot be simply attributed to species difference, because the protective effect of clopidogrel was also observed in a mouse model of polymicrobial sepsis [77]. Further work is needed to elucidate the causal relation between antiplatelet effects of clopidogrel and inflammation [78]. A simplified overview of $P2Y_{12}$ receptor signaling pathways and its co-transduction pathways with $P2Y_1$ receptor and PAR receptor is illustrated by Fig. 1.

3 Abnormalities of $P2Y_{12}$ Receptors

3.1 $P2Y_{12}$ Gene Polymorphisms

There are four $P2Y_{12}$ gene polymorphisms in total linkage disequilibrium, determining haplotypes H1 and H2, with respective allelic frequencies of 0.86 and 0.14 [80]. Carriers of the H2 haplotype exhibit increased ADP-induced platelet aggregation; thus they may have an increased risk of atherothrombosis

or a lesser clinical response to drugs inhibiting platelet function [80]. Several studies show that H2 haplotype is associated with the risk of peripheral arterial disease (PAD) or contributes to clopidogrel resistance [81, 82]. However, most studies report that $P2Y_{12}$ polymorphisms are not associated with platelet-relative diseases such as coronary artery disease (CAD) or altered platelet function inhibition by $P2Y_{12}$ antagonists [83–89]. Whether people of H2 haplotype have a tendency of thrombotic events are not clearly evidenced yet.

3.2 Congenital Deficiency of $P2Y_{12}$ Receptor

Congenital $P2Y_{12}$ deficiency is an autosomal recessive disorder [90]. Patients of congenital severe $P2Y_{12}$ deficiency exhibit excessive bleeding and prolonged bleeding time [91]. Coagulant defects in patients of heterozygous $P2Y_{12}$ deficiency are less severe, mainly characterized by that low concentrations of ADP ($\leq$10 μM) can only induce reversible platelet aggregation [92]. Treatment for these patients is intravenous infusion of desmopressin, a vasopressin analog [93].

3.3 $P2Y_{12}$ Receptor Abnormal Expression in Diseases

$P2Y_{12}$ receptor abnormal expression is detected in some diseases, which may explain the high rate of clinical phenomenon "clopidogrel resistance" (referring to failure of clopidogrel to achieve antiplatelet effects) in some patients of certain diseases [54]. Typical diseases are listed below for references but further elucidation of the molecular mechanism is needed.

3.3.1 Diabetes Mellitus

Platelet function in diabetes mellitus patients is altered in the following aspects: accelerated platelet turnover, increased TXA_2 release and platelet aggregation [94, 95]. Diabetes patients, with standard clopidogrel treatment or combined aspirin and clopidogrel treatment, have high on treatment platelet reactivity (HTPR) [96], an independent risk factor of recurrent ischemic events [97]. It is hypothesized that $P2Y_{12}$ receptor expression is upregulated or the downstream signaling is amplified in diabetes patients [98–100]. We found that type II diabetes mellitus patients have increased $P2Y_{12}$ expression on platelet, and the platelet $P2Y_{12}$ level correlates with platelet reactivity to multiple agonists including ADP, thrombin and AYPGKF (Hu et al., unpublished data). For diabetes patients with "clopidogrel resistance", alternative antiplatelet drugs like prasugrel or ticagrelor can be used for preventing cardiovascular events [101]; adjunctive use of cilostazol can also be applied to reduce platelet reactivity in diabetes patients [102].

3.3.2 Chronic Kidney Disease

Like diabetes, chronic kidney disease patients have high residual platelet reactivity (HRPR); chronic kidney disease and diabetes confer a synergistic impact on HRPR [103]. Studies from randomized trials suggest that renal function has an influence on clinical efficacy of clopidogrel [104]. Whether $P2Y_{12}$ receptor upregulation or increased signaling activation downstream of $P2Y_{12}$ participates in the increased platelet reactivity and impaired clopidogrel response in chronic kidney disease, as in the case of diabetes, is not clear.

4 Antiplatelet Drugs Targeting $P2Y_{12}$ Receptor

The common pathological basis of coronary artery disease and ischaemic stroke is the arterial thrombosis, a result of aberrant platelet activation. $P2Y_{12}$ plays a central role in platelet activation [105] and mainly distributed in platelets [6], therefore $P2Y_{12}$ is an ideal target for antiplatelet drug development. In fact, $P2Y_{12}$ receptor is the most successful antiplatelet target so far. Four $P2Y_{12}$ receptor antagonists have been approved by FDA as antiplatelet drugs, including ticlopidine, clopidogrel, prasugrel, and ticagrelor. Among them, ticlopidine, clopidogrel and prasugrel belong to thienopyridine and are

prodrugs, which need to be transformed in liver to form active metabolite to exert their $P2Y_{12}$ antagonizing roles [106].

Clopidogrel is the most widely used antiplatelet drug antagonizing $P2Y_{12}$ receptor with proved benefits over aspirin and the first $P2Y_{12}$ antagonist ticlopidine. The main limitations of clopidogrel include slow onset, slow offset of action, modest platelet inhibition, individual variability compared with 3rd generation of thienopyridine $P2Y_{12}$ receptor antagonist prasugrel and direct $P2Y_{12}$ receptor antagonist ticagrelor [43, 79]. Besides, $P2Y_{12}$ receptor inverse agonists exhibit more potent antiplatelet effects on platelets expressing constitutively active $P2Y_{12}$ receptor, and therefore may have better antithrombotic efficacy [35, 37]. Dual antiplatelet therapy (DAPT) has been the standard of care for patients with ACS and those undergoing stenting, which triggers researches on antiplatelet compounds with dual or multiple targets like BF061 [107]. In this part, we will briefly introduce the antiplatelet agents targeting $P2Y_{12}$ receptor in clinical use and under development. For more detailed information about the pharmacology and clinical use of the marketed $P2Y_{12}$ receptor antagonists, please refer to two excellent reviews published recently [43, 108].

4.1 Thienopyridines

Among the five marketed $P2Y_{12}$ receptor antagonists, ticlopidine, clopidogrel and prasugrel belong to thienopyridine family. All of them are prodrugs, which are transformed into thiol-containing active metabolites and covalently bind to $P2Y_{12}$ receptor [106]. The binding inhibits ADP-induced platelet activation irreversibly.

4.1.1 Ticlopidine

Ticlopidine is the first antiplatelet drug targeting $P2Y_{12}$ receptor in thienopyridine family.

Pharmacodynamics and Pharmacokinetics

Ticlopidine is absorbed from the gastrointestinal tract rapidly and the oral bioavailability is 80 % [109]. For a single oral dose, half life of ticlopidine is 12–22 h but the effect increases with repeated dosing and peaks in 5 days. Oral administration requires 250 mg once daily [110].

Side Effect

Ticlopidine has severe side effects including neutropenia, aplastic anemia, thrombotic thrombocytopenic purpura (TTP) and gastrointestinal reactions, which limit its clinical uses [111].

Clinical Application

Ticlopidine is seldom used in acute ischemic cardiovascular events due to its slow onset and the serious adverse effects described above. Studies showed that high administration dose (500 mg daily) with aspirin could have rapid antiplatelet effects in ACS patients [112].

4.1.2 Clopidogrel

Clopidogrel is the second generation of thienopyridines that outweighs ticlopidine with better effects against platelet aggregation and fewer side effects [113]. In 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes, clopidogrel is under class I recommendation [114].

Pharmacodynamics and Pharmacokinetics

Eighty five to ninety percent of the absorptive drugs are hydrolyzed to inactive metabolites by esterase and only 10–15 % are converted into active metabolites by hepatic CYP [109]. The active metabolites bind irreversibly to the cysteine residue of $P2Y_{12}$ extracellular domain and the effect could last the whole life span of platelets [106]. The onset and peak time are similar to ticlopidine and the metabolites also excrete from both urine and feces [109].

Clinical Application

Clopidogrel is the routine medicine in preventing thrombotic events in diseases like ACS, the loading dose administration of which could have apparent antiplatelet aggregation effects before ACS patients undergo percutaneous coronary intervention (PCI) [115]. For patients with ST-segment elevation myocardial infarction (STEMI), an ACS clinical manifestation of high mortality, if clopidogrel was used as an adjunctive therapy to support reperfusion with primary PCI,

the loading dose is 600 mg as early as possible or at the time of PCI, 75 mg daily thereafter; if with fibrinolytic therapy, loading dose is 300 mg by 75 mg daily [116]. Some studies also show that a high loading dose of 900 mg could give stronger inhibition of platelet aggregation but the safety issue is questionable [117].

Side Effects

Clopidogrel could induce severe rashes in some patients and gastrointestinal reactions such as nausea and vomiting, with rare cases of neutropenia compared with ticlopidine [118]. Clopidogrel is also a cause of gastrointestinal bleeding [119]. But in the case of co-medication of clopidogrel and proton pump inhibitors (PPIs), PPIs with weaker inhibition of CYP2C19 are preferred due to its potential negative clinical impacts on therapeutic efficacy of clopidogrel [120]. Although clopidogrel is widely used clinically, it's still not an ideal antiplatelet drug. Low onset is mainly due to the metabolism process in the liver [106]. Individual variability is associated with genes related to drug metabolism, which may cause "clopidogrel resistance" and impair the prevention from thrombotic events among certain patient groups [54, 121–123]. Besides the gene polymorphism that causes change of CYP activity, "clopidogrel resistance" could also result from increased platelet $P2Y_{12}$ in some patients such as in type II diabetes mellitus [37] and the low inverse agonist activity (Hu et al., unpublished data), or combination of multiple factors [124]. Moreover, clopidogrel, as an irreversible $P2Y_{12}$ receptor antagonist, could retard the recovery of platelets after withdraw; thus clopidogrel has the bleeding risk if emergency surgery is needed.

4.1.3 Prasugrel

Prasugrel (CS-747, LY640315) is the third generation of thienopyridines.

Pharmacodynamics and Pharmacokinetics

Compared to clopidogrel, prasugrel is absorbed more quickly that it could be detected in plasma in 15–30 min after oral administration with a 7 h half life [125]. Seventy percent excretion of metabolites is from urine [126].

Clinical Application

The phase III clinical trial of prasugrel (a 60 mg loading dose and a 10 mg daily maintenance dose) compared with clopidogrel (a 300 mg loading dose and a 75 mg maintenance dose) showed that prasugrel therapy owned significantly reduced rates of ischemic events in patients with ACS treated by PCI, but had an increased risk of major bleeding events including fatal bleeding; consequences were that mortality rate was similar between those two groups [127]. Conclusions still differ in many recent researches investigating whether prasugrel has more advantages over clopidogrel for ACS: Delia et al. did retrospective investigation of 525 ACS in-hospital patients and the results showed no significant changes, after changing clopidogrel to prasugrel, in terms of bleeding or thrombotic events [128]. Olson et al. compared 10,963 ASC patients taking clopidogrel or prasugrel in Truven Health Analytics MarketScan database, and concluded that the two had similar effects while clopidogrel is better than prasugrel in the long run [129]. In contrast, Koziński et al. demonstrated that prasugrel could lower the high on-treatment platelet reactivity (HTPR) in 71 ACS patients who showed HTPR after taking clopidogrel [130]. So prasugrel is still not able to substitute clopidogrel as routine medication for ACS patients; it is an alternative for patients who have "clopidogrel resistance". The reason behind may be that mutations of CYP2C9 and CYP2C19 affect platelet aggregation heavily on clopidogrel but not on prasugrel [131].

Side Effects

Clinical trials revealed excess bleeding mainly occurring in maintenance phase, which reminds that patient selection for prasugrel is necessary [126].

4.2 $P2Y_{12}$ Receptor Direct Antagonists

In order to reach rapid and reversible antiplatelet effects, $P2Y_{12}$ receptor direct antagonists with short half life are developed.

4.2.1 Ticagrelor

Ticagrelor (AZD6140, Brilinta) is the first marketed $P2Y_{12}$ receptor antagonist that reversibly and directly blocks $P2Y_{12}$ receptor; it is a cyclopentyltriazolopyrimidine and can be used orally [132, 133]. Radioligand binding assay demonstrates that ticagrelor is a non-competitive antagonist that has a binding site in $P2Y_{12}$ receptor independent of ADP [42, 133].

Pharmacodynamics and Pharmacokinetics

Compared to thienopyridines, ticagrelor can inhibit $P2Y_{12}$ receptor directly without any hepatic biological conversion [133]. The inhibition rate could reach 95 % in 2–4 h and it can take effects in 2 h without loading dose [132]. The half life is 6–9 h so that residual effect is shorter than thienopyridines [134]. Tests of [^{14}C]-labeled ticagrelor administrated in healthy subjects showed that the mean radioactivity recovery was 58 % from feces and 27 % from urine [135]. Gene polymorphism of CYP has no impacts on ticagrelor so it is effective for patients with "clopidogrel resistance" [136].

Clinical Application

For ACS patients with or without ST-segment elevation, ticagrelor of 180 mg loading dose and 90 mg twice daily thereafter could significantly reduce the cardiovascular events compared with clopidogrel of 300–600 loading dose and 75 mg daily thereafter [137]. Ticagrelor has higher and more consistent antiplatelet effects and could lower mortality of cardiovascular diseases, myocardial infarction and stroke in ACS patients and patients with prior myocardial infarction [138–140]. Shah et al. ever reported that ticagrelor can be used as alternative in clopidogrel-induced neutropenia [141].

Side Effects

In a phase III clinical trial, ticagrelor was demonstrated to increase non-procedure related bleeding in 18,624 ACS patients with or without ST-segment elevation [137]. Dyspnea was more frequently observed in patients using ticagrelor than clopidogrel, which might be due to the constant inhibition of $P2Y_{12}$ receptors on neurons by ticagrelor resulting in increased sensitivity to dyspnea [142].

4.2.2 Cangrelor

Cangrelor (ARC69931MX) is a direct and reversible $P2Y_{12}$ antagonist. It is developed as antiplatelet agent for intravenous use with rapid onset and offset action. Structurally, cangrelor is the analog of ATP, the weak endogenous antagonist of $P2Y_{12}$ receptor [143]. Cangrelor has won European approval in March 2015 and may also get approved by FDA as an intravenous antiplatelet drug to prevent thrombosis during angioplasty.

Pharmacodynamics and Pharmacokinetics

Similarly to ticagrelor, cangrelor does not need biological metabolism to achieve platelet inhibition [144]. Because of the direct reaction with $P2Y_{12}$ receptor, cangrelor takes effects in 2 min and reaches steady inhibition state of platelet aggregation in 3–5 min [143].

Clinical Application

Cangrelor is administrated intravenously [144]. -Champion-Phoenix in more than 11,000 patients undergoing PCI, demonstrated that cangrelor is superior to clopidogrel to reduce the combined risk of death, heart attack, repeat procedures and stent thrombosis [145]. Compared with clopidogrel, cangrelor slightly increased bleeding.

Side Effects

Besides bleeding, dyspnea was also observed in clinical trials [142, 143].

4.2.3 Elinogrel

Elinogrel (PRT060128), is a potent competitive direct $P2Y_{12}$ receptor antagonist developed for both oral and intravenous use [146, 147]. The development of elinogrel was terminated before phase III study by Novartis in 2012.

Pharmacodynamics and Pharmacokinetics

The average half life is 11 h of 40 mg elinogrel administered intravenously, and the peak

antiplatelet effect reaches in 20 min but totally reversed in 8–24 h [148].

Clinical Application

Elinogrel can be orally or intravenously administered, in two pharmacologically identical forms with different dosages [147]. In phase I clinical trial, elinogrel had potent antiplatelet aggregation effects with similar bleeding side effects as the placebo group [149]. In phase II clinical trial for non-urgent patients undergoing PCI, the potential bleeding risk of elinogrel was higher than clopidogrel [150].

Side Effects

Besides bleeding risks, elinogrel also has side effects on respiratory system such as dyspnea and elevated liver enzymes [147].

4.3 $P2Y_{12}$ Receptor Inverse Agonists

The discovery of constitutive activity of G protein coupled receptors (GPCRs) and inverse agonists has significantly changed our understanding of receptor activation, disease pathogenesis, and mechanisms of drug action. GPCRs can be active in the absence of agonists (i.e. have constitutive activity), owing to receptor overexpression or mutation, both of which have been reported to cause human diseases. To treat such diseases, classical GPCR antagonists blocking agonist binding to the receptors are ineffective, whereas the inverse agonists have therapeutic advantages. In the case of $P2Y_{12}$ receptor, inverse agonist may be therapeutically beneficial compared to the neutral antagonists as antiplatelet agents [37, 151].

Schmidt et al. ever screened out a potent $P2Y_{12}$ receptor inverse agonist, mant-dATP, using several different constitutively active $P2Y_{12}$ mutants [151, 152]. Using a cell line expressing constitutively active $P2Y_{12}$ receptor, we found that $P2Y_{12}$ receptor AR-C78511 is a potent inverse agonist while cangrelor (AR-C69931MX) is a neutral antagonist at $P2Y_{12}$ receptor [35]. We further found that the transgenic mice expressing the constitutively active $P2Y_{12}$ receptor exhibited increased platelet activation and thrombosis, and AR-C78511 exerted superior antiplatelet effects to that of cangrelor [35, 37]. More physiologically, we recent found that type II diabetes mellitus patients have increased platelet $P2Y_{12}$ expression and the $P2Y_{12}$ expression level is associated the platelet reactivity (Hu et al., unpublished data). Moreover, our preliminary results show that AR-C78511 has more potent antiplatelet effects than cangrelor on platelets from diabetes patients. Whether the inverse agonist activity of AR-C78511 and mant-dATP can be translated into more advantageous antithrombotic effects without increasing bleeding risk deserves further study.

4.4 New Dual Antiplatelet Agent

Combined antiplatelet therapy has been widely used to treat arterial thrombotic diseases with improved efficacy and safety. In our pursuit to develop more efficacious and safer antiplatelet drugs, we identified a novel antiplatelet agent BF061 targeting both $P2Y_{12}$ and phosphodiesterase (PDE) [107]. BF061 robustly inhibited platelet aggregation and ATP release induced by multiple platelet agonists. Atomic microscopy confirmed the $P2Y_{12}$ antagonizing effects of BF061 and PDE activity assay revealed its inhibition on platelet PDE. The antithrombotic effect of BF061 was evaluated in mice using intravital microscopy in $FeCl_3$-induced mesenteric and laser-induced cremasteric arterial thrombosis models. In $FeCl_3$-induced mouse mesenteric arterial thrombosis model, BF061 effectively prevented thrombus formation similarly to clopidogrel with dramatically less bleeding [107]. Given the prevalence of combined antiplatelet therapy targeting $P2Y_{12}$, COX1 and PDE in clinical practice, antiplatelet agents bearing dual targets $P2Y_{12}$ and PDE may have therapeutic advantage as potential antithrombotic agent, which deserves further development.

Table 2 is the summary of the antiplatelet drugs targeting $P2Y_{12}$ receptor.

Table 2 Main characteristics of $P2Y_{12}$ receptor antagonists as antiplatelet agents

Drugs		Phase	Mechanism	Pharmacodynamics & pharmacokinetics					Clinical administration for ACS	Side effects
				$T_{1/2}$	Onset	Peak	Platelet recovery	Excretion		
Thienopyridines [109–113, 115–118, 121, 125]	Ticlopidine	Off-market	Prodrug, hepatic metabolites covalently and irreversibly binding with $P2Y_{12}$ receptor, noncompetitive with ADP	12–22 h	2 h	5 h	14 days	60 % from kidney; 23 % from bile acid/ gastrointestinal duct	p.o: 250 mg o.d	Neutropenia, TTP, aplastic anemia, gastrointestinal reactions
	Clopidogrel	Launched		6 h	2 h	2–4 h	5–10 days	50 % from kidney; 48 % from gastrointestinal duct	p.o: 300-/600-mg loading dose, 75 mg o.d	Severe rashes, gastrointestinal reactions
	Prasugrel	Launched		7 h	0.25–0.5 h	1 h	10–15 days	70 % from kidney	p.o: 60-mg loading dose, 10 mg o.d	Excess bleeding during maintenance phase
Direct antagonists [42, 132, 133, 138, 146, 147, 153]	Ticagrelor	Launched	Noncompetitive with ADP and reversibly direct-acting on $P2Y_{12}$ receptor	6–9 h	2 h	2–4 h	5 days	27 % from kidney; 58 % from gastrointestinal duct	p.o: 180-mg loading dose, 90 mg b.i.d	Non-procedure related bleeding, dyspnea
	Cangrelor	Phase III trial finished	ADP analogue: weak, nonselective but competitive $P2Y_{12}$ receptor antagonist	<5 min	3–5 min	0.5 h	1 h after the end of infusion	Fast clearance from plasma	i.v (continuous): 30 μg/kg bolus, 0.5–4 μg/kg/min infusion	Major or minor bleeding events, dyspnea
	Elinogrel	I-II, determinated	Reversible	8–12 h	15 min	20 min	8–24 h	–	p.o: 50–150 mg i.v: 80 or 120 mg bolus	Bleeding events, dyspnea, elevated liver enzymes
Inverse agonists [35, 151]	ARC-78511	In vitro, ex vivo	Inverse agonist	–					–	–
	Mant-dATP			–					–	–
Dual-/multi-target drugs [107]	BF061	Animal Exp	Inhibit both $P2Y_{12}$ receptor and PDE	–					–	–

5 Conclusion and Prospective

$P2Y_{12}$ receptor plays a central role in platelet activation, hemostasis, and thrombosis. Therefore, $P2Y_{12}$ receptor has been the most successful antiplatelet target. Though antiplatelet agents targeting $P2Y_{12}$ have proven benefits clinically, and four $P2Y_{12}$ receptor antagonists have been marketed as antiplatelet drugs, there is still room to develop novel antiplatelet agent with improved efficacy and safety. Considering the success of dual antiplatelet therapy consisting of thienopyridine $P2Y_{12}$ receptor and aspirin as the stand of care, novel antiplatelet agents targeting multiple targets including $P2Y_{12}$ with similar improved efficacy and safety profile as dual antiplatelet therapy may have advantage, because it's more convenient and will increase patient compliance for long time use. Also, we think that $P2Y_{12}$ receptor with potent inverse agonist activity may have therapeutic advantage, which may be effective on patients with poor clopidogrel response without increase bleeding risk, especially to the patients with increased platelets expression as in type II diabetes patients. With more reliable and user-friendly platelet test available, we believe that tailored antiplatelet therapy based on patient platelet $P2Y_{12}$ receptor expression may give patients more efficacious, safer and economic antiplatelet therapy and better outcome.

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Proton Pump Inhibitors in Cardiovascular Disease: Drug Interactions with Antiplatelet Drugs

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Abstract

Aspirin and $P2Y_{12}$ receptor antagonists are widely used across the spectrum of cardiovascular diseases. Upper gastrointestinal complications, including ulcer and bleeding, are relatively common during antiplatelet treatment and, therefore, concomitant proton pump inhibitor (PPI) treatment is often prescribed.

PPIs provide gastroprotection by changing the intragastric milieu, essentially by raising intragastric pH. In recent years, it has been heavily discussed whether PPIs may reduce the cardiovascular protection by aspirin and, even more so, clopidogrel. Pharmacodynamic and pharmacokinetic studies suggested an interaction between PPIs and clopidogrel, and subsequent clinical studies were conducted to evaluate the clinical impact of this interaction. More recently, it was reported that PPIs may also attenuate the antiplatelet effect of aspirin. This may be clinically important, because a fixed combination of aspirin and a PPI (esomeprazole) has recently been approved and because aspirin is the most widely used drug in patients with cardiovascular disease. The antiplatelet effect of the new $P2Y_{12}$ receptor antagonists, ticagrelor and prasugrel, seems less influenced by PPI co-treatment.

Given the large number of patients treated with antithrombotic drugs and PPIs, even a minor reduction of platelet inhibition potentially carries considerable clinical impact. The present book chapter summarizes the evidence regarding the widespread use of platelet inhibitors and PPIs in combination. Moreover, it outlines current evidence supporting or opposing drug interactions between these drugs and discusses clinical implications.

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ADP receptor antagonists • Aspirin • Clopidogrel • Drug interactions • Proton pump inhibitors

1 Introduction

In 2009, European and American regulatory authorities issued public warnings discouraging co-prescription of clopidogrel and proton pump inhibitors (PPIs) "unless absolutely necessary" [1, 2]. These recommendations were based on pharmacological studies suggesting that platelet inhibition with clopidogrel was reduced by PPIs and by observations of increased coronary event rates in patients taking both drugs. In 2010, the European Medicines Agency amended its statement to include only omeprazole and esomeprazole [3], and according to current clinical guidelines, PPIs are still recommended in combination with clopidogrel and other antiplatelet drugs in patients at high risk of gastrointestinal complications [4, 5].

Given the vast use of polypharmacy in the treatment of cardiovascular disease, insight into drug interactions is pivotal. When a doctor prescribes two drugs or more at the same time, each drug potentially loses efficacy due to a reduction in bioavailability, chelation of compounds, altered cytochrome P450 (CYP) enzyme activity, altered protein binding, *etc*. [6]. A strong relationship exists between the number of dispensed drugs and the occurrence of drug interactions [7], and drug interactions are a common cause of treatment failure and adverse drug reactions [8].

The number of patients treated with platelet inhibitors and PPIs is high, so even modest drug interactions may have considerable clinical impact. The present book chapter summarizes the evidence regarding the widespread use of platelet inhibitors and PPIs. Moreover, it outlines current evidence supporting or opposing drug interactions between these drugs and discusses clinical implications.

2 Aspirin: Pharmacology and Clinical Use

2.1 Pharmacology

Platelet inhibition by aspirin results from irreversible blockage of the cyclooxygenase (COX)-1 enzyme. COX-1 is responsible for converting arachidonic acid to thromboxane A_2, which is a potent platelet activator and vasoconstrictor. By acetylating a serine moiety in COX-1, aspirin prevents arachidonic acid from accessing the catalytic site of the enzyme thereby lowering the production of thromboxane A_2 [9]. The inhibition of COX-1 is virtually complete even at low doses (30 mg/day). In addition, the inhibition is rapid, dose-independent, and largely irreversible because mature platelets retain only limited capacity to re-synthesize COX-1 [10]. Aspirin also inhibits endothelial COX-dependent synthesis of prostacyclin, which, contrary to TXA_2, acts as a vasodilator and inhibitor of platelet aggregation. However, once aspirin has been cleared from the circulation, nucleated endothelial cells readily produce new unacetylated COX-1. Importantly, this does not occur in platelets due to their lack of a nucleus. Overall, this yields an antithrombotic net result of treatment with low-dose aspirin [6]. Aspirin has a higher affinity for COX-1 than for COX-2 inhibiting COX-1 50–100 times more potently than COX-2 [11]. Sufficient COX-2 inhibition requires considerably larger doses and a shorter dosing interval because COX-2 is expressed by nucleated cells capable of re-synthesizing COX-2 [12]. Accordingly, aspirin must be administered in analgesic or anti-inflammatory doses (500–1000 mg) several times daily to sustainably inhibit the COX-2 system [13].

2.2 Clinical Use

In cardiology, the therapeutic utility of aspirin spans the continuum from primary prevention through stable coronary artery disease to acute coronary syndrome (ACS). A widespread appreciation of aspirin in secondary cardiovascular prevention was founded during the 1980s. The landmark ISIS-2 trial convincingly demonstrated the superiority of aspirin over placebo in patients with suspected acute ST elevation MI [14]. At 15-month follow-up, 1 month of low-dose aspirin (162.5 mg, enteric-coated), either alone or in combination with fibrinolytic streptokinase, conferred a relative risk reduction of non-fatal reinfarction (23 %) and death (42 %). The benefit was sustained at 10 years [15]. During the same period, four clinical trials documented the benefit of aspirin in the setting of non-ST elevation ACS [16–19]. Today, aspirin is a first-line antiplatelet drug for secondary cardiovascular prevention conferring a 25 % reduction in serious vascular events compared to placebo [20].

3 ADP Receptor Antagonists: Pharmacology and Clinical Use

ADP receptor antagonists target the $P2Y_{12}$ receptor on the platelet membrane thereby inhibiting ADP-mediated platelet activation. Four different oral ADP receptor antagonists are approved for clinical use: ticlopidine, clopidogrel, prasugrel, and ticagrelor. Due to its poor safety profile and the need for twice-daily dosing, ticlopidine has been almost completely replaced by clopidogrel, prasugrel, and ticagrelor. Therefore, ticlopidine will not be reviewed herein, while the characteristics of clopidogrel, prasugrel, and ticagrelor are provided in Table 1.

3.1 Pharmacology

Clopidogrel is a second-generation thienopyridine, which became available in its generic form in 2012. Clopidogrel is a prodrug, which is well absorbed from the gut, but remains pharmacologically inert until activated in the liver through the CYP system (Fig. 1). The majority of administered clopidogrel is metabolized by an esterase pathway not resulting in active drug metabolites, and only 15 % reaches the liver for active metabolite transformation [14]. This is mediated by a two-step oxidative process regulated by the CYP system. Ultimately, as little as 2 % ends up irreversibly inhibiting the $P2Y_{12}$ receptor [21]. Among the different CYP variants involved in the hepatic conversion of clopidogrel, CYP2C19 is the major variant responsible for approximately 45 % [21].

Prasugrel is activated in a one-step oxidative process and, unlike clopidogrel, none of the drug is shunted to an inactive pathway (Fig. 1). Compared to clopidogrel, the hepatic conversion of prasugel is less dependent on CYP2C19 [22]. Ticagrelor is an adenosine triphosphate analogue not belonging to the thienopyridine family. Ticagrelor inhibits the $P2Y_{12}$ receptor reversibly and does not require hepatic bioactivation (Table 1 and Fig. 1). Prasugrel and ticagrelor are more potent platelet function inhibitors than clopidogrel and are now being widely used in combination with aspirin in the setting of ACS.

Table 1 Pharmacology and dosing of aspirin and ADP receptor antagonists

Drug	Primary mode of action	Metabolism and platelet inhibition	Platelet inhibition	Dosing
Aspirin	COX-1 inhibition	Prodrug	Irreversible	Once daily
Clopidogrel	$P2Y_{12}$ receptor antagonism	Prodrug	Irreversible	Once daily
Prasugrel	$P2Y_{12}$ receptor antagonism	Prodrug	Irreversible	Once daily
Ticagrelor	Allosteric $P2Y_{12}$ receptor antagonism	Direct-acting	Reversible	Twice daily

ADP adenosine diphosphate, *COX* cyclooxygenase

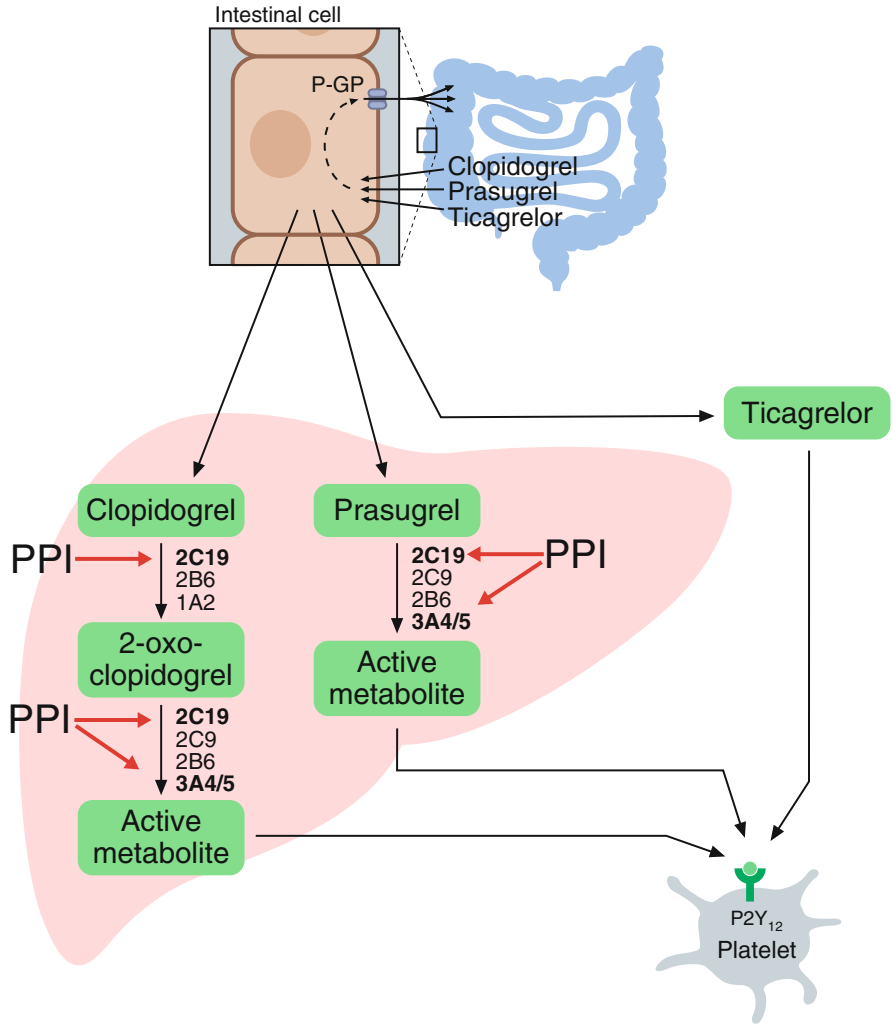

Fig. 1 A schematic presentation of the absorption and metabolism of clopidogrel, prasugrel, and ticagrelor (Adapted from Würtz et al. [112]). Clopidogrel is activated by a two-step oxidative process in the liver, whereas only one oxidative step is needed for the activation of prasugrel. The most important CYP enzymes mediating hepatic bioactivation of clopidogrel and prasugrel are depicted. CYP2C19 and CYP3A4/A5 are highlighted because they are strongly involved in the metabolism of certain PPIs, in particular omeprazole, thereby competitively inhibiting the bioactivation of clopidogrel and prasugrel. Ticagrelor does not require hepatic bioactivation. *CYP* cytochrome P450, *P-GP* P-glycoprotein (multidrug resistance protein), *PPI* proton pump inhibitor

3.2 Clinical Use

The CURE trial from 2001 documented the benefit of clopidogrel in addition to aspirin in patients with non-ST elevation MI [23]. The relative risk for the primary end point (cardiovascular death, non-fatal MI, or stroke) with aspirin and clopidogrel was 0.80 (95 % confidence interval [CI] 0.72–0.90) compared to aspirin alone. Since then, clopidogrel has been used in combination with aspirin in the setting of percutaneous coronary intervention (PCI), especially in the treatment of ACS. In 2005, a similar benefit was documented in patients with ST elevation MI [24, 25]. Overall, dual antiplatelet therapy with aspirin and clopidogrel in patients with ACS reduced cardiovascular risk by approximately 10 % compared to aspirin alone

[23–25]. Documenting its widespread use, clopidogrel was the second most prescribed drug worldwide in 2010 (atorvastatin was the most prescribed) [26].

From 2009 to 2011 ticagrelor and prasugrel received authorization from European and American authorities for use in combination with aspirin for prevention of atherothrombotic events in patients with ACS undergoing PCI. Approvals were based on two phase III trials, TRITON-TIMI 38 (prasugrel) [27] and PLATO (ticagrelor) [28], documenting significant reductions in cardiovascular death, non-fatal MI, or stroke when using prasugrel or ticagrelor instead of clopidogrel. In TRITON-TIMI 38 the hazard ratio with prasugrel was 0.81 (95 % CI 0.73–0.90), and in PLATO the hazard ratio with ticagrelor was 0.84 (95 % CI 0.77–0.92). Although prasugrel and ticagrelor increased the risk of non-coronary artery bypass grafting-related major bleeding according to the Thrombolysis in Myocardial Infarction criteria (by 32 % and 25 %, respectively), both drugs are now widely used as treatment and short-term prevention of atherothrombotic events in patients with ACS [4].

4 Antiplatelet Treatment and Gastrointestinal Bleeding

Cardiovascular protection by aspirin and ADP receptor antagonists accrue at the expense of an increased risk of upper gastrointestinal bleeding [29, 30]. Gastrointestinal bleeding is life-threatening, especially in patients presenting with ACS [31] and documenting this, aspirin remains the dominant contributor to gastrointestinal bleeding-related mortality [32].

The gastrotoxic effects of aspirin that cause ulceration and bleeding have been attributed to (1) topical mucosal injury caused by inhibition of prostaglandin and (2) systemic antiplatelet effects driven by inhibition of thromboxane A_2 generation [33, 34]. Prostaglandins are essential in protecting the gastric mucosa. They increase mucosal blood flow, promote proliferation of gastric epithelial cells, and stimulate mucus and bicarbonate secretion. Therefore, inhibition of prostaglandin synthesis by aspirin makes the gastric mucosa susceptible to ulcer formation and bleeding in the highly acidic environment. Furthermore, platelet inhibition with aspirin impairs healing of the vulnerable gastric mucosa [33, 34].

Unlike aspirin, ADP receptor antagonists do not cause injury of the gastric mucosa, but their inhibition of platelet aggregation are likely to impair healing and aggravate already existing gastric injuries caused by acidic drugs such as aspirin [33, 34].

5 Proton Pump Inhibitors: Pharmacology and Clinical Use

Strategies to prevent gastrointestinal discomfort, ulceration, and bleeding during antiplatelet treatment include the identification and modification of associated risk factors as well as concomitant treatment with gastroprotective agents, mainly histamine H_2 receptor antagonists and PPIs [33, 35]. For more than two decades, PPIs have been used extensively for the treatment of gastric acid-related disorders. Even though H_2 receptor antagonist are effective in preventing gastrointestinal complications [36], PPIs produce a higher degree and longer duration of gastric acid suppression than H_2 receptor antagonists leading to higher healing rates [8]. Although PPIs have widely been considered harmless, there are studies associating these drugs with serious adverse effects such as pneumonia, interstitial nephritis, osteoporotic fractures, and intestinal *Clostridium difficile* infections [37].

Under acidic conditions, PPIs are protonated and converted to cyclic sulphenamides. These active PPI metabolites reduce gastric acid production by irreversibly inhibiting the enzyme responsible for gastric acid secretion: the H^+/K^+ -exchanging adenosine triphosphatase, often referred to as "the proton pump" [8]. The proton pump, which is located on gastric parietal cells, is directly responsible for H^+ secretion into the gastric lumen. It follows that PPIs, as opposed to

H_2 receptor antagonists, target the terminal step in gastric acid secretion making the gastric acid suppression particularly strong. PPIs have a short plasma half-life of 30–120 min depending on pH level, yet the antacid effect is sustained for days due to the irreversible inhibition as well as accumulation of the drug in parietal cells [8].

6 Biochemical Background for Putative Drug Interactions Between Proton Pump Inhibitors and Antiplatelet Drugs

Under physiological conditions, aspirin is absorbed in its non-ionized lipid state across the gastric mucosal barrier. A pH-dependent mechanism has been suggested to explain a drug interaction between aspirin and PPIs. PPI reduce gastric acid production by inhibiting the enzyme responsible for gastric acid secretion from gastric parietal cells: the H^+/K^+-exchanging adenosine triphosphatase (Fig. 2) [103]. According to the pH partition hypothesis [38], modifying the intragastric milieu by raising pH potentially reduces the bioavailability of drugs, in particular those being absorbed across the gastric mucosal membrane, such as aspirin [39]. During PPI treatment, intragastric pH does indeed rise above the pK_a (3.5) of aspirin potentially reducing its lipophilicity and gastric absorption [39, 40].

The activity of CYP2C19 is altered by PPIs, which are CYP2C19 substrates and thus may interact with clopidogrel and prasugrel metabolism through competitive antagonism. It follows that the interaction between PPIs and thienopyridines depends on the capacity of each PPI subtype to inhibit CYP2C19. Omeprazole, esomeprazole, and lansoprazole have a relatively high potency towards CYP2C19, while rabeprazole and pantoprazole have less potency.

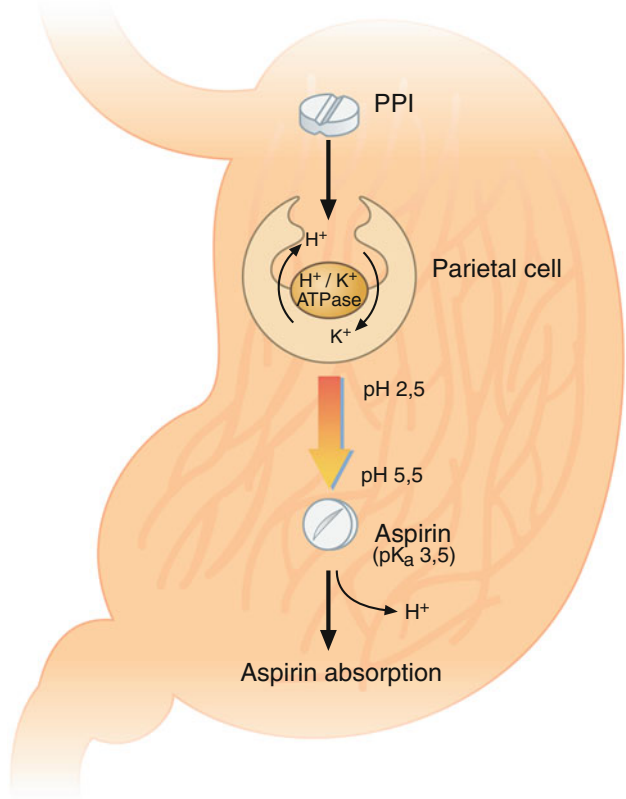

Fig. 2 Suggested biochemical background for a drug interaction between aspirin and proton pump inhibitors (Adapted from Würtz and Grove [113]). Under normal physiological conditions, aspirin is absorbed in its non-ionized lipid state across the gastric mucosal barrier. Proton pump inhibitors inhibit the H^+/K^+-exchanging ATPase of the gastric parietal cells. Intragastric pH rises above the pK_a (3.5) of aspirin and reduces the lipophilicity of aspirin thereby lowering its gastric absorption. *ATP* adenosine triphosphate, *PPI* proton pump inhibitor

Accordingly, PPIs with low inhibitory effect on CYP219 are recommended if combined treatment with a thienopyridine and a PPI is required [35].

7 Interactions Between Proton Pump Inhibitors and Aspirin

The number of studies addressing a drug interaction between PPIs and aspirin remains relatively sparse (Table 2). Evidence is gathered from statistical modeling [41], pharmacokinetic measurements [42–44], large observational studies with clinical end points [45, 46], *post-hoc* analyses of large clinical trials [47], smaller interventional studies with clinical end points [48], or derived from studies utilizing *ex vivo* platelet function tests as a marker for the clinical effect of aspirin [49–53].

In previous animal studies, omeprazole reduced the analgesic and antipyretic effects of aspirin, which was measured by means of reduced gastric aspirin absorption [40, 54]. Similar findings were reported from a study of humans [55]. On the other hand, Iñarrea et al. measured the antiplatelet effect of aspirin in 14 healthy individuals before and after 4 days of 20 mg/day omeprazole treatment. Bleeding time and platelet aggregation levels were both unaffected by omeprazole [49]. In a randomized cross-over study of 24 healthy individuals, 100 mg of enteric-coated aspirin was given for 4 weeks with or without concomitant 30 mg/day lansoprazole. Thereafter, participants were switched to the other treatment regimen for another 4 weeks. Platelet function assessed by light transmittance aggregometry (APACT 4) and shear stress-stimulated closure time (Platelet Function Analyzer-100) suggested no difference in antiplatelet potency between aspirin with lansoprazole and aspirin alone [51]. Another study showed no pharmacokinetic interaction based on measurements of acetylsalicylic acid plasma concentrations in 55 healthy volunteers subjected to three treatment periods comprising esomeprazole, aspirin, and both [42]. Subsequently, the authors evaluated the bioequivalence between 40 mg esomeprazole and 325 mg aspirin given separately and as a single-tablet formulation including both agents. Analyzing the same end point of acetylsalicylic acid maximal plasma concentration, the two treatment schemes remained bioequivalent [43]. In a randomized cross-over study, 29 healthy individuals received low-dose aspirin with or without esomeprazole 20 mg once daily for 5 days followed by 14-day washout and subsequent treatment cross-over. Platelet aggregation evaluated with the VerifyNow® Aspirin test did not differ between the two treatment regimens, neither did levels of serum thromboxane B_2 [53].

In a pharmacodynamic study by Würtz et al., we included 418 aspirin-treated patients with stable coronary artery disease, of whom 54 were PPI users. In multivariable adjusted analyses, platelet aggregation (median 180 [interquartile range 119–312] vs. 152 [84–226] aggregation units*minute, $p = 0.013$) and platelet activation measured by soluble serum P-selectin (88.5 [65.2–105.8] vs 75.4 [60.0–91.5] ng/ml, $p = 0.013$) were significantly higher in patients treated with a PPI. In contrast to many other pharmacodynamic studies, a non-enteric coated formulation of aspirin was used in this study, which may be important given that gastric absorption of enteric-coated aspirin has been shown to increase during omeprazole-treatment [56]. The findings by Würtz et al. were supported by a large Danish register-based study of 19,925 patients suffering a first-time MI. All patients were treated with aspirin, while almost 30,000 patients treated with clopidogrel were excluded. The risk of cardiovascular death, recurrent MI, or stroke was increased in patients receiving a PPI (adjusted hazard ratio 1.46, 95 % CI 1.33–1.61), but not in patients receiving a gastroprotective H_2 receptor antagonist [45].

Whellan et al. tested the hypothesis that a single-tablet formulation (PA32540) [57] of enteric-coated aspirin (325 mg) and immediate-release omeprazole (40 mg) would reduce gastrointestinal complications without promoting thrombotic complications compared to aspirin

Table 2 Studies evaluating the association between proton pump inhibitor use and the antiplatelet effect of aspirin

Study	Participants (n)	Antiplatelet treatment	PPI type (n)	Design	Test/end point	Main results
Iñarrea et al. [49]	Healthy volunteers (14)	Non enteric-coated ASA 125 mg ± PPI	Omeprazole	Cross-over study	Skin bleeding time, light transmittance aggregometry (Aggrecorder), plasma levels of ASA and salicylic acid	Omeprazole did not affect bleeding time, platelet aggregation, or plasma levels of ASA and salicylic acid
Adamopoulos et al. [51]	Hypertensive subjects with indication for primary prophylaxis with aspirin	Enteric-coated ASA 100 mg ± PPI	Lansoprazole	Cross-over study	Light transmittance aggregometry (APACT4) and closure time (PFA-100)	Platelet aggregation and closure time during ASA treatment were unaffected by lansoprazole
Niazi et al. [42]	Healthy volunteers (55)	Non enteric-coated ASA 325 mg ± PPI	Esomeprazole	Cross-over study	Maximum ASA plasma concentration and steady-state area under the concentration-time curve	Pharmacokinetic measures of ASA were unaffected by esomeprazole
Kasprzak et al. [50]	PCI for ACS (31)	Enteric-coated ASA 75 mg ± PPI	Pantoprazole	Cross-over study	Platelet aggregometry (Multiplate Analyzer)	Reduced platelet aggregation in PPI users compared to non-users
Andersson et al. [53]	Healthy volunteers (29)	ASA 81 mg (coating not specified) ± PPI	Esomeprazole	Cross-over study	Optical aggregometry (VerifyNow Aspirin) and thromboxane B_2	The drop in platelet aggregation and thromboxane B_2 from baseline (no aspirin) to post-treatment was equal whether treatment was ASA + PPI or ASA alone
Würtz et al. [52]	Coronary artery disease (418)	Non enteric-coated ASA 75 mg PPI: 54 users, 364 non-users	Pantoprazole, esomeprazole, omeprazole, and lansoprazole	Cohort study	Platelet aggregometry (Multiplate Analyzer) and platelet activation level (soluble P-selectin)	Increased platelet aggregation, platelet activation, and thromboxane B_2 levels in PPI users compared to non-users

Charlot et al. [45]	30-day survivors of a first-ever MI between 1997 and 2006 (19,925)	ASA (dose and coating not specified), clopidogrel users excluded	Pantoprazole, omeprazole, lansoprazole, and esomeprazole	Retrospective nationwide register-based study	1-year composite of cardiovascular death, MI, or stroke	PPI use, but not H_2 receptor antagonist use, at any time following discharge associated with increased risk of the composite end point compared with non-use in the multivariable adjusted (multivariable adjusted hazard ratio 1.46, 95 % CI 1.33–1.61; propensity score-matched hazard ratio 1.61, 95 % CI 1.45–1.79)
Dunn et al. [47]	*Post-hoc* analysis of the CAPRIE trial Previous MI, ischemic stroke, or peripheral vascular disease (ASA arm, 9586)	ASA 325 mg or CLO 75 mg	Omeprazole and lansoprazole	*Post-hoc* analysis of a clinical trial	1-year composite of ischemic stroke, MI, or vascular death	In ASA-treated patients, PPI use was not associated with an increased risk of the composite end point compared to non-use (adjusted hazard ratio 1.04, 95 % CI 0.70–1.57)
Whellan et al. [48]	Users of ASA for secondary cardiovascular prevention (1049)	Enteric-coated ASA 325 mg ± PPI PPI was given as a single-tablet combination of ASA and omeprazole	Omeprazole	Randomized PPI assignment	6-month major adverse cardiovascular events and upper gastrointestinal symptoms	The rate of cardiovascular events was equal between treatment arms, but upper gastrointestinal symptoms were reduced with the combination tablet compared to ASA alone
Garcia Rodriguez et al. [46]	Users of ASA for secondary cardiovascular prevention (39,513) or in patients with previous ACS (42,542) between 2000 and 2007	ASA 75–300 mg (>85 % received 75 mg, coating not specified)	Not specified	Cohort study	Composite of non-fatal MI or coronary death	PPI use not associated with increased risk of non-fatal MI or coronary death in neither of the study cohorts (pooled relative risk 0.96, 95 % CI 0.62−1.48)

ACS acute coronary syndrome, *ASA* acetylsalicylic acid (aspirin), *CI* confidence interval, *CLO* clopidogrel, *MI* myocardial infarction, *PPI* proton pump inhibitor

alone. A coordinated-delivery tablet was used, in which omeprazole is embedded within a film coat enabling instantaneous dissolution, whereas aspirin release occurs only when gastrointestinal pH reaches a level of 5.5 [48]. The primary end point of endoscopically verified gastric ulcer at 6 months occurred less frequently among users of the combined formulation (3.2 % vs. 8.6 %, $p < 0.001$), while the rate of major adverse cardiovascular events did not differ between treatment arms (1.7 % vs. 2.5 %, $p > 0.05$). Importantly, the study had a low rate of cardiovascular events, for which the study was underpowered [48].

Most recently, the combined analysis of coronary event rates in two large cohorts of first-time users of aspirin for secondary prevention was published [46]. The first cohort included first-time users of aspirin for any secondary prevention indication, while the second cohort consisted of patients who initiated aspirin treatment following an acute coronary event. Looking at the cohorts separately or combined, PPI treatment was not associated with an increase in the risk of non-fatal MI or coronary death [46], and the results thus contrast those of the above mentioned large registry-based study [45].

A recent analysis showed that co-prescription of low-dose aspirin and a PPI turned out to be cost-effective by reducing gastrointestinal as well as cardiovascular events [41]. This cost-effectiveness analysis was based on previously published clinical studies, and the cardiovascular benefit appeared to be partly driven by increased adherence to aspirin in PPI users. Furthermore, even in patients with cardiovascular disease who continue aspirin treatment after suffering a gastrointestinal bleeding event, aspirin seems to confer a net clinical benefit because the risk of bleeding is outbalanced by improved cardiovascular outcome [58]. This was shown in a small randomized study, in which aspirin users who suffered a peptic ulcer bleeding were given either aspirin or placebo on top of pantoprazole. While increasing the risk for recurrent gastrointestinal bleeding, continued aspirin treatment reduced mortality [58]. Although these interesting results should be confirmed in larger studies, they stress that discontinuing aspirin upon gastrointestinal events should be carefully considered in patients with increased risk of cardiovascular events.

Altogether, studies exploring whether PPIs reduce the effect of aspirin are sparse. Studies are small and relatively heterogeneous and this, coupled with the fact that only one randomized, yet underpowered, study has been performed makes it premature to change clinical recommendations at present as reflected in current guidelines [4, 5, 35].

8 Interaction Between Proton Pump Inhibitors and Clopidogrel

8.1 Pharmacological Studies

Since 2006, several observational studies have reported an attenuation of the antiplatelet effect of clopidogrel when given concomitantly with PPI, particularly omeprazole (Table 3). Gilard et al. used the vasodilator-stimulated phosphoprotein (VASP) phosphorylation assay to assess platelet function 48 h after treatment initiation in 105 patients undergoing angiography. All patients were treated with aspirin and clopidogrel, and 24 patients were also treated with a PPI. PPI users had a significantly higher platelet reactivity index than non-users (61.4 ± 23.2 % vs. 49.5 ± 16.3 %, $p = 0.007$) [59]. Indeed, the VASP assay reflects the extent of intracellular $P2Y_{12}$ pathway inhibition and is therefore considered the pharmacologically most specific test of platelet inhibition by ADP receptor antagonists [60]. Pursuing more firm documentation, the authors conducted the double-blind placebo-controlled OCLA trial published in 2008 [61]. A total of 124 patients undergoing PCI received standard doses of aspirin and clopidogrel and were randomized to either omeprazole 20 mg/day or placebo for 7 days. Platelet inhibition was assessed at days one and seven using the platelet reactivity VASP index. On day seven, the omeprazole-arm had significantly higher platelet reactivity than the placebo-arm (51.4 ± 16.4 % vs. 39.8 ± 15.4 %,

Table 3 Studies with pharmacokinetic and/or pharmacodynamic end points suggesting an association between proton pump inhibitor use and the antiplatelet effect of clopidogrel

Study	Participants (n)	Antiplatelet treatment	PPI type (n)	Random PPI assignment?	Test	Main results
Gilard et al. [59]	High-risk coronary angioplasty (105)	ASA and CLO for a minimum of 48 h	Not specified	No	VASP-PRI	Increased PRI in PPI users (61.4 ± 23.2 vs. 49.5 ± 16.3, p = 0.007)
		PPI: 24 users, 81 non-users				No association found with statins, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonist, or beta blockers
Gilard et al. [61]	Elective PCI (124)	ASA and CLO + PPI or placebo (7 days)	Omeprazole	Yes	VASP-PRI	Increased PRI in the PPI-arm at day 7 (39.8 ± 15.4 % vs. 51.4 ± 16.4 %), but not at day 1 (83.2 ± 5.6 % vs. 83.9 ± 4.6 %, not significant)
Small et al. [63]	Healthy volunteers (24)	CLO 300 mg or PRA 60 mg ± PPI	Lansoprazole	Yes (cross-over design)	Pharmacokinetics: Maximum CLO plasma concentration and area under the concentration-time curve	PPI use did not affect the pharmacokinetics of CLO, but tended to reduce maximal inhibition of platelet aggregation, which was most pronounced in subjects with aggregation levels
					Pharmacodynamics: Optical platelet aggregometry	
O'Donoghue et al. [64]	Elective PCI (201). *Post-hoc* analysis of PRINCIPLE-TIMI 44	Random assignment to CLO 600 mg LD/300 mg MD or PRA 60 mg LD/10 mg MD	Not specified	No	Light transmittance aggregometry	Reduced platelet inhibition in CLO-treated PPI users compared to non-users 2, 6, and 18–24 h after PCI
						2 h: 10.4 ± 16.2 % vs. 24.2 ± 20.5 %, p = 0.003
						6 h: 23.2 ± 19.5 % vs. 35.2 ± 20.9 %, p = 0.02
						18–24 h: 23.8 ± 14.4 % vs. 36.1 ± 20.8 %, p = 0.03
						No differences 30 min nor 15 days after PCI

(continued)

Table 3 (continued)

Study	Participants (n)	Antiplatelet treatment	PPI type (n)	Random PPI assignment?	Test	Main results
Sibbing et al. [65]	Scheduled for control angiography after PCI (1000)	ASA 75 mg and CLO 75 mg	Pantoprazole, omeprazole, and esomeprazole	No	Platelet aggregometry (Multiplate Analyzer)	Increased platelet aggregation in omeprazole users compared to non-users (295.5 [IQR 193.5–571.2] aggregation units*min vs. 220.0 [IQR 143.8–388.8] aggregation units*min; $p = 0.001$). No differences between pantoprazole/esomeprazole users and PPI non-users
Zuern et al. [67]	Elective or urgent PCI (1425)	ASA 100 mg and CLO 600 mg LD/75 mg MD	Pantoprazole, esomeprazole, and omeprazole	No	Optical aggregometry (Chronolog Lumi Aggregometer)	Increased platelet aggregation in PPI users compared to non-users (34.0 ± 21.4 % vs. 29.8 ± 20.2 %, $p < 0.001$). PPI use was an independent predictor of residual platelet aggregation
Cuisset et al. [66]	PCI for non-ST elevation MI (104)	ASA 250 mg LD/75 mg MD and CLO 600 mg LD/150 mg MD plus PPI	Omeprazole and pantoprazole	Yes	VASP-PRI and optical aggregometry (PAP4 Aggregometer)	12–24 h after LD: No differences in terms of PRI or aggregation 1 month after discharge: Increased PRI in omeprazole users compared to pantoprazole users (36 ± 20 % vs. 48 ± 17 %, $p = 0.007$). Using PRI, more CLO non-responders among omeprazole users than pantoprazole users (44 % vs. 23 %, $p = 0.04$. Odds ratio 2.6, 95 % CI 1.2–6.2). No differences found by aggregometry

Fontes-Carvalho et al. [68]	PCI for MI (34)	ASA 150 mg and CLO 75 mg plus PPI	Omeprazole or pantoprazole (cross-over, 1 month washout)	Yes (cross-over design)	Optical aggregometry (VerifyNow P2Y12)	1 month after PCI: Significant increase in platelet aggregation during omeprazole-treatment compared to PPI non-use (235 ± 58 PRU vs. 201 ± 48, $p < 0.001$). The number of clopidogrel non-responders almost doubled during omeprazole-treatment. No differences seen with pantoprazole compared to PPI non-use
Angiolillo et al. [69]	Healthy volunteers (282)	CLO 300 mg LD/75 mg MD	Omeprazole or pantoprazole	Yes (cross-over design)	VASP-PRI and platelet aggregometry	Significant increase in platelet aggregation and PRI during omeprazole-treatment compared to PPI non-use. The drug interaction was not mitigated by increasing clopidogrel dose or administering clopidogrel and omeprazole apart (spaced administration). Pantoprazole only affected platelet aggregation and VASP-PRI sparsely compared to omeprazole
Parri et al. [73]	Primary PCI for ST elevation MI (105)	ASA 100 mg and CLO 300 mg LD/75 mg MD and optional glycoprotein IIb/IIIa inhibition	Pantoprazole or ranitidine (H_2 receptor antagonist)	Yes	Light transmittance aggregometry and closure time (PFA-100)	Increased maximal platelet aggregation stimulated with ADP in pantoprazole users compared to ranitidine users after correction for CYP2C19*2 genotype both five (median 29 % vs. 19 %, $p = 0.01$) and 30 days (median 35 % vs. 27 %, $p = 0.03$) after PCI. No difference observed with other agonists or with the PFA-100

ACS acute coronary syndrome, *ASA* acetylsalicylic acid (aspirin), *CI* confidence interval, *CLO* clopidogrel, *LD* loading dose, *MD* maintenance dose, *MI* myocardial infarction, *PPI* proton pump inhibitor, *VASP-PRI* vasodilator-stimulated phosphoprotein platelet reactivity index

$p < 0.0001$) [61]. Given the rigorous design of the OCLA trial, the results were convincing, and many, but not all [62], subsequent studies supported the findings [63–69].

Of interest, some studies suggested a differential impact of proton pump inhibitors on the antiplatelet effect of clopidogrel. Four studies independently argued in favor of preferentially using non-omeprazole PPIs, namely pantoprazole, to avoid a drug interaction [65, 66, 68, 69]. In the PACA study, a total of 104 patients with non-ST elevation ACS were randomized to omeprazole or pantoprazole on top of aspirin and clopidogrel. After 1 month, platelet inhibition assessed by the VASP index was significantly greater with clopidogrel in patients receiving pantoprazole (36 ± 20 % vs. 48 ± 17 %, $p < 0.007$) [66].

Angiolillo et al. performed a complex study including four randomized, placebo-controlled, cross-over studies among 282 healthy individuals. The purpose was (1) to explore any drug interaction between clopidogrel and omeprazole, (2) to test if such interaction could be mitigated by administering clopidogrel and omeprazole 12 h apart, (3) or by doubling the clopidogrel maintenance dose to 150 mg daily, and (4) to compare the drug interaction caused by omeprazole with that caused by pantoprazole. Essentially, the study showed that omeprazole, but not pantoprazole, reduced the pharmacodynamic effect of clopidogrel through a pH-independent mechanism mediated by the CYP2C19 enzyme [69]. Since all PPIs lower gastric pH to roughly the same extent at equipotent doses [70, 71], the differential impact of PPIs on the platelet inhibitory effect of clopidogrel may rather be attributable to differences in the inhibitory potency towards CYP2C19. In particular, pantoprazole seems to interfere little, if at all, with the metabolism of clopidogrel and is known to have very little affinity for CYP2C19 [72]. Notwithstanding, a recent study suggested that pantoprazole increases platelet aggregation irrespective of *CYP2C19*2* genotype in clopidogrel-treated patients with ST elevation MI undergoing PCI [73]. According to a *post-hoc* subgroup analysis of the PRINCIPLE-TIMI 44 trial, treatment with a PPI and clopidogrel increased the number of non-responders to a clopidogrel loading dose in the acute phase and to a 150 mg daily maintenance dose 15 days after PCI [64].

Few studies have investigated to what extent the influence of PPIs on clopidogrel's antiplatelet potency differs according to *CYP2C19* genotype, however there is evidence suggesting that *CYP2C19* inhibition is the main cause of drug-drug interaction between clopidogrel and PPIs, especially omeprazole [74]. Furuta et al. reported that the likelihood of converting from clopidogrel responder to non-responder during PPI treatment (omeprazole, lansoprazole, rabeprazole) was much higher in slow metabolizers carrying the *CYP2C19*2* and/or **3* allele [75]. Based on these findings, which were derived from healthy volunteers only, PPI treatment seems to be particularly problematic in patients carrying a *CYP2C19 *2* and/or **3* allele, as supported by a very recent clinical study [76]. Depta et al. showed that among PPI users, *CYP2C19*2* and *CYP2C19*17* carriers tended to have a poorer 1-year clinical outcome, while carriers of *CYP2C19*1* did not. However, there are contrasting reports. One study showed no difference between *CYP2C19* genotypes [77], while two studies showed that fast metabolizers (*CYP2C19 *1* homozygotes) experienced the largest reduction in clopidogrel's antiplatelet potency [78, 79].

In summary, there is quite strong evidence that PPIs reduce the pharmacodynamic effect of clopidogrel. This has been documented with conventional aggregometry as well as with VASP assays. However, pharmacodynamic end points do rarely translate directly into comparable clinical end points.

8.2 Clinical Studies

Since 2008, numerous studies investigating hard clinical end points have been performed to determine if the drug interaction documented in pharmacological studies would affect the risk of adverse clinical outcomes (Table 4). Most

Table 4 Studies with clinical end points suggesting an association between proton pump inhibitor use and the antiplatelet effect of clopidogrel

Study	Participants (n)	Antiplatelet treatment	PPI generic (n)	Random PPI assignment?	End point	Main results
Juurlink et al. [84]	Acute MI (13,636). Cases (734) = patients who died or were readmitted for MI within 90 days after hospital discharge. Controls (2057) = patients at risk who were not readmitted for MI	CLO at discharge (dose not specified) Among cases, 26.4 % were current PPI users Among controls, 20.6 % were current PPI users	Not specified	No	90-day and 1-year readmission for acute MI	Current PPI use associated with increased risk of reinfarction compared with non-use (adjusted odds ratio 1.27, 95 % CI 1.03–1.57). Former PPI use showed no association
Ho et al. [85]	ACS (8205).	CLO at discharge (dose not specified). 90 % received ASA 63.9 % were prescribed PPI a at discharge, during follow-up, or both and 36.1 % were not	Omeprazole, rabeprazole, lansoprazole, and pantoprazole. One third received more than one PPI type	No	All-cause mortality or rehospitalization for ACS	PPI use at any time following discharge associated with increased risk of the composite end point compared with non-use (adjusted odds ratio 1.25, 95 % CI 1.11–1.41). The risk for rehospitalization for ACS alone was increased by 86 % PPI use not associated with clinical outcomes in patients not taking CLO
Kreutz et al. [83]	Previous PCI (16,690).	CLO 75 mg (0.3 % received 150 mg). ASA use not specified 40.9 % were prescribed a PPI during the 1-year study period	Omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole	No	1-year composite of hospitalization for a cerebrovascular event or ACS, cardiovascular death, or coronary revascularization	PPI use at any time following discharge associated with increased risk of the composite end point compared with non-use (adjusted hazard ratio 1.51, 95 % CI 1.39–1.64). No differences between PPI generics PPI use not associated with clinical outcomes in patients not taking CLO

(continued)

Table 4 (continued)

Study	Participants (n)	Antiplatelet treatment	PPI generic (n)	Random PPI assignment?	End point	Main results
Siller-Matula et al. [114]	Meta-analysis of randomized studies, *post-hoc* analyses of randomized studies, and observational studies with data on PPI exposure in CLO-treated patients (159,138)	CLO ± PPI	Omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole	No	Major adverse cardiac events, MI, stent thrombosis, death, and gastrointestinal bleeding	Overall conclusion: PPI use might be associated with increased risk of cardiovascular events, but does not seem to influence mortality
Dunn et al. [47]	*Post-hoc* analyses of the CAPRIE and CREDO trials	CAPRIE: ASA 325 mg or CLO 75 mg	CAPRIE: Lansoprazole and omeprazole	No	CAPRIE: 1-year composite of ischemic stroke, MI, or vascular death	CAPRIE: In CLO-treated patients, PPI use associated with an increased risk of the composite end point compared to non-use (adjusted hazard ratio 2.39, 95 % CI 1.74–3.28)
	CAPRIE: Previous MI, ischemic stroke, or peripheral vascular disease (CLO arm, 9599)	CREDO: CLO 300 mg LD/75 mg MD for 1 year or CLO 75 mg for 28 days (placebo thereafter)	CREDO: Lansoprazole, omeprazole, pantoprazole, and rabeprazole		CREDO: 1-year composite of all-cause death, MI, or stroke	CREDO: In CLO-treated patients, PPI use associated with an increased risk of the composite end point compared to non-use (hazard ratio 1.67, 95 % CI 1.06–2.64). PPI use associated with a similar risk in patients not treated with CLO
	CREDO: Planned to undergo PCI (CLO arm, 1053)					
Kwok et al. [90]	Meta-analysis of randomized and non-randomized studies with data on PPI exposure in CLO-treated patients (222,311)	CLO ± PPI	Omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole	No	Major adverse cardiovascular events or MI	Overall conclusion: PPI use seems to be associated with clinical outcome, but also in the absence of CLO. Uncontrolled confounding is an important limitation of studies investigating the influence of PPI use on cardiovascular outcome in CLO-treated patients

Rassen et al. [82]	Previous PCI or previous hospitalization for ACS (18,565, pooled from 3 cohort studies)	CLO (dose not specified). ASA use not specified, but likely to be almost 100 % 21.5 % were prescribed a PPI during the 6-month study period	Omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole	No	6-month composite of hospitalization for MI and all-cause mortality	PPI use associated with an increased risk of the composite end point compared to non-use after multivariable adjustment (relative risk 1.32, 95 % CI 1.08–1.61). In propensity score-matched analyses, results were not significant
Burkard et al. [88]	ACS or stable coronary artery disease undergoing PCI (801)	ASA 250–500 mg LD/100 mg MD and CLO 300 mg LD/75 mg MD 13 % were prescribed a PPI at discharge	Omeprazole, esomeprazole, pantoprazole, and lansoprazole	No	3-year composite of cardiac death, non-fatal MI, and target vessel revascularization	PPI use associated with an increased risk of the composite end point compared to non-use (30.3 % vs. 20.8 %, $p = 0.027$) and MI (14.7 % vs. 7.4 %, $p = 0.01$), but not target vessel revascularization or cardiac death
Gaglia et al. [86]	ACS or stable coronary artery disease undergoing PCI (820)	ASA 325 mg LD/325 mg MD and CLO 300–600 mg LD/MD not specified 38.8 % were prescribed a PPI at discharge	Omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole	No	1-year composite of all-cause mortality, MI, target vessel revascularization, and stent thrombosis	PPI use associated with an increased risk of the composite end point compared to non-use (adjusted hazard ratio 1.8, 95 % CI 1.1–2.7). No differences between PPI generics
Bhurke et al. [87]	ACS (10,101)	CLO (dose not specified). ASA use not specified 41.4 % were prescribed a PPI during the study period	Omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole	No	Rehospitalization or emergency department visit for MI, PCI, or intermediate coronary syndrome	PPI use at any time following ACS diagnosis associated with an increased risk of the composite end point compared to non-use (propensity score-matched hazard ratio 1.4, 95 % CI 1.2–1.7)

(continued)

Table 4 (continued)

Study	Participants (n)	Antiplatelet treatment	PPI generic (n)	Random PPI assignment?	End point	Main results
Bhatt et al. [80]	ACS or elective PCI (3761)	ASA 75–325 mg MD and CLO 75 mg MD Patients were randomized to a fixed-dose separate-release combination of clopidogrel (75 mg) and omeprazole (20 mg) or clopidogrel alone	Omeprazole	Yes	Primary cardiovascular end point: 6-month composite of cardiovascular death, non-fatal MI, revascularization, or stroke. The study was powered for the primary gastrointestinal end point of overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction, or perforation	PPI use reduced the 6-month rate of gastrointestinal events (hazard ratio 0.34, 95 % CI 0.18–0.63) and upper gastrointestinal bleeding (hazard ratio 0.13, 95 % CI 0.03–0.56) without increasing the rate of cardiovascular events (hazard ratio 0.99, 95 % CI 0.68–1.44)

ACS acute coronary syndrome, *ASA* acetylsalicylic acid (aspirin), *CI* confidence interval, *CLO* clopidogrel, *LD* loading dose, *MD* maintenance dose, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *PPI* proton pump inhibitor

studies are register-based studies or *post-hoc* sub-analyses of clinical trials, in which PPI treatment was not randomly assigned, which potentially introduces confounding by indication. So far, only one large randomized placebo-controlled trial has been performed showing no interaction [80]. In general, some studies suggest an interaction [47, 81–88], whereas others do not [47, 64, 80, 82, 89, 90].

Ho et al. performed a retrospective study of 8205 ACS patients treated with clopidogrel, of which two-thirds were prescribed a PPI at discharge, during follow-up, or both. Upon adjustment, any PPI prescription during follow-up (n = 5244) was associated with an increased risk of death or ACS rehospitalization compared with the use of clopidogrel only (odds ratio 1.25, 95 % CI 1.11–1.41) [85]. In a population-based case-control study of 734 cases and 2057 controls, Juurlink et al. found that in clopidogrel-treated patients suffering an MI, the 90-day risk of re-infarction was increased by 40 % in current users of a non-pantoprazole PPI, whereas the risk was unchanged in pantoprazole users. Importantly, PPI use did not affect mortality risk [84]. In the Clopidogrel Medco Outcomes Study, including 16,690 clopidogrel-treated patients undergoing PCI, a more than 50 % increased risk of major adverse cardiovascular events was found in patients receiving adjunctive PPI treatment with whatever type of PPI. A subgroup analysis of PPI treatment before PCI among 1641 patients showed that the cardiovascular risk was not associated with PPI exposure in the absence of clopidogrel treatment [83].

Dunn et al. looked at data from the well-known CAPRIE (aspirin vs. clopidogrel in ACS) and CREDO (clopidogrel vs. placebo in PCI) trials. These are the only two placebo-controlled trials using clopidogrel as an active comparator, in which PPI use was documented [47]. In CAPRIE, clopidogrel increased the 1-year risk for the primary end point (ischemic stroke, MI, or vascular death) among PPI users (estimated hazard ratio 2.66, 95 % CI 0.94–7.50), while lowering it for non-users (0.90, 95 % CI 0.83–0.99). Furthermore, PPI use was associated with worse outcomes in patients treated with clopidogrel (estimated hazard ratio 2.39, 95 % CI 1.74–3.28), but not with aspirin (1.04, 95 % CI 0.70–1.57). In CREDO, clopidogrel did not influence the risk of the primary end point (all-cause death, MI, or stroke) after 1 year among PPI users (0.82, 95 % CI 0.48–1.40), while lowering it for PPI non-users (0.71, 95 % CI 0.52 to 0.98) [47].

Charlot et al. performed a nationwide cohort study of Danish patients with a first-ever MI (n = 56,406). Among clopidogrel-treated patients, PPI use was associated with a 29 % increased risk of cardiovascular death or re-hospitalization for MI or stroke. Interestingly, no statistically significant interaction between clopidogrel and PPI use was found, and PPI use also increased cardiovascular risk by 29 % in patients not treated with clopidogrel [89]. This premise, that PPI use may be a marker of increased cardiovascular risk rather than the actual cause of this risk, is consistent with other studies [47, 91–94]. Importantly, this highlights unmeasured confounding as an important limitation of studies, in which PPI treatment is not assigned randomly.

Among three randomized placebo-controlled trials to address this topic [80, 95, 96], the trial that most soundly appraised and defined the impact of PPI treatment on cardiovascular protection accounted for by clopidogrel is the COGENT trial, published in 2010 [80]. In this trial, 3873 patients undergoing PCI were randomized to receive either clopidogrel and omeprazole (administered as a combination tablet of clopidogrel 75 mg and omeprazole 20 mg) or clopidogrel only on top of aspirin. As expected, PPI reduced upper gastrointestinal events (1.1 % vs. 2.9 %; hazard ratio 0.34, 95 % CI 0.18–0.63) and upper gastrointestinal bleeding (0.2 % vs. 1.2 %; hazard ratio 0.13, 95 % CI 0.03–0.56) at 6 months, and this was achieved without increasing cardiovascular event rates or mortality (4.9 % vs. 5.7 %, hazard ratio 0.99, 95 % CI 0.68–1.44) [80]. The primary limitation of COGENT was that the trial was halted prematurely due to lack of funding, thus making it underpowered for cardiovascular end

points. Furthermore, event rates were very low, and no genotyping was performed. Finally, the investigators employed a proprietary formulation of omeprazole and clopidogrel intended for the separated release of the two drugs. In theory, this would tend to attenuate a potential drug interaction [97, 98], although this hypothesis was discredited in a meticulous pharmacodynamic study [99]. Despite these important limitations, the key lesson learned from COGENT is that a clinically meaningful interaction between PPIs (omeprazole) and clopidogrel is unlikely, and even if PPIs reduce the antiplatelet effect of clopidogrel and/or aspirin, such effects seem to be outweighed by a reduction in bleeding events, presumably by increased adherence to antiplatelet medications. The results of two other randomized trials, although underpowered for clinical end points, suggest no increased cardiovascular risk in PPI users compared to non-users [95, 96].

Most recently, a meta-analysis scrutinized the conflicting results between randomized trials and observational studies [100]. In particular, co-treatment with dual antiplatelet therapy (aspirin and clopidogrel) and PPIs as a class was associated with a poor clinical outcome in patients with unstable angina or non-ST elevation MI. PPIs increased the 1-year composite end point (all-cause mortality and non-fatal MI) as well as the 1-year rates of all-cause mortality, non-fatal MI, and revascularization. In contrast, four randomized trials (omeprazole versus placebo) found no differences in terms of ischemic events. The authors conclude that unmeasured confounding in observational studies is the likely explanation of the discordant results between randomized trials and observational studies [100, 101].

9 Interaction Between Proton Pump Inhibitors and Prasugrel or Ticagrelor

Pharmacodynamic studies have shown that PPIs (lansoprazole, pantoprazole, and esomeprazole) do not reduce the antiplatelet effect of prasugrel among healthy individuals [63] or patients with ACS [102]. In a *post-hoc* analysis of PRINCIPLE-TIMI 44, in which platelet inhibition with clopidogrel vs. prasugrel was evaluated by platelet aggregometry, a modest difference was seen between patients with and without PPI treatment in the prasugrel-arm (69.6 ± 13.5 % vs. 76.7 ± 12.4 %, p = 0.054) [64]. However, in the TRITON-TIMI 38 trial comparing clopidogrel vs. prasugrel in ACS, PPI use was not associated with the occurrence of the primary end point for patients treated with prasugrel (adjusted hazard ratio 1.00, 95 % CI 0.84–1.20) [64].

Ticagrelor is not a prodrug (Table 1), and the antiplatelet effect of this drug is not dependent on the hepatic CYP system. Intuitively, a drug interaction between ticagrelor and PPIs is therefore unlikely. According to a *post-hoc* analysis of PLATO, the use of PPIs in the ticagrelor-arm was associated with increased risk of cardiovascular events. However, a similar association was seen with non-PPI antacid drugs (H_2 receptor antagonists) [94]. Non-use of gastroprotective agents (PPIs or H_2 receptor antagonists) was associated with a significantly better cardiovascular prognosis, which may indicate that the association between PPI use and cardiovascular events merely represents confounding rather than a true drug interaction [94].

10 Discussion

PPIs should be reserved for patients at increased risk of gastrointestinal complications, as reflected by European and American recommendations on the combined use of antiplatelet agents and PPIs [4, 5]. Patients at increased risk are those with previous ulcer or bleeding, but other important risk factors to consider are *Helicobacter pylori* colonization, hemorrhagic diathesis, high age (≥65 years), and concomitant use of drugs that may increase the risk of bleeding risk, such as anticoagulant drugs, non-steroidal anti-inflammatory drugs, steroids, *etc*. In the presence of these risk factors, PPIs should always be considered, simply because they are the most effective means to prevent gastrointestinal bleeding in high-risk patients [103]. PPIs with low potency towards

CYP2C19 (*e.g.* pantoprazole) may preferably be used with clopidogrel, although the clinical support for this recommendation is rather weak [35]. Concerning aspirin, low doses should be used. In the setting of ACS, cardiovascular protection with aspirin doses <100 mg is just as effective as higher doses, but with reduced risk of gastrointestinal bleeding [104].

Gastrointestinal discomfort is an important cause of non-adherence to antiplatelet medications, especially aspirin. This was reflected in the pivotal CAPRIE trial (aspirin 325 mg vs. clopidogrel 75 mg in cardiovascular high-risk patients), in which 40 % of patients who discontinued aspirin treatment did so because of dyspepsia [41, 105]. The importance of this can hardly be overestimated, as premature discontinuation of antiplatelet treatment in patients with cardiovascular disease dramatically increases the risk of adverse outcomes [106, 107]. This obviously argues in favor of concomitant PPI treatment to avoid gastrointestinal complications during antiplatelet treatment. On the other hand, the number of prescribed medications [108] and the dosing frequency [109] are known to be inversely related to treatment adherence. In essence, this means that the more medications prescribed by the doctor, the less likely the patient will be to adhere to drug therapy. Nonetheless, continued aspirin treatment in patients suffering aspirin-related gastrointestinal bleeding reduces overall mortality [58], and PPI co-treatment likely carries a beneficial risk-to-benefit profile in patients at risk of gastrointestinal complications [41]. In this context it is interesting that single pill combinations (aspirin + esomeprazole) have been developed and likely provide a level of platelet inhibition equal to that provided by aspirin alone [43]. Indeed, single pill combinations have been shown to increase treatment adherence by 30 % compared to the same drugs given as free-drug combinations [110]. A combination tablet containing aspirin and omeprazole (PA32540) has recently been tested in two phase III trials [48] and an open-label safety trial [57] for secondary cardiovascular prevention, while formulations combining an ADP receptor antagonist with a PPI have not been developed.

The intense debate throughout the last decade has been nourished mainly by studies, of which the design, end point, and/or statistical power was insufficient to definitively determine the clinical impact of combining PPIs with antiplatelet drugs. Extrapolating from surrogate end points (*e.g.* *ex vivo* platelet function) to hard clinical end points (*e.g.* MI or death) carries a considerable risk of reaching faulty conclusions. As documented in a recent systematic review, there are strong indications of reduced antiplatelet activity *ex vivo* in clopidogrel users taking a PPI, while data on the clinical consequences are controversial [111]. In conclusion, there is no one-to-one translation of impaired *ex vivo* platelet inhibition into adverse clinical outcome. In observational studies, statistical methods like multivariable adjustment and propensity score-matching may reduce, yet never eliminate the risk of residual confounding. The main problem is that cohort studies and registries are inherently limited by the fact that PPIs were not randomly assigned in the study population. True cause-and-effect relationships thus cannot be inferred. This, however, does not mean that non-randomized studies are redundant. They are inexpensive, practically feasible, and hypothesis-generating, and they often serve as precursors for randomized studies with more solid conclusions. Reflecting the suboptimal evidence in this field, the only large randomized clinical trial, the COGENT trial [80], was underpowered for its cardiovascular end point, thus leaving us with few definitive answers. Of particular importance, as suggested in several studies [47, 89, 91–94], we cannot exclude that PPI use merely represents a marker of increased cardiovascular risk rather than the actual cause of the risk.

11 Conclusion

Current evidence argues in favor of continued use of PPIs in patients at risk of gastrointestinal complications, particularly bleeding [4, 5, 35]. However, more studies are warranted, preferably randomized placebo-controlled trials, and we should embrace any attempt to advance our understanding of PPIs and antiplatelet drugs. Prasugrel and ticagrelor have recently been

introduced, but evidence is particularly sparse for these drugs. At present, clinically important drug interactions do not seem to exist between PPIs and antiplatelet drugs, but given the vast number of patients treated with these drugs, even minor drug interactions in subsets of patients may have profound clinical impact.

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The Risk of Thromboembolism in Users of Antidepressants and Antipsychotics

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Abstract

Arterial and venous thromboembolism are common causes of morbidity and mortality in the Western world. Mental disorders are also highly prevalent with a lifetime risk of experiencing any psychiatric disease ranging between 32 % and 37 %. Depression and schizophrenia may increase the risk of thromboembolism through genetic, behavioral, and biological mechanisms. Treatment of psychiatric patients with psychotropic drugs is imperative to improve quality of life and to reduce morbidity and mortality. However, studies have shown that psychotropic drugs themselves may modify the risk of arterial and venous thromboembolism, which should be taken into consideration when using these drugs in clinical practice. This association is, however, multifactorial, complex and susceptible to several confounding factors. Psychotropic drugs are widely prescribed, also among patients with cardiovascular disease. Therefore, understanding the association with thromboembolism and the underlying pathophysiological mechanisms is of major importance and will be reviewed in this chapter.

Keywords

Antidepressive agents • Depression • Psychotrophic drugs • Schizophrenia • Serotonin uptake inhibitors • Thromboembolism

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1 Introduction

Arterial and venous thromboembolism are frequent causes of morbidity and mortality in the Western world (World Health Organisation 2015; Oger 2000). Mental disorders are also highly prevalent with a lifetime risk of experiencing any psychiatric disease ranging between 32 % and 37 % (Pedersen et al. 2014). Depression is one of the most common mental disorders and is becoming increasingly prevalent with a lifetime risk higher than 15 % (Pedersen et al. 2014; Kessler et al. 2007), while the lifetime risk of schizophrenia and related disorders is smaller and has been reported to be approximately 4 % (Pedersen et al. 2014).

Depression may increase the risk of thromboembolism through genetic and behavioral mechanisms (*e.g.,* smoking and alcohol or drug abuse) as well as through biological mechanisms (*e.g.,* elevated levels of inflammatory biomarkers, autonomic dysfunction, elevated platelet activation, coagulation and platelet abnormalities, and vascular endothelial dysfunction) (Stapelberg et al. 2011). In addition, accumulating evidence suggests that depression and ischemic heart disease may in part represent different phenotypic expressions of the same genetic material (Lichtman et al. 2014). Accordingly, genes related to inflammation, platelet aggregation and the serotonin system may be predictors of both depression and ischemic heart disease (Lichtman et al. 2014). Likewise, similar mechanisms may play important roles for the risk of thromboembolism in patients with other mental disorders.

Treatment of psychiatric patients with psychotropic drugs is imperative to improve quality of life and to reduce morbidity and mortality (Sadock et al. 2009). Several psychotropic drugs exist of which the most commonly used will be discussed in this chapter. A classification of antidepressants and antipsychotics is provided in Table 1. Selective serotonin reuptake inhibitors (SSRI) are the most frequently prescribed antidepressant drugs owing to a perceived superior safety and tolerability profile compared with other antidepressants (Draper and Berman 2008; Harman et al. 2009; Newman and Schopflocher 2008). Second and third generation antipsychotics are also gaining ground at the expense of older antipsychotics, mainly due to fewer side effects (Leucht et al. 2013).

Table 1 Classification of antidepressants and antipsychotics

Antidepressants
Selective serotonin reuptake inhibitors (SSRI)
Serotonin and norepinephrine reuptake inhibitors (venlafaxine, duloxetine)
Noradrenergic and specific serotonergic antidepressants (mirtazapine, mianserine)
Tricyclic antidepressants
Antipsychotics
Typical antipsychotics (First generation)[a]
Low-potency
High-potency
Atypical antipsychotics (Second and third generation)

[a]Typical antipsychotics are classified on a spectrum of low to high potency, with potency referring to the ability of the drug to bind dopamine receptors

Importantly, studies have shown that psychotropic drugs *per se* may modify the risk of arterial and venous thromboembolism, which should be taken into consideration when using these drugs in clinical practice. The association with cardiovascular disease is, however, multifactorial and complex. Because psychotropic drugs are widely prescribed, also among patients with cardiovascular disease, understanding the association with thromboembolism and the underlying pathophysiological mechanisms is of great importance and will be reviewed in this chapter.

2 Antidepressants and Arterial Thromboembolism

Ischemic heart disease and stroke are major causes of death worldwide (World Health Organisation 2015). Several studies have addressed the association between antidepressants, particular SSRI, and the risk of arterial cardiovascular events, such as stroke and myocardial infarction, in the general population (MacDonald et al. 1996a; Meier et al. 2001; Bak

et al. 2002; Hamer et al. 2011), the elderly (Trifiro et al. 2010), patients with cardiovascular disease (Monster et al. 2004), and in postmenopausal women (Smoller et al. 2009). Noteworthy, the results of studies investigating the risk of myocardial infarction among SSRI users have been inconclusive with some studies suggesting a *protective effect* (relative risk estimates between 0.4 and 0.9) (Meier et al. 2001; Monster et al. 2004; Smoller et al. 2009; Schlienger et al. 2004; Sauer et al. 2001, 2003; Cohen et al. 2000; Kimmel et al. 2011), others *no effect* (de Abajo 2011) and even an *increased risk* (relative risk estimates between 1.4 and 1.9) (Hamer et al. 2011; Tata et al. 2005; Hippisley-Cox et al. 2001; MacDonald et al. 1996b; Blanchette et al. 2008) has been reported.

Recently, a meta-analysis of 13 studies assessed the association between SSRI and stroke found an increased risk of all types of stroke (odds ratio 1.40, 95 % CI: 1.09–1.80), ischemic stroke (odds ratio 1.48, 95 % CI: 1.08–2.02) and hemorrhagic stroke (odds ratio 1.32, 95 % CI: 1.02–1.71) (Shin et al. 2014). This association was more pronounced in the elderly than in the general population group. In the same study, when restricting analyses to studies in which confounding by depression was addressed, the risk of stroke among SSRI users compared with non-users was still significantly elevated. This slightly increased risk may be partly explained by subclinical cardiovascular disease preceding the depression, since depression in elderly people are often caused by "silent infarcts" as a result of an ongoing and long-lasting atherosclerotic process (Taylor et al. 2013; Xekardaki et al. 2012; Wu et al. 2014). Consequently, the use of SSRI might be more frequent among individuals with subclinical cardiovascular disease. Clinical randomized trials are currently exploring potential vascular and neuro protective effects of SSRI treatment in patients with recent stroke, since depression is very frequent in this population and has major impact on mortality and potential rehabilitation (Shi et al. 2014).

With the aim of reducing the risk of recurrent ischemic events, studies have investigated the benefit of antidepressants, especially SSRI. In this context, results have also been equivocal and in most cases based on secondary and post hoc analyses. A meta-analysis of 39 randomized trials from 1967 to 2005 found a tendency towards a lower rate of serious cardiovascular events among SSRI users compared with placebo (odds ratio 0.7, 95 % CI: 0.4–1.2) and a lower rate of non-serious cardiovascular events compared with patients receiving tricyclic antidepressants (odds ratio 0.5, 95 % CI: 0.2–0.9) (Swenson et al. 2006). More recently, a meta-analysis of 5 randomized trials comparing SSRI and placebo among patients with acute coronary syndrome reported no difference in the risk of recurrent myocardial infarction (Mazza et al. 2010).

Possible explanations of the contradictory results may include heterogeneous study populations, different exposure classification, small studies not powered to draw firm conclusions, selection bias, different information sources, and lack of adjustment for cardiac risk factors and socioeconomical status. Finally, confounding by indication is a major problem in some of these studies, as strong evidence indicates that depression is associated with cardiovascular disease, such as coronary artery disease and stroke (Elderon and Whooley 2013; Dong et al. 2012; Kales et al. 2005; Rugulies 2002; Meijer et al. 2011).

On one hand, SSRI use may be associated with an increased risk of atherothrombotic events, but on the other hand studies have raised concern about an increased risk of bleeding. A recent meta-analysis, which included 22 studies thus examined the association between SSRI and risk of upper gastrointestinal bleeding. Comparing SSRI use with non-use, relative risk estimates ranged from 0.90 to 3.6 with an overall relative risk of 1.55 (95 % CI: 1.35–1.78) (Jiang et al. 2015). In a subgroup analysis, concurrent SSRI and nonsteroidal anti-inflammatory drug use and combined use of SSRI and antiplatelet drugs further increased the risk of bleeding. In the same study, the association with gastrointestinal bleeding was strongest for paroxetine (1.68, 95 % CI: 1.08–2.26), sertraline (1.67, 95 % CI: 1.37–2.04), fluoxetine (1.77, 95 % CI: 1.32–2.38), citalopram (2.07, 95 % CI: 1.47–2.92), and escitalopram (2.45, 95 % CI: 1.35–4.42), while no significant association was

found among patients using fluvoxamine and venlafaxine (a serotonin and norepinephrine reuptake inhibitor).

The association between SSRI and intracranial hemorrhage has also been studied. Although a recent meta-analysis found that SSRI use compared with non-use was significantly related to an increased risk of intracranial hemorrhage (Hackam and Mrkobrada 2012) other studies reported no association (de Abajo 2011). In the same meta-analysis, a tendency towards an increased risk of hemorrhagic stroke (defined as intracerebral or subarachnoid hemorrhage) and no association with subarachnoid bleeding was reported in patients treated with SSRI. In patients concomitantly using SSRI and oral anticoagulants, the risk of bleeding has been shown to increase compared with patients using oral anticoagulants only (Hackam and Mrkobrada 2012; Quinn et al. 2014). Studies comparing use of SSRI to non-use on the risk of perioperative bleeding (coronary artery bypass graft surgery, postpartum, orthopedics, and breast cancer) have reported contradictory results (de Abajo 2011).

3 Potential Mechanisms Between Antidepressants and Arterial Atherothrombotic Events

The clinical effects of SSRI are mainly linked to inhibition of the serotonin reuptake transporter (5-HTT) (Berger et al. 2009). Serotonin is synthesized by the enterochromaffin cells in the gut and mainly transported in dense granules by platelets; however, there is limited passage of serotonin across the blood brain barrier. In the central nervous system, serotonin is almost exclusively produced by neurons in the brainstem. The central serotonin regulation is important for appetite, mood, sleep, cognition, temperature and motor control (Jacobs and Azmitia 1992), whereas the cardiovascular roles of serotonin include regulation of heart rate, blood pressure, vascular tone, and platelet aggregation (Berger et al. 2009).

In addition to its effects in neurons, the SSRI receptor has also been found in platelets, smooth muscle cells, and intestinal epithelial cells with the potential to exert extra-neuronal effects (Berger et al. 2009). Since platelets play a key role in cardiovascular disease, the effect of SSRI on platelets has been studied extensively (Maurer-Spurej 2005). In patients treated with SSRI for several weeks, SSRI have been suggested to cause depletion of serotonin storage in platelets (Halperin and Reber 2007), attenuate platelet adhesion to collagen and fibrinogen (Halperin and Reber 2007), and to potentiate the aggregation induced by adenosine diphosphate, epinephrine and collagen (Halperin and Reber 2007). Theoretically, this may lead to bleeding – or to cardiovascular protection in patients at increased risk of thrombosis. Serotonin also plays a role as a potent vasoactive substance, which may cause vasoconstriction in cerebral arteries leading to ischemic stroke (Muhonen et al. 1997). Apart from its inhibitory effects on platelet function, rat studies have indicated that SSRI (paroxetine) might have a direct toxic effect on gastric mucosa (Takeuchi et al. 2011; Yamaguchi et al. 2008). Consistent with this finding and the ability of SSRI to inhibit platelet aggregation, a higher prevalence of gastric mucosal injuries in patients treated with SSRI compared with control patients has been reported (Dall 2010).

4 Clinical Implications

Due to contradictory findings and sparse data, the link between antidepressants and arterial events remains to be fully established. If any association exists, antidepressants most likely only play a minor role as a risk factor for arterial cardiovascular events compared with classical risk factors for atherothrombosis. On the other hand, use of SSRI may increase the risk of bleeding; however, compared with antiplatelet drugs such as aspirin and clopidogrel, the risk is only moderate. Nonetheless, co-treatment with proton pump inhibitors may decrease the risk of upper gastrointestinal bleeding and should therefore be considered

(Jiang et al. 2015; de Abajo and Garcia-Rodriguez 2008). In patients with other risk factors for bleeding (high age, previous bleeding, use of NSAID, antiplatelets or oral anticoagulants) caution is advised when prescribing SSRI. In addition, in order to reduce the risk of bleeding, it is important to make a thorough review of these patients' medication list and e.g. reduce dose of glucocorticoid or change treatment with NSAIDs to Paracetamol. The potential antiplatelet and neuro protective effects of SSRI are currently being investigated in three large randomized clinical trials on patients with recent stroke (clinicaltrials.gov) (Kraglund et al. 2015).

5 Antipsychotics and Arterial Events

A systematic review published in 2011 studied the association between antipsychotic drugs and myocardial infarction. However, due to substantial clinical and methodological heterogeneity between the five studies in the review, no firm conclusions were possible, albeit the largest included study demonstrated no association (Brauer et al. 2011). In contrast, and more recently, a self-controlled case series study from the United Kingdom (UK) found an increased 30-day risk of myocardial infarction following initiation of antipsychotic treatment with higher risk estimates (non-significant) for typical than atypical antipsychotics (Brauer et al. 2014). This finding was partly supported by a Taiwanese study of 59,806 psychiatric patients later found to have a myocardial infarction. The study showed that use of any type of antipsychotics 30 days prior to myocardial infarction increased the risk significantly (odds ratio 2.52, 95 % CI: 2.37–2.68). The use of amisulpride was associated with the highest risk of myocardial infarction. In contrast to the study from UK, a higher risk of myocardial infarction was found among patients using atypical compared with typical antipsychotics (odds ratio 1.63, 95 % CI: 1.29–2.05) (Lin et al. 2014).

The association between antipsychotics and stroke has received attention since 2002, when four randomized studies in dementia patients with 1–3 months of follow-up found an increased risk of cerebrovascular events in patients receiving risperidone (4 %) compared with placebo (2 %) (Wooltorton 2002). Although some contradictory findings have been reported, antipsychotics increase the risk of stroke in demented patients (Sacchetti et al. 2010a). The risk of stroke associated with typical and atypical antipsychotics seems to be similar (Sacchetti et al. 2010a). A study found that the risk of stroke was 12.4-fold (95 % CI: 8.4–18.1) higher in antipsychotic drug users in the first month of treatment compared with non-users. After this initial period, the risk returned to almost normal levels (Sacchetti et al. 2010b).

6 Potential Mechanisms Between Antipsychotics and Arterial Atherothrombotic Events

The mechanisms underlying the possible association between use of antipsychotics and risk of arterial events have not been established. Hypotheses about drug-induced obesity, hyperleptinaemia, antiphospholipid antibodies, and an increased activity in the coagulation system might add to the increased risk of arterial events (Hagg and Spigset 2002). Antipsychotics have also been associated with an increased risk of diabetes and hence they may also increase the risk of arterial events (Sohn et al. 2015). Again, confounding by indication may play an important role, because patients receiving long-term antipsychotic treatment mainly suffer from schizophrenia and thus tend to have lower socioeconomic status, unhealthy lifestyle, increased smoking, alcohol and drug abuse, less somatic hospitalization than needed, and are less likely to receive invasive cardiac procedures compared with matched controls (Laursen and Nordentoft 2011).

7 Clinical Implications

Despite the need for further investigation, awareness of a possible increased risk of myocardial infarction and stroke in patients prescribed with typical or atypical antipsychotic drugs especially in the early period after initiation of treatment is essential. Physicians should hold particular attention towards any new cardiac and neurological symptoms in patients initiating antipsychotic treatment. Especially in elderly patients with dementia, use of antipsychotics should be prescribed with great caution. Importantly, many psychotic patients do not react appropriately to alarm symptoms indicating cardiovascular disease, as many individuals with schizophrenia are less sensitive to pain than normal individuals (Dworkin 1994; Potvin and Marchand 2008).

8 Antidepressants and Venous Thromboembolic Events

Venous thromboembolism (VTE) is a common disorder affecting nearly one in 1000 adults annually (Oger 2000). It is an important and potentially preventable disease accounting for substantial morbidity and mortality (Kobberoe Sogaard et al. 2014). Known precipitants for VTE include acquired risk factors such as pregnancy, surgery, immobilization or active malignancy, and inherited risk factors such as deficiency of protein S or protein C, and factor V Leiden mutation (Goldhaber 2010).

Studies examining the association between antidepressants and VTE are limited and ambiguous. A case-control study conducted in New Zealand found an almost fivefold (odds ratio 4.9, 95 % CI: 1.1–22.5) increased risk of fatal pulmonary embolism in users of any antidepressant drug compared with non-use (Parkin et al. 2003). This finding was supported by another case-control study from the Netherlands reporting a 2.3-fold increased risk for venous thromboembolism in users of antidepressants compared with non-users (odds ratio 2.3, 95 % CI: 0.6–10.2) (Thomassen et al. 2001). Both studies were, however, small and confidence intervals accordingly wide. Furthermore, both studies are >10 years old and neither discriminated dose or type of drug, or accounted for the important fact that the frequency of smoking is markedly higher among patients with depression. A more recent, nested case-control study from UK compared current use of antidepressant drugs with non-use and also addressed the specific type of drug (Jick and Li 2008). In this study, use of tricyclic antidepressants was associated with a small but significantly increased risk of VTE (odds ratio 1.4, 95 % CI: 1.1–1.8), whereas no increased risk was found for SSRI. In a recent Taiwanese study, an approximately 1.5-fold increase in VTE risk was reported for users of any antidepressants (odds ratio 1.59, 95 % CI: 1.27–2.00) (Wu et al. 2013), and as opposed to the UK study, both tricyclic antidepressants and SSRI showed increased risk of VTE (tricyclic antidepressants: odds ratio 1.56, 95 % CI: 1.11–2.18; serotonin 5-HT_{2A} receptor blockers: odds ratio 2.03, 95 % CI: 1.27–3.24; and antidepressants with a low potency of serotonin reuptake inhibition: odds ratio 1.57, 95 % CI: 1.18–2.08).

Contrary to the studies above, several studies have reported no association between antidepressants and VTE. A case-control study of 214 patients aged <60 years thus reported no association between antidepressant use and subsequent risk of VTE when controlling for antipsychotic drug exposure (odds ratio 1.7, 95 % CI: 0.8–3.7) (Zornberg and Jick 2000). This null result was supported by a larger (n = 1354) and more recent case-control study reporting an odds ratio of 1.1 (95 % CI: 0.9–1.5) (Lacut et al. 2007) and by a cohort study of patients aged age > 65 years where users of antidepressants were compared with users of thyroid replacement therapy (hazard ratio 1.02, 95 % CI: 0.91–1.14) (Ray et al. 2002).

9 Clinical Implications

The evidence of increased risk of VTE among users of antidepressants is sparse and inconsistent. The increased risk reported in some studies is modest and most pronounced for tricyclic antidepressants. The association, if any, is weak and the psychiatric indication of treatment is therefore the primary determinant when prescribing antidepressants. However, in patients with a strong predisposition or history of VTE, the psychiatric indication of use should be substantial, and treatment with SSRI should presumably be preferred. Further studies examining the type of drug, dose and duration of use are warranted.

10 Antipsychotics and Venous Thromboembolism

The evidence for an association between antipsychotics and VTE is more robust and consistent than the association between antidepressants and venous thromboembolism. Current evidence is based primarily on case-control and cohort studies.

In 2011, a meta-analysis of seven case-control studies concluded that use of antipsychotics was associated with an almost 2,5-fold increase in the risk of VTE (odds ratio 2.39, 95 % CI: 1.71–3.35) (Zhang et al. 2011). Pooled estimates by drug type showed that use of low-potency antipsychotics (odds ratio 2.91, 95 % CI: 1.80–4.71) is the most important risk factor for VTE followed by atypical (odds ratio 2.20, 95 % CI: 1.22–3.96), typical (odds ratio 1.72, 95 % CI: 1.31–2.24) and high-potency drugs (odds ratio 1.58, 95 % CI: 1.50–1.67). The results of this meta-analysis was driven by two important case-control studies of which a Danish study reported a more than twofold increased risk of VTE compared with non-users (odds ratio 2.27, 95 % CI: 1.55–3.31) (Jonsson et al. 2009) and a study from UK reported an almost two-fold increase (odds ratio 1.80, 95 % CI: 1.49–2.18) (Parker et al. 2010). More recently, a meta-analysis of 12 observational studies (case-control and cohort studies) reported a more moderate increase in the risk of VTE (odds ratio 1.54, 95 % CI: 1.28–1.86) (Barbui et al. 2014). In the same study, an analysis restricted to cohort studies (n = 5) revealed an even smaller risk of VTE (odds ratio 1.34, 95 % CI: 1.13–1.58).

11 Potential Mechanisms Between Antipsychotics and Venous Thromboembolism

The underlying causal mechanisms explaining the association between antipsychotics and VTE have not been clarified yet, although numerous mechanisms have been proposed. Antipsychotic drugs, especially the atypical drugs, are known to cause weight gain and metabolic syndrome, which are well known risk factors for VTE (Osborn et al. 2008). The causal pathway may also include drug-induced sedation or physical restraining, which consequently increases the risk of VTE through immobility and venous stasis. Increased aggregation of platelets has also been suggested for typical antipsychotics (Boullin et al. 1975; Orr and Boullin 1976). It may constitute a confounding problem that the vast majority of studies included in the aforementioned meta-analyses did not adjust for the psychiatric disease *per se* (Chapelle et al. 2013) or complications of the disease, such as a sedentary lifestyle, poor diet, smoking, and drug abuse (Hagg et al. 2009).

12 Clinical Implications

The association between antipsychotics and VTE is well documented in recent meta-analyses of cohort and case-control studies. As for most other safety and tolerability questions, evidence in the form of randomized trials is not available. Several mechanisms are likely to be responsible for this association and confounding factors cannot be ruled out; however, physicians should consider that current best evidence shows a moderate, but statistically significant increased risk of VTE in individuals exposed to antipsychotics, and this risk equally applies to typical and atypical antipsychotics. The prescription of these

drugs should be carefully weighed against the risk of VTE, especially in susceptible, predisposed patients. Moreover, the physician should seek to reduce other risk factors for VTE commonly seen in psychiatric patients, such as metabolic syndrome, smoking and overweight. Furthermore, the physician should be aware that patients suffering from schizophrenia often tend to ignore symptoms of acute disease. To reduce the risk of VTE, initiation of thromboprophylaxis should be strongly considered for belt-restrained patients.

13 Conclusion

Antidepressants and antipsychotics modify the risk of arterial and venous thromboembolism. The strongest associations have been found between SSRI and risk of gastrointestinal and intracerebral bleeding, and antipsychotics and risk of both arterial and venous cardiovascular events. In general, however, these associations are not sufficient to outweigh the benefits of treatment in patients with a strong indication for psychotropic drugs. Before prescribing psychotropic drugs, clinicians should carefully assess classic thromboembolic risk factors and patients' risk of bleeding. Caution is advised in patients with a high risk of thrombosis or bleeding. More research on the association between psychotropic drug use and risk of thromboembolism is highly warranted and the underlying mechanism requires further clarification. The threshold for performing relevant somatic examinations must be kept low in users of psychotropic drugs, as many psychiatric patients tend to ignore even alarming symptoms of arterial and venous thromboembolism.

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Post Thrombotic Syndrome

Andrew Busuttil, Chung Sim Lim, and Alun H. Davies

Abstract

Venous insufficiency following deep venous thrombosis is known as the post thrombotic syndrome. Whilst its presentation and symptoms can vary slightly between individuals, it can have a profound effect on quality of life. Symptoms range from mild limb swelling to severe intractable ulceration. A number of scoring systems have been developed to help monitor the disease progression, response to treatment as well as to classify patients for research purposes.

Treatment involves a combination of therapies, including compression stockings, venous stenting for out flow obstruction and in some instances deep venous bypass. A considerable effort is made in preventing post thrombotic syndrome with a number of trials looking into the effect of prompt and stable anticoagulation, the effect of compression stockings, the effect of exercise and the outcomes following early thrombus removal strategies such as catheter directed and pharmacomechanical thrombolysis.

Keywords

Post thrombotic syndrome • Chronic venous insufficiency • Venous reflux • Venous outflow obstruction • Catheter directed thrombolysis • Ulcer • Venous hypertension • Venous stenting

Abbreviations

PTS	post thrombotic syndrome
DVT	deep vein thrombosis
CDT	catheter directed thrombolysis
LMWH	Low molecular weight heparin
VKA	Vitamin K Antagonists
PMT	Pharmaco-mechanical thrombolysis

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1 Introduction

In 1271 a young Norman labourer presented with a painful swollen limb, which eventually led to an ulcer forming. After numerous failed

treatments, the young man turned to the sacred tomb of King Saint Louis and rubbed dust into his wounds which is reported to have healed the ulcer. In this account we have the first reported case of post thrombotic syndrome with the first potential treatment [1].

Post thrombotic syndrome, PTS, is a collection of signs and symptoms seen as a long term sequel of deep venous thrombosis (DVT). Symptoms can range from mild swelling with minimal impact on quality of life, to debilitating pain and ulceration. Just like DVT, PTS can occur in both upper and lower limb although is more often seen in the latter. As the incidence and diagnosis of DVT have increased and our understanding of PTS has improved, there has been a shift in the treatment objective for DVT, with the fear of mortality in the pre-anticoagulant era shifting to the fear of morbidity, with physicians interested in reducing PTS. The aim of this chapter is to discuss the pathophysiology, clinical features, current understanding, prevention and management of PTS.

2 Pathophysiology of PTS

PTS is caused by chronic venous insufficiency and venous hypertension after DVT. There are two postulated mechanisms responsible for the pathophysiology of PTS; firstly there is venous outflow obstruction due to either incomplete clot resorption or scarring of the proximal vein, and secondly venous reflux or valvular incompetence secondary to the inflammatory response generated by the thrombosis [2]. This renders the calf muscle pump ineffective and ambulant venous pressure does not fall significantly with walking or exercise (as it does in the healthy state) leading to venous claudication, ankle swelling, skin changes and even ulceration (Fig. 1).

The exact cause of venous skin changes and venous ulceration is not yet known although the most prominent theory is that of an inflammatory cascade initiated by venous hypertension, leading to a fibrin cuff forming around capillaries. This is thought to render tissues more hypoxic and create a chronic inflammatory response leading to leukocyte recruitment and increased vascular permeability, which is thought to lead to lipodermatosclerosis and damage to the skin.

3 Incidence

The incidence of PTS after a proximal DVT varies according to the diagnostic criteria applied. A recent review on PTS [4] reported the incidence of PTS after a proximal or iliofemoral DVT in 50–60 % of patients. The peak incidence is at 2 years after which the rate plateaus, indicating that if there are no symptoms after 2 years, it is unlikely they will develop

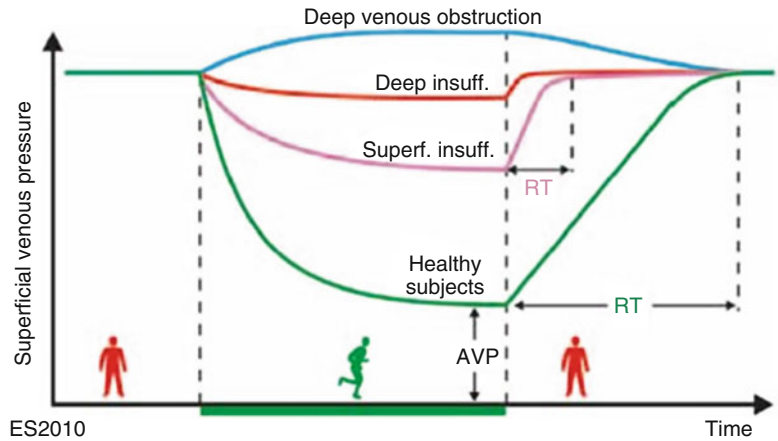

Fig. 1 Changes in ambulatory venous pressure [3]

subsequently. The chances of the PTS setting in after a distal DVT are lower, with some studies reporting 30–40 % of patients going on to develop the PTS [4], although the data is conflicting regarding distal DVT's patients. There is evidence however, that once patients have symptoms of PTS, they show evidence of progression, with worsening of symptoms and deteriorating clinical scores.

Interestingly, the scoring system used for diagnosis has a significant impact of the incidence of PTS after DVT. Kahn et al. [5] examined a cohort of patients belonging to the VETO (Venous Thrombosis Outcomes) study [6] which is a multicentre prospective registry following up DVT patients, and found that there was a fivefold increase in the diagnosis of PTS when the Villalta score was used over the Ginsberg score.

4 Clinical Presentation of PTS

In general, it is felt that a diagnosis of PTS should not be made within the first 3 months of a DVT episode as the initial symptoms of swelling and pain tend to subside once anticoagulation is instituted. Presentation is normally within 2 years of an index DVT event, although some may present as a delayed diagnosis of DVT.

The diagnosis of PTS is often a clinical one requiring a full history and physical examination. Patients with PTS complain symptoms of chronic venous insufficiency including pain and discomfort, heaviness, restlessness, itchiness, swelling, presence of varicose veins, venous skin changes including eczema and atrophy blanche, and ulceration. Skin changes are often the preceding symptoms in PTS, and include venous eczema, atrophy blanche and lipodermatosclerosis (Fig. 2).

These changes result in thinner skin, which is prone to injury and healing is often delayed due to the presence of venous hypertension. Patients may also exhibit venous claudication, which is often described as a bursting pain brought on by exertion and relieved by rest and leg elevation.

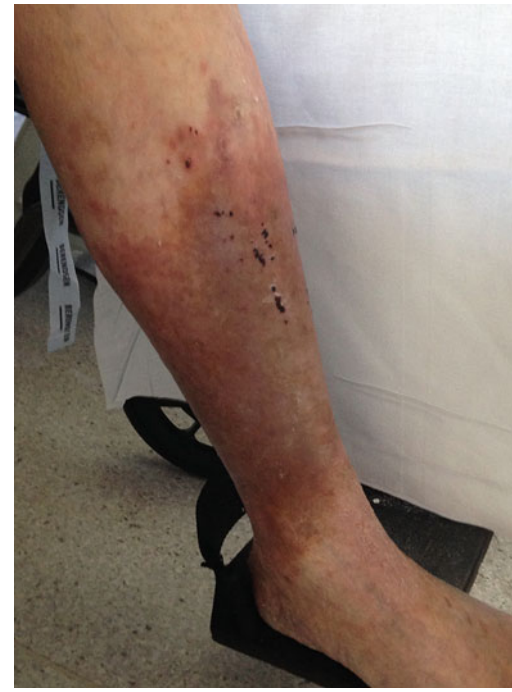

Fig. 2 Typical appearance of venous skin changes

The lower limb oedema may improve after the initial episode of DVT, but the limb may not return to pre-morbid sizes. This is normally worse towards the end of the day and aggravated by prolonged periods standing. Skin changes may accompany limb swelling, and are normally the direct result of venous hypertension.

Venous ulceration secondary to PTS often occurs in the gaiter area although, can extend to the shin and calf, and has the propensity to be very extensive. Venous ulcers are often shallow, with sloping edges and are accompanied by large volumes of exudate. The base of the ulcer is often covered in slough and the size of the ulcer is considerably larger than what is seen in arterial ulcers. Pain is also an accompanying feature of venous ulcers, and features of chronic venous insufficiency, such as lipodermatoscleoris, varicose veins or previous healed venous ulcers are often present.

Diagnosis of venous ulceration may be accomplished by taking a thorough history taking and examination of the wound and surrounding tissues. This is often supported by investigations

seeking venous incompetence and/or obstruction such as duplex ultrasound, and when other investigations are inconclusive, a biopsy of the ulcer edges may show evidence of venous engorgement or venous hypertension, and may be done to exclude squamous cell carcinoma or vasculitis ulceration.

5 Investigations

In patients with PTS it is important to obtain as much information as possible as to the pattern of disease and where the relevant occlusions or reflux zones are located. The first step in investigation is a duplex ultrasound, which incorporates the use of Doppler looking for flow and its reversal (reflux) and a 2-D ultrasound looking into the structure of the named veins. Duplex ultrasound scan has the advantages of being a dynamic and non-invasive imaging modality. It is a very useful tool when performed by experienced vascular scientists and is able to provide a detailed map of the pattern of incompetence and obstruction. The two limitations of this non invasive investigation is that patients would need to be able to stand for up to 45 min (per leg scanned) and visualising the iliac and inferior vena cava, IVC, venous systems is often difficult and may require further modalities.

Computerised Tomography, CT, venography, using intravenous contrast and timing the scan when the contrast has reached the venous phase has proved a useful tool in investigating iliac and IVC segments, particularly when outflow obstruction is suspected. Whilst CT venography is useful for excluding iliac outflow obstruction and IVC anomalies, it is unable to detect reflux.

Ascending and descending venography is the gold standard investigative modality and allows the performing radiologist to tilt the patient cranially and caudally and to observe the flow of contrast detecting outflow restriction and reflux. This can pick out with a high degree of specificity and sensitivity, areas of valvular incompetence and outflow obstruction, whilst also allowing the clinician to treat any outflow lesion with angioplasty and venous stenting. As venography is an invasive procedure, it is reserved for specialist units and is used to help plan venous reconstruction/stenting procedures.

Magnetic resonance imaging, MRI, is also used in patients in whom IV contrast for CT venography is contraindicated and is also able to show reflux when dynamic sequences are used. Interpretation of these scans requires significant expertise and patients would need to be able to tolerate an extended period within the MRI scanner.

A link between the location of the lesion and the severity of the symptoms has been established, and more proximal lesions (iliofemoral) result in higher rates of recurrence as well as more severe symptoms. This makes accurate description of the anatomical location of the thrombus an integral part of the management plan for PTS patients. It is important to note that PTS remains a clinical diagnosis and imaging mainly helps identify the pattern of disease and can help with further management.

6 Severity Scores for PTS

The Villalta score (Table 1) has been developed and used to help ascertain the diagnosis (a score greater than five) and asses the severity. It was developed in the mid 1990s by Prandoni [7] as a scale to diagnose and stratify the severity of PTS symptoms and was based on the work Villalta had undertaken a few years earlier. A recent review [8] has shown that it is the most widely used scoring system as it is reproducible and takes into account subjective and objective parameters. It has good inter-observer and validity scores, and also considers the pathophysiology association. The Villalta score allows the clinician to asses objective signs such as pre-tibial oedema, induration, hyper pigmentation, venous ectasia, redness pain on calf compression and ulceration, and then grade each one (mild, moderate or severe scoring 1, 2 or 3 respectively). The subjective symptoms – pain, heaviness, cramps pruritus and paraesthesia are graded by the patient to give an overall score. The presence of a venous ulcer automatically results in a

severe score, regardless of the other aspects of the score. The usefulness of the Villalta score lies in its ability to accurately diagnose PTS, grade severity as well as monitor the response to treatment. This means that the Villalta score is a useful and powerful research tool whilst also providing clinicians with a diagnostic assessment and is the suggested scoring system by the International Society on Thrombosis and Haemostasis [9].

Table 1 Villalta prandoni score [7]

Symptom/Sign	None (0)	Mild (1)	Moderate (2)	Severe (3)
Heaviness				
Pain				
Cramps				
Pruritus				
Paresthesia				
Pretibial Oedema				
Induration of the skin				
Hyperpigmentation				
Venous Ectasia				
Redness				
Pain on Calf Compression				
Ulcer				
Total				

Other grading systems such as the CEAP (Clinical, Aetiology, anatomy and pathophysiology) [10] classification (Table 2) take the pattern of the disease into account but not the severity as classified by the patient. CEAP takes into account the clinical manifestations, aetiology, anatomy and pathophysiological process but do not give the clinician the ability to monitor severity of the symptoms. CEAP has been found to be more useful as a research tool when investigating patients with chronic venous disease.

The Venous Clinical Severity Score [11, 12], VCSS, which was developed by the American Venous Forum and validated using data from the national venous screening program in the United States of America, is also useful in grading severity, and monitoring response to treatment. Like the Villalta score, VCSS provides the clinician with mild, moderate and severe scores for each of the fields (Table 3).

7 Quality of Life

PTS has a significant impact on the quality of life of patients [13], which has been demonstrated in various studies. Also a number of scores exist to help quantify and monitor the symptomatology. Quality of life impact is

Table 2 CEAP classification [10]

C-Clinical class	Characteristics[a]		
0	No clinical findings or symptoms	**E-Etiology**[b]	
1	Telangiectasia or reticular veins	C	Congenital
2	Varicose veins	S	Secondary
3	Oedema, only due to a venous etiology	P	Primary
4	(a) Pigmentation and/or eczema	**A-Anatomy**[b]	
	(b) Lipodermatosclerosis, *atrophie blanché*	S	Superficial
5	Prior ulceration, now healed	P	Perforator
6	Active ulceration	D	Deep
A,S	Subscript: Asymptomatic, Symptomatic	**P-Pathophysiology**[b]	
Date	Date of investigation	R	Reflux
Level	Level of investigation (I, II, III)	O	Obstruction
		R-O	Both
		N[b]	No evident disease[b]

[a]Complaints are expected to be related to venous insufficiency and are not classified if another etiology is present (i.e. oedema secondary to heart failure)

[b]The N subscript indicates no evidence of disease. It is applicable to E, A, and/or P of CEAP

Table 3 The venous clinical severity score [11, 12]

	None: 0	Mild: 1	Moderate: 2	Severe: 3
Pain or other discomfort (i.e.: aching, heaviness, fatigue, soreness, or burning) Presumes venous origin		Occasional pain or other discomfort (i.e.; not restricting regular daily activities)	Daily pain or other discomfort (i.e.; interfering with but not preventing regular daily activities)	Daily pain or discomfort (i.e.; limits most regular daily activities)
Varicose veins				
Varicose veins >3 mm in diameter to qualify in the standing position.		Few: scattered (i.e.; isolated branch varicosities or clusters) Also includes corona phlebectatica (ankle flare)	Confined to calf or thigh	Involves calf and thigh
Venous edema				
Presumes venous origin		Limited to foot and ankle area	Extends above ankle but below knee	Extends to knee and above
Skin pigmentation				
Presumes venous origin Does not include focal pigmentation over varicose veins or pigmentation due to other chronic diseases	None or focal	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Inflammation				
More than just recent pigmentation (i.e.; erythema; cellulitis; venous eczema; dermatitis)		Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Induration				
Presumes venous origin of secondary skin and subcutaneous changes (i.e.; chronic edema with fibrosis; hypodermitis). Includes white atrophy and lipodermatosclerosis		Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Active ulcer number	0	1	2	>3
Active ulcer duration (longest active)	N/A	<3 months	>3 months but <1 year	Not healed for >1 year
Active ulcer size (largest active)	N/A	Diameter <2 cm	Diameter 2-6 cm	Diameter >6 cm
Use of compression therapy	0; Not used	1; Intermittent use of stockings	2; Wears stockings most days	3; Full compliance: stockings

significant, and using various quality of life questionnaires, PTS patients have worse scores than patients suffering from chronic lung disease, or arthritis [14]. Severe PTS patients have quality of life scores akin to patients with congestive heart failure and cancer [14]. Patients with moderate to severe PTS often miss work or forgo employment all together and the overall cost to the economy is estimated to be 2 % of the total healthcare budget of a developed nation [15, 16]. This figure only includes direct costs but including the costs of days of work lost, attendance to dressing clinics as well as the difficult to quantify cost of district and community nursing would raise the figure significantly.

8 Treatment

8.1 Lifestyle Changes and Conservative Treatment

Lifestyle modification plays a significant role in the treatment of patients with PTS. All patients should be advised to elevate their legs when possible, avoid standing for excessive periods of time and preferably seek employment in desk/office jobs. Weight loss is also encouraged as this is thought to have a beneficial effect on venous return. Whilst all patients should receive lifestyle advice, many would struggle to accept this as the only form of treatment.

Several studies have highlighted the importance of exercise in the treatment of PTS, in a similar way that supervised exercise programmes help patients with stable intermittent claudication in peripheral arterial disease. The full effect of exercise is yet to be evaluated and may prove to be more complex than for arterial disease, but it no doubt would offer patients another avenue to pursue. A recent small randomised control trial performed by Kahn et al. [17] compared active exercise, supervised by a health professional against regular follow up and information on PTS, found a statistically significant improvement in patients severity score (Villalta) in the active exercise sub group. Whilst this was a small study, it no doubt has paved the way for further, large scale trials looking into this treatment modality.

8.2 Compression

Compression hosiery has for long been the mainstay of the treatment for PTS patients. Multilayer compression bandages such as four layer bandaging have been employed when skin ulceration is present. Meanwhile, compression stockings of various grades are often prescribed to PTS patients with no venous ulcers. Compression aims to reduce the venous pressure in the affected limb and reduce the symptoms. A study carried out by Agu et al. [18] demonstrated an improved deep tissue oxygenation and reduced venous pooling in patients with chronic venous insufficiency when compression stockings were applied. Evidence for compression hosiery is still the source of much debate. Dr Susan Kahn and colleagues conducted a small study [19] into the effects of compression stockings in patients 1 year after a DVT with and without PTS. She compared exercise tolerance, limb volumes and patient perception of symptoms and found no evidence supporting their use. Compliance with compression hosiery will remain an issue for most patients [10], particularly so in warm climates and when elderly patients are involved, due to the dexterity and force needed to apply the garments.

Two small trials [20, 21] using intermittent compression devices with the aim of improving venous return both reported improvement in quality of life scores as well as improvement in Villalta scores in patients with confirmed PTS. Whilst the authors showed statistical significance, the numbers were small, and larger multicentre trials are needed, but they serve to highlight yet another option available for clinicians treating PTS patients.

The American College of Chest Physicians in its most recent guidance on the treatment of DVT and PTS suggests that ECS should be used for at least 2 years after an episode of DVT and for patients with established PTS [22].

The American Heart Association issued guidance in 2014 recommending the use of ECS, but stating that the evidence for preventing PTS in DVT patients is uncertain, but noted that they may bring about improvement in symptomatology (swelling) [23].

8.3 Pharmacological Agents

Pharmacological agents have been the issue of some debate as to their use in PTS patients. These are extensively used in mainland Europe and other countries, but not available in the United Kingdom and USA. A large study found that circulating inflammatory markers are reduced when patients are treated with

micronized purified flavonoid fractions or MPFF (Daflon 500 mg) and a meta analysis [24] of a number of clinical trials found that when combined with compression MPFF can improve ulcer healing rates. Pentoxyfiline has also been shown to improve ulcer healing rates when combined with compression in a number of studies [25, 26] to improve ulcer healing rates when combined with compression. The RELIEF study [27] was a large multi centred study which was carried out in 23 countries over 2 years, recruiting over 5000 patients. Patients were treated with MPFF over a 6 month period and showed a consistent improvement in symptoms and quality of life and clinical scoring (CEAP).

8.4 Endovascular Intervention

Endovenous treatment, often involving venous stenting is fast becoming the treatment of choice for chronic venous outflow obstruction particularly so in larger veins such as the iliocaval system. PTS is more common after ilio-femoral DVT than femoro-popliteal thrombosis [4].

Whilst still in its infancy, there are now venous specific stents available, such as the Sinus-Venous stent (Optimed, Ettlingen, Germany), Zilver Vena™ (Cook® Medical, Bloomington, Indiana, USA), and VICI VENOUS STENT® (Veniti, St Louis, Missouri, USA) which take into account the particular haemodynamic properties of the venous system. Venous stents rely on radial force to maintain contact with the vein wall, and need to be considerably oversized during their deployment, a marked shift from arterial stenting.

There is a growing body of evidence that percutaneous stenting of the iliac veins is safe, with good patency results and leads to improvement in PTS severity scores and ulcer healing. Whilst there are no large randomised controlled trials comparing the use of stents to conventional therapy or surgery, it is clear that in large case series by pioneers of the technique like Neglen [28] that patients are benefiting from this new technique, and further work is needed to standardise follow up and scoring practices.

Patency of venous stents as reported in a number of trials and case series is encouraging, with a study conducted by Raju [29] reporting up to 69 % and 93 % primary and secondary patency rates accordingly, however, patency rates do differ significantly from one case series to another and large randomised, case controlled trials have not yet been reported.

Various anti-coagulation regimens, including low molecular weight heparin (LMWH), coumarins, fondaparinux and new oral anticoagulants, as well as anti-platelet agents are employed based on the experience or local protocol of the particular centre or clinician involved. Unfortunately, to date there is still no robust evidence supporting one particular anticoagulation/antiplatelet regimen for maintaining long-term stent patency.

8.5 Deep Venous Surgery

Deep venous reconstruction encompasses venous diversion/bypass procedures as well as valve transposition, both of which are invasive and carry operative morbidity, meaning that careful patient selection is needed.

8.6 Venous Bypass Procedures

Venous diversion procedures such as the May-Husni procedure (anastomosing the patent and competent greater saphenous vein, GSV, to the ipsilateral stenosed/occluded superficial femoral vein) and the Palma Procedure (anastomosis of the patent and competent GSV to the contralateral common femoral vein treating iliac occlusion) have varying degree of success, with 50–80 % patency rates reported. These procedures are therefore restricted to younger and fitter patients with specific patterns of incompetence and obstruction. The main indication of performing such procedures would be worsening condition of the skin in the effected leg, in particular ulceration which is recurrent and not responding to conventional therapy.

8.7 Valve Transposition

Venous valve transposition is another surgical alternative for treating patients with PTS, and gives the surgeon the option of treating both incompetence as well as obstruction. A segment of healthy vein, containing valves, normally from the upper limb (axillary or superficial) is used as a short interposition bypass for a diseased segment, and an end to end anastomosis performed.

8.8 Venous Valvuloplasty

Venous valve repair has been trialled a number of times and a minority of patients may be suitable for venous valve repair. This is a technically difficult procedure with variable success rates. It involves open venotomy at the site of a valve, and plicating the valve leaflets in order to give them a firmer structure and reduce the degree of reflux.

8.9 Deep Venous Valve Substitutes

Research teams working on deep venous valve substitutes have been generating interest for some time now but have not to date been able to offer patients with a viable treatment alternative. A number of groups are developing prosthetic and bio-prosthetic venous valves as a treatment for venous incompetence, aiming to provide patients with a percutaneous treatment option. The pioneer of such techniques, Pavcnik [30] has shown in a small pilot study that a percutaneous bio-prosthetic valve can provide symptomatic relief, speed up ulcer healing and would remain patent for a considerable length of time. This treatment option would be an attractive one as it would be able to offer patients an endovenous option, far less invasive than any open approach, and would be available to more patients. Deep venous valve substitutes still have a number of hurdles to overcome, namely the choice of material; which would need to mimic venous valve leaflets; the resistance to thrombosis, as the venous system is a low flow system and thrombosis plagues many treatment options as well as durability. Nevertheless, a treatment option using endovenous prosthesis is likely to make a significant impact on the treatment of PTS in the not too distant future.

8.9.1 Risk Factors for the Development of PTS

In recent published reviews [4, 31], the risk factors for developing PTS have been identified and include recurrent DVT, obesity (although the evidence to support this is not strong) and location of the thrombus, with PTS being more common in proximal lesions (above the inguinal ligament). With regards to age and gender conflicts reports have been published but no adequately powered study has been published to identify a link t either gender or age.

9 Prevention Strategies

As the treatment for DVT has evolved, the focus has started to shift, with the aim to reduce the long term sequel of DVT. Particular attention has been paid to iliofemoral DVT for two reasons, firstly that this is a main outflow tract for venous drainage to the limb, with only small collaterals being present, so any damage caused to the veins at this level is more likely to result in PTS setting in. Secondly, many have postulated that the PE rate is higher in iliac and IVC DVT so these patients would require close monitoring until anti-coagulation has been established. Current medical practice lies with prompt diagnosis and anti-coagulation and the use of compression hosiery. This is changing with thrombus removal being considered for most patients with iliofemoral DVTs in high volume centres and their catchment areas.

9.1 Anticoagulation

A study published in 2005 [32] found that one of the predictors of PTS was time spent below the therapeutic range whilst being treated with

vitamin K antagonists, VKA. A significant portion of patients have periods of sub therapeutic levels whilst on VKA and effective bridging from LMWH to VKA combined with strict control of the international normalised ratio will help reduce the incidence of PTS. It is still unclear what the effect of the routine use of new oral anti-coagulants will have on the PTS rate, but this will undoubtedly be followed up in due course.

Anti-coagulation, when compared to no intervention, has the largest, proven benefit in reducing the incidence of PTS [33]. Many feel that prompt treatment with anti-coagulants is invaluable when treating these patients.

In a randomised controlled trial [34] Hull et al. showed a significant reduction in PTS symptoms in patients treated with LMWH vs. bridging anticoagulation and VKA for 3 months. This further highlights the importance of effective anti-coagulation as a preventative strategy for these patients.

9.2 Early Thrombus Removal

Early thrombus removal strategies have been evolving over the past few decades as physicians treating DVT patients became more mindful of the vein wall damage caused by thrombus. The first attempts at thrombus removal where open surgical thrombectomy which had good thrombus clearance rates, however resulted in significant morbidity. This procedure is still carried out, in particular when phlegmasia cearulea dolens is present, but has fallen out of favour with the increasing use of thrombolysis such as streptokinase and later recombinant tissue plasminogen activator, rTPA.

As the use of these drugs increased in the 1960s more uses were sought for them and systemic administration for iliofemoral thrombus dissolution was trialled. Whereas thrombus removal rates were acceptable, the side effects were not, and after a number of case series reported fatal intracranial haemorrhages as complications, systemic administration of thrombolytic medication was deemed too high risk for ilio-femoral DVT, in particular when safer alternatives, namely heparin and coumarins were able to prevent pulmonary embolism effectively. With the advancement of endovascular techniques, catheter directed thrombolysis offered good thrombus dissolution rates using much smaller doses of thrombotic agents [1].

Catheter directed thrombolysis, CDT, has been shown to effectively reduce the thrombus burden in ilio-femoral DVT whilst having an acceptable safety profile. A more recent addition is pharmacomechanical thrombolytic catheters such as EKOS (EKOS corporation, WA, USA), Angiojet (Boston Scientific, MA, USA) and Trellis (Medtronic, MI, USA), which combine mechanical clot disruption and thrombolytic agents. For example, EKOS uses ultrasonic waves in combination with pharmacological thrombolysis which allows for an even smaller dose of thrombolytic agent to be used, potentially reducing the rate of bleeding complications. The use of CDT and PMT is still under evaluation, with only one randomised controlled trial being published at time of writing, the CAVENT [35] trial.

This study randomised 209 patients with iliofemoral DVT to either anticoagulation alone or CDT and anticoagulation in 20 centres in Norway. The primary outcome measured was the presence of PTS at 2 years following the intervention. Other outcome measures included thrombus resolution success rates as well as patency at 2 years and quality of life.

Whereas the procedure was deemed safe, with no intra cranial haemorrhage episodes and only a handful of bleeding complications, the procedure conferred a 14.4 % absolute risk reduction of PTS (95 % CI $0 \cdot 2 - 27 \cdot 9$, $p = 0 \cdot 047$) in these patients [35]. Patients undergoing CDT did have a slightly longer hospital stay with an associated increase in cost, at least in the short term as the long term benefit has yet to be determined. What was interesting is that the study revealed that at 2 years, there was no significant improvement in the quality of life in patients who had undergone CDT, calling into question whether the use of such techniques, with the associated cost, in patient stay and potential for

complications should be continued. Whilst the CAVENT study was the first to follow up patients for a 2 year period, further trials which will be published in coming years will help provide more data for clinicians and commissioning bodies to base decisions on.

9.3 Compression

Compression hosiery and anti-coagulation have long since been the treatment of choice for DVT providing there are no signs of venous ischaemia. Compression stockings have long been thought to reduce post thrombotic complications by improving venous return and preventing venous pooling. This belief however, was not demonstrated during the SOX trial [36], which was a large trial involving over 800 patients. These patients were randomised to either elastic compression stockings or a placebo (stockings two sizes too large) in patients who had their first episode of proximal DVT. Patients were followed up for 2 years and the trial showed no reduction in PTS symptoms in the treatment group. This trial is the largest of its kind and results from other trials looking at proximal DVT patients are needed to add to the pool of data. Currently compression stockings are still routinely used as a preventive measure following deep venous thrombosis although their use as a preventative measure has now been put into question.

Current recommendations from the national institute of health and clinical excellence, NICE [37], in the UK are that patients suffering from a proximal DVT should be treated with prompt anti-coagulation, assessment for suitability for early thrombus removal and with compression stockings.

Previous trials [38] investigating the effect of compression stockings on reducing PTS have found this to be effective although these were not as exhaustive as the SOX trial. Further work is needed to ascertain the efficacy of compression stockings to reduce the incidence of PTS.

10 On-Going Trials

On-going trials looking into PTS prevention strategies focus mainly on the use of CDT and/or pharmaco –mechanical thrombolysis, PMT, and these include the ATTRACT trial, which is comparing PMT versus anticoagulation and compression stockings for the treatment of proximal DVT with the aim of reducing PTS. Recruiting has been complete and patients will be followed up for 2 years.

The CAVA Trial (CAtheter Versus Anticoagulation) is a randomised controlled Dutch multi centre trial comparing ultrasound-accelerated catheter-directed thrombolysis (EKOS) and standard anticoagulant therapy, with standard anticoagulant therapy alone, in acute primary ilio-femoral DVT following up patients for up to a year to identify any difference in the PTS rates. Undoubtedly, the above mentioned trials as well as other on-going trials will be a welcome contribution to the body of evidence on CDT and PTS reduction strategies.

The Ideal DVT study (NCT01429714) in the Netherlands is currently on going and expected to publish results on the PTS rates with/without the use of compression stockings in July 2016.

11 Conclusions

Patients with PTS often have a significant impact on their quality of life, ranging from mild discomfort, to having to change or even forgo employment due to the symptoms. The most debilitating complication of PTS is lower limb ulceration, often needing many months of wound care to heal. Venous skin changes, once present are permanent and leave the skin liable to ulceration in the future, adding more weight to prevention strategies. Most patients with PTS will have periods of mild/moderate symptoms and some will go on to have ulceration which may need intervention in form of compression. In a few cases ulceration may be recurrent, difficult to

treat and lead to systemic upset needing urgent surgical admission, debridement and limb elevation. Limb loss secondary to venous ulceration, whilst uncommon, serves to highlight the potentially devastating effect of PTS.

More work is needed to further evaluate the effect deep venous stenting has on the disease trajectory in PTS patients as well as further work into the development of prosthetic deep venous valves for the treatment of deep venous incompetence that is often present in these patients.

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A Review of the Evidence to Support Neuromuscular Electrical Stimulation in the Prevention and Management of Venous Disease

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Abstract

Introduction

The prevention and management of venous disease is a therapeutic challenge. Movement of blood through the venous system is augmented by the action of muscles on the deep veins, and can be achieved through the application of electrical current. The efficacy of currently available clinical devices for this purpose is unknown, and is investigated here.

Methods

A literature search of the EMBASE and Medline databases was performed, and studies were included if they were full text articles, written in english, pertaining to venous disease and neuromuscular electrical stimulation (NMES).

Results

NMES devices increase venous haemodynamic parameters such as peak velocity and volume flow. Studies report them to be non-inferior to intermittent pneumatic compression. They are effective in the prevention of venous thromboembolism, though inferior to low molecular weight heparin. NMES can reduce symptoms of chronic venous disease.

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Discussion
NMES is an important tool in the prevention and management of venous disease, and avoids the significant risks associated with heparin administration. Data explored here is heterogenous in device, protocol, and reported end-points, therefore should be interpreted with care. Long term effects of treatment with NMES have not been explored.

Keywords
Venous • Thrombosis • VTE • Electrical stimulation • Heparin

1 Introduction

Venous disease is common in the general population. Dysfunction of the venous system in the form of obstruction, incompetence or failure of the muscle pump leads to venous hypertension. Chronic venous hypertension manifests as a wide spectrum of venous disorders in the lower extremities, such as varicose veins, oedema, skin changes and ulceration. Up to 20 % of the general population suffer from uncomplicated varicose veins, 1.1–14.9 % complain of oedema, and up to 5 % have skin changes or ulceration (Meissner et al. 2007).

Deep venous disease is less prevalent than its superficial counterpart, however morbidity and mortality from deep venous thrombosis (DVT), venous thromboembolism (VTE), and post thrombotic syndrome (PTS) are significant (Baldwin et al. 2013). DVT is recognised as an increasingly important and frequent cause of venous disease, has an incidence of 0.2 % in the general population, and up to 25 % in the hospital population (Clagett and Reisch 1988). Factors affecting venous flow (e.g. immobility, dehydration, sepsis) predispose to venous thromboembolism, and are commonly seen after long haul flights and hospital inpatient episodes (MacDougall et al. 2006). Reversal of these risk factors is thought to be protective against venous thromboembolism, and underlies government anti-VTE initiatives in hospitals. Despite this, 1000 people in the UK are diagnosed with DVT every week, and roughly 50 % of these will go on to develop pulmonary embolism, a potentially life-threatening condition (Howard and Hughes 2013). In 2007 nearly 17,000 recorded deaths in England and Wales recorded DVT or PE as either the primary cause of death or a contributory factor (Office of National Statistics 2007).

The muscular pumps of the lower limb (foot, calf and thigh) consist of deep venous plexi surrounded by muscle groups in tight ensheathing fascia, and are credited with providing approximately 90 % of venous return during ambulation (Meissner 2005). The calf muscle pump, first described by William Harvey in 1928, has an ejection fraction of approximately 65 % in healthy individuals (Harvey 1928; Williams et al. 2014a). In a normal individual, resting standing venous pressure is 80–90 mmHg, which drops by more than 50 % with calf exercise (Eberhardt and Raffetto 2005). This pumping effect is blunted in patients with venous reflux (Eberhardt and Raffetto 2005). An effective calf muscle pump in the presence of valvular dysfunction or obstruction plays a compensatory role, and may offset symptoms in chronic venous disease (Davies et al. 2008). Therefore it is not surprising that stimulation of the calf muscle pump has been the target for a number of potential clinical applications in the prevention and management of venous disease. The calf muscle pump can be augmented passively or actively. Applying external pressure to the calf results in passive augmentation of the calf muscle pump. This pressure can be applied continuously (compression stockings) or intermittently (intermittent pneumatic compression – IPC; or calf squeezes). Alternatively, active stimulation can be achieved by voluntary calf muscle exercises.

Neuromuscular Electrical Stimulation (NMES) utilises transcutaneous electrodes to cause muscle contraction either by activating the muscle itself (direct), or the nerve supplying a muscle group (indirect). Electrical stimulation has been used to elicit muscle contraction since the time of Galvani (1791), however has never attained true popularity due to problems associated with electricity supply, peri-operative safety, and portability of equipment (Cambridge 1977). A wide variety of commercial and medical products are emerging in the market with applications such as strength training, exercise recovery tools, rehabilitation in immobilised patients, and in the management of acute pain (e.g. child birth). The aim of this review is to provide a summary of the available literature on the use of electrical stimulation in the management of venous disease, and its relevance in the modern era.

2 Methods

The MEDLINE and Embase databases were searched to identify all articles relating to application of electrical muscle stimulation in treating venous disease on 15th August 2014. The following search string was applied:

(Electric$) AND ("calf" OR "foot" OR "thigh" OR "buttock" OR "gluteal) AND ("vein" OR "venous" OR "oedema" OR "edema"). English language and human subject limitations were applied.

Studies were included if they contained venous haemodynamic or clinical data for the use of electrical muscle stimulation (regardless of device or protocol involved). The full articles of studies that appeared to meet the demands of the inclusion criteria were then independently assessed using the STROBE statement to verify the methodological quality of the studies (von Elm et al. 2007). Studies were excluded if results did not relate to electrical muscle stimulation and venous flow. Wound healing studies where devices did not cause muscle contraction were also excluded.

3 Results

The search strategy returned a total of 265 articles. Articles were screened by title, abstracts and full text (RR and KW). Following screening 46 articles met the inclusion criteria and were included in the review. The search strategy is illustrated in the PRISMA diagram in Fig. 1.

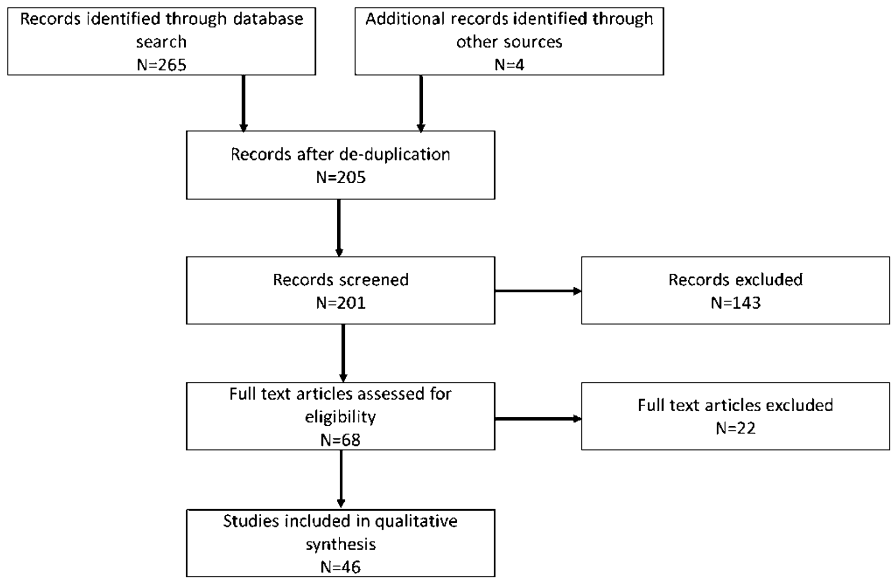

Fig. 1 PRISMA flow diagram of systematic review evaluating the role of neuromuscular stimulation in venous disease

4 Physical Parameters

Comparison between trials is hindered by variations in protocols and outcome measures, however some investigators have made comparisons varying parameters of electrical stimulation. All studies showed an improvement in venous haemodynamics with stimulation of the calf muscle pump compared to rest:

- Volume flow in the calf increased 50–719 % from baseline (Heath and Gibbs 1992) (venous occlusion plethysmography), 60–614 % (ultrasound) (Broderick et al. 2009, 2010a, 2011, 2013; Izumi et al. 2010)
- Femoral and popliteal peak velocity increased by 25–650 % (Broderick et al. 2009, 2010a, b, 2013; Izumi et al. 2010; Lyons et al. 2002; Kaplan et al. 2002; Tucker et al. 2010) (ultrasound)
- Time averaged maximum velocity (TAMV) increased by 178–354 % (Broderick et al. 2013).
- Ejection volume due to electrical stimulation was 60–100 % of that elicited by voluntary contraction (Faghri et al. 1998; Miller et al. 2000) and popliteal venous velocity "strongly correlated" to force of plantar flexion (Corley et al. 2009).
- Calf vascular resistance was significantly reduced after electrical stimulation (Miller et al. 2000), equivalent to post-exercise (voluntary calf contractions to a metronome).

Kaplan et al. found that stimulation of the foot and calf are equivocal in their effect on popliteal flow (Kaplan et al. 2002).

4.1 Effect of Electrical Parameters on Venous Haemodynamics

4.1.1 Direct Stimulation of the Muscle

Nicolaides et al. report that electrical stimulation of the muscle directly using pulse width 50–100 ms and frequency 25 mHz (15/min) produced maximal venous velocity without discomfort (Nicolaides et al. 1972). Settings above this were untenable. Griffin et al. increased the frequency of stimulation between 2 and 120 stimulations per minute and found that the popliteal vein peak velocity increased for stimulations up to 10 mHz, but decreased towards 2 Hz (Griffin et al. 2010). Ejected calf volume per minute increased from 20 to 120 ml/min with increasing stimulation frequency.

4.1.2 Indirect Stimulation

Lyons et al. found that pulse duration 300 μs and frequency of 35 Hz applied to nerve produced the greatest increase in popliteal peak venous velocity with a pulse width 200–300 μs, and frequency 24–35 Hz (Lyons et al. 2002). Tucker et al. found that increasing stimulation frequency from 1 to 5 Hz and pulse amplitude from 1 to 40 mA had a positive correlation with increasing venous volume flow peak venous velocity and microcirculatory flux (Tucker et al. 2010).

Izumi et al. (2010) compared two different electrical stimulation frequencies (10 Hz vs 50 Hz) using the same stimulator and found that the lower frequency produced a higher peak velocity compared to 50 Hz stimulation, however the findings seem to be confounded by a mix of direct and indirect stimulation.

4.2 Comparison of NMES to Other Medical Devices

Four studies compared the effect of electrical stimulation to IPC (Laverick et al. 1990; Czyrny et al. 2010; Williams et al. 2014b; Jorgensen et al. 1994). Both indirect stimulation via the common peroneal nerve, and direct stimulation of calf muscles have been shown to be non-inferior to calf and/or foot IPC.

On comparing calf IPC to electrical stimulation via the common peroneal nerve, Williams et al. (2014b) demonstrated that whilst peak venous velocity increased significantly with both methods, only NMES had a significant

effect on time averaged mean velocity (TAMV) and volume flow. On comparing foot IPC to calf NMES, Laverick et al. demonstrated a greater increase in mean venous velocity and peak venous velocity with NMES.

Faghri et al. demonstrated increased cardiac stroke volume (24 %), cardiac output (26 %) and a reduced total peripheral resistance (21 %) with electrical stimulation when compared to IPC of the calf and thigh (Faghri et al. 1997).

Lyons et al. demonstrated that the effect of electrical stimulation is augmented by a factor of 2 with the addition of graduated compression stockings (Lyons et al. 2002).

Nicolaides reported an increased incidence of peri-laparotomy DVT with NMES when compared to a combination of graduated compression stockings and calf/thigh IPC (18 % vs 4 %) (Nicolaides et al. 1983).

5 Efficacy of Clinical Application

5.1 Electrical Stimulation as a Method of Thromboprophylaxis

Outcome parameters for DVT detection in these studies are heterogenous, and include presence of clinical symptoms, phlebography, I-125 fibrinogen uptake tests and duplex ultrasound.

Between 1967 and 1973, four case series looked at treatment of one leg with direct muscle stimulation, using the contralateral leg as a no-treatment control. An absolute risk reduction (ARR) of 2–12.7 % was seen when compared to control leg (Doran and White 1967; Doran et al. 1970; Browse and Negus 1970; Dejode et al. 1973).

Randomised trials with subjects undergoing open abdominal surgery, used direct muscle stimulation of the calf versus heparin versus no-treatment controls. This showed a DVT ARR 16–26.3 % (Nicolaides et al. 1972; Becker and Schampi 1973; Lindstrom et al. 1982; Pollock 1977) for NMES, and 26–54 % for subcutaneous heparin three times daily. There was a 2.1 % declared major haemorrhage rate requiring transfusion for those on heparin, whereas there were no adverse events reported with NMES (Rosenberg et al. 1975). One study reported that NMES gave a DVT ARR 39 % over no-treatment control when the laparotomy indication was for malignancy (Lindstrom et al. 1982). One paper reports of NMES use in major trauma, where heparin is contraindicated for VTE prophylaxis – DVT incidence was equivocal (27 % NMES versus 29 % control, $n = 47$) (Velmahos et al. 2005). Studies in surgical patients comparing heparinised patients with or without NMES have mixed results, some showing no difference in DVT rates (Bostrom et al. 1986), whilst other show ARR DVT 22.5 % and ARR death 5 % (Lobastov et al. 2014). When combined together, NMES and heparin gave an ARR 40.4 % when compared to placebo (Merli et al. 1988).

Figures 2, 3 and 4 summate meta-analysis of NMES under three conditions. NMES versus no treatment favours NMES, with DVT odds ratio 0.4 ($p < 0.0001$). NMES versus heparin results in DVT odds ratio 1.84 ($p = 0.03$), whilst NMES and heparin versus heparin alone give an odds ratio 0.07 ($p < 0.001$).

5.2 Effect of Electrical Stimulation on leg Oedema/Chronic Venous Disease

Five studies examined the effect of NMES on oedema, four of which were on healthy individuals (Broderick et al. 2010a; IO et al. 2003; Green et al. 2008; Goddard et al. 2008) and one study involved patients with evening oedema (Bogachev et al. 2011). Healthy volunteers showed significant increase in foot and ankle volume when standing still over 30 min, which was abolished with NMES use (IO et al. 2003). Both leg volume measurements and air plethysmography, in the

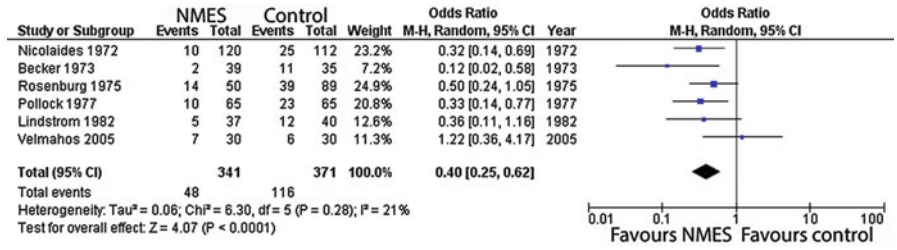

Fig. 2 Meta-analysis of trials evaluating deep venous thrombosis risk: NMES versus no-treatment control

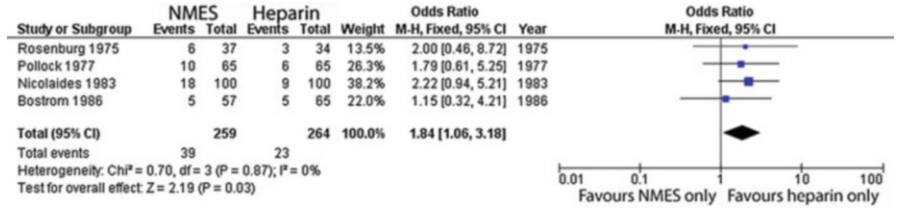

Fig. 3 Meta-analysis of trials evaluating deep venous thrombosis risk: NMES versus heparin

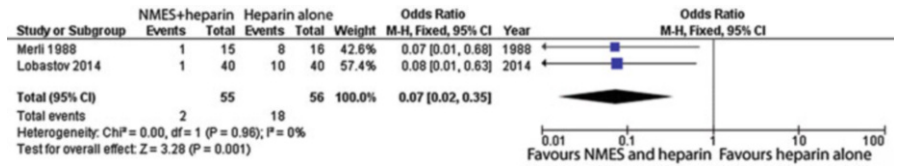

Fig. 4 Meta-analysis of deep venous thrombosis risk: dual therapy with NMES and heparin versus heparin alone

seated position, demonstrated reversal of fluid pooling in the legs with electrical stimulation of the calf (Green et al. 2008; Goddard et al. 2008). Broderick tested leg swelling in supine subjects, and unsurprisingly showed no leg swelling over 4 h bed rest, and no additional effect with NMES (Broderick et al. 2010a).

In trials on patients with venous disease, 20 min of treatment over a 30 day period resolved evening oedema in 59.4 % of cases, reduced it in 34.4 %, and remained unchanged in 6.2 % of cases (Bogachev et al. 2011). This resulted in a significant reduction in group average supramalleolar circumference, reduced pain score and improved quality of life.

5.3 The Effect of Electrical Stimulation in Patients with Impaired Calf Muscle Pump

Patients with neurological disorders affecting the lower limb will suffer from impaired muscle pump activity. In addition to increasing their risk of developing deep vein thrombosis, this group of patients are at a higher risk of cardiovascular failure because of autonomic dysfunction and have impaired venous return to the heart. Van Beekvelt et al. (2000) using strain gauge plethysmography demonstrated that electrical stimulation can improve muscle pump activity in spinal cord injured patients. Although the

spinal cord injury patients could tolerate higher current (60 mA), their muscle pump action was significantly lower than that of able bodied subjects (21.5 % vs 67.7 %). Effects of long term treatment were not investigated.

6 Discussion

Electrical stimulation has been shown to improve venous haemodynamics, however the reporting of stimulation parameters varies greatly between trials. It is not clear from the evidence which are the optimum parameters for stimulation, and it may be that clinical indication will dictate whether direct or indirect stimulation is most suitable. Electrode placement determines the effectiveness of calf muscle stimulation due to the particular nerve or muscle bulk targeted, with direct comparisons being misleading. The contraction relaxation times are variable which would affect venous filling and therefore the calf muscle pump function. Subject position is heterogenous, and comparing studies with standing, seated, prone and supine subjects may be injudicious. Haemodynamic outcome measures include air plethysmography, photoplethysmography, strain gauge plethysmography, venous occlusion plethysmography and venous duplex. The site of duplex scanning varies between the femoral, popliteal, posterior tibial and peroneal veins, whilst assorted haemodynamic parameters are reported, and the clinical significance of each parameter is poorly understood. Similarly, the techniques for detecting DVT in the initial studies lacked the sensitivity and specificity of today's imaging techniques.

NMES is non-inferior to IPC in terms of venous haemodynamics, and does not carry the complications associated with IPC (mainly excessive heat and sweating under the inflatable cuffs). However some subjects have found NMES uncomfortable (Lachmann et al. 1992). One of the benefits of electrical stimulation over IPC is that the action increases the activity of the users own muscles, as opposed to a passive compression system. A randomised control trial of intensive care patients demonstrated an improvement in muscle strength with electrical stimulation (Karatzanos et al. 2012). It has been shown that aerobic exercise of any type, even just the arms, has a positive effect on walking distances in claudicants, and may alter metabolic profile (Zwierska et al. 2005). The cardiovascular benefits from NMES are unknown.

Venous stasis is thought to be a major contributor in the pathogenesis of deep vein thrombosis, and is the main mode of action targeted by electrical stimulation in VTE prevention (Mackman 2012). In our meta-analysis, heparin has been shown to be most efficacious in the prevention of DVT when compared to NMES alone. However where heparin is contraindicated, NMES significantly reduces VTE risk. In cases of very high risk, the addition of NMES to a heparin thromboprophylaxis regime increases efficacy. Katz observed a fibrinolytic effect with the use of NMES, and when twinned with increased venous velocities in the deep veins may work in synergy with heparin (Katz et al. 1987). It must also be kept in mind that there are significant risks associated with heparin, such as major haemorrhage, stroke, exacerbation of post-operative bleeding, heparin-induced thrombocytopaenia, and osteoporosis. There is also a need to adjust dose in extremes of body mass, pregnancy and renal impairment (Gouin-Thibault et al. 2005). These problems are not encountered with NMES. High risk peri-operative patients are likely to benefit from electrical stimulation in addition to low molecular weight heparin. In particular, patients who are regarded as high risk such as those undergoing bariatric surgery and laparoscopic cancer surgery, or immobile patients with spinal cord injuries. The combination of NMES with graduated compression stockings may further enhance the haemodynamic effects.

The potential clinical application of electrical stimulation in venous disease is largely unexplored, but given the dependence of the venous system on the calf muscle pump, and the large

numbers of people with CVD, this is worth exploring. Given that orthostatic oedema can be reversed with NMES, and the ability of the calf muscle pump to be trained over time, NMES may be very successful in this area. Increased impedance of skin and subcutaneous tissues in the presence of oedema requires higher stimulation settings to achieve muscle contraction, but may be limited by pain threshold. Venous haemodynamic measurements tell part of the story, but we recommend future trials should concentrate on translating these effects into clinical practice. Clinical outcomes (e.g. ulcer healing rates) and quality of life data will be most useful in analyzing NMES as a clinical tool, especially given the success of IPC in this cohort (Dillon 1986; Kolari and Pekanmaki 1986; Kolari et al. 1988; Smith et al. 1990; Nelson et al. 2011).

The field of electrotherapy is interesting and currently underutilized, despite the emergence of various new devices with improved safety profiles and portability. However, the lack of uniformity of nomenclature impedes comparison between devices. A consensus needs to be achieved on reporting of electrical parameters such as pulse width, frequency of stimulation, intensity and waveform. Research should also investigate the effects of dosing, duration of treatment and long term effects of electrical stimulation in treating venous disease.

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Non-Invasive Management of Peripheral Arterial Disease

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Abstract

Background

Peripheral arterial disease (PAD) is common and symptoms can be debilitating and lethal. Risk management, exercise, radiological and surgical intervention are all valuable therapies, but morbidity and mortality rates from this disease are increasing. Circulatory enhancement can be achieved using simple medical electronic devices, with claims of minimal adverse side effects. The evidence for these is variable, prompting a review of the available literature.

Methods

Embase and Medline were interrogated for full text articles in humans and written in English. Any external medical devices used in the management of peripheral arterial disease were included if they had objective outcome data.

Results

Thirty-one papers met inclusion criteria, but protocols were heterogenous. The medical devices reported were intermittent pneumatic compression (IPC), electronic nerve (NMES) or muscle stimulators (EMS), and galvanic electrical dressings.

In patients with intermittent claudication, IPC devices increase popliteal artery velocity (49–70 %) and flow (49–84 %). Gastrocnemius EMS increased superficial femoral artery flow by 140 %. Over 4.5–6 months IPC increased intermittent claudication distance (ICD) (97–150 %) and

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absolute walking distance (AWD) (84–112 %), with an associated increase in quality of life. NMES of the calf increased ICD and AWD by 82 % and 61–150 % at 4 weeks, and 26 % and 34 % at 8 weeks.

In patients with critical limb ischaemia IPC reduced rest pain in 40–100 % and was associated with ulcer healing rates of 26 %. IPC had an early limb salvage rate of 58–83 % at 1–3 months, and 58–94 % at 1.5–3.5 years. No studies have reported the use of EMS or NMES in the management of CLI.

Conclusion

There is evidence to support the use of IPC in the management of claudication and CLI. There is a building body of literature to support the use of electrical stimulators in PAD, but this is low level to date. Devices may be of special benefit to those with limited exercise capacity, and in non-reconstructable critical limb ischaemia. Galvanic stimulation is not recommended.

Keywords

Chronic venous disease • Thrombosis • DVT • Pulmonary embolism • Electrical stimulation • NMES

1 Background

Peripheral arterial disease (PAD) is common, and often co-exists with cardio-respiratory disease, stroke, and diabetes [1]. Its incidence is estimated at 7–14 % in the general population [1, 2], increasing with age to approximately 20 % in the over-seventies [3]. It is associated with progressive and profound effects on mobility, skin integrity and quality of life [4]. Significant clinical manifestations include intermittent claudication, rest pain, gangrene, and limb loss. Risk management, exercise, radiological and surgical intervention are all valuable therapies, but morbidity and mortality rates from this disease are increasing [3, 5, 6]. Due to the nature of the disease, exercise tolerance can be limited by performance status. Invasive procedures carry with them significant risks, and patients with diffuse disease are often not suitable for revascularisation [7].

Maximal medical and surgical therapy has been shown in the past to be augmented by the use of medical devices such as intermittent pneumatic compression [8]. Electronic muscular stimulation (EMS) and neuromuscular stimulation (NMES) devices can cause contraction of the leg muscles in similar ways to IPC, and may have similar beneficial effects. The supporting evidence for neuromuscular stimulation in peripheral arterial disease is variable in scientific and clinical content or relevance, and prompted further exploration.

This review aims to identify and analyse studies of non-invasive haemodynamic devices applicable to this cohort, and extrapolate evidence with a view to modulating current clinical practice. This is also relevant in the light of recent technological advances of electrical stimulation devices, becoming more portable, affordable, and accessible to health professionals.

2 Methods

A systematic review of Embase and Medline was undertaken, with the search string:

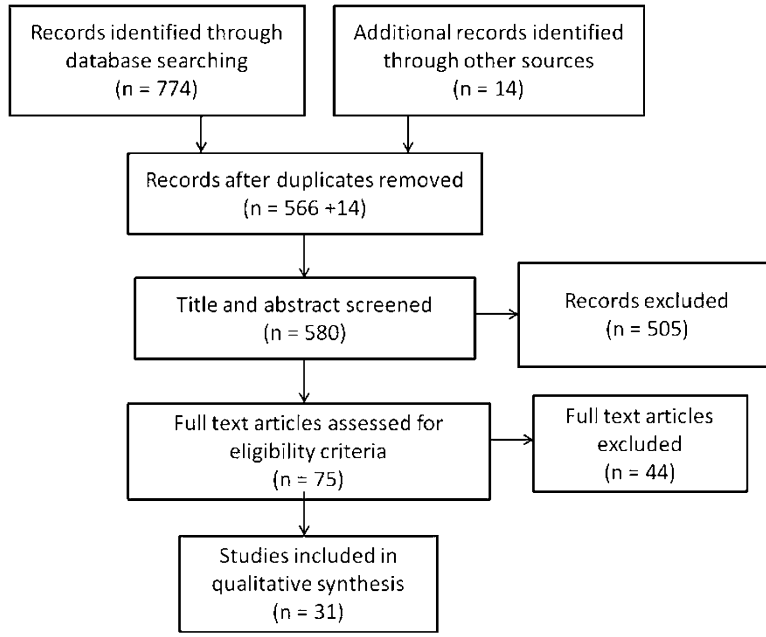

Fig. 1 PRISMA diagram

("device" OR "electric" OR "stimulation" OR "pneumatic" OR "compression" OR "IPC") AND ("peripheral arterial diseas*" OR "isch*" OR "peripheral vascular diseas*" OR "claudication") AND ("leg" OR "limb" OR "foot") (No Related Terms)

The search was performed on 8th July 2013 and repeated by the Royal College of Surgeons of England library. A PRISMA diagram shows the paper selection process (Fig. 1).

Abstracts were screened and included or eliminated by title, abstracts and full texts were screened for the peripheral use of non-invasive medical devices in humans for the management of lower limb peripheral arterial disease.

Inclusion criteria were clinical or haemodynamic data related to the device use. Exclusion criteria were animal studies, studies pertaining to epidemiology, diagnosis or pure imaging. Non-electrical devices were excluded (e.g. vascular closure devices), as were invasive therapies such as endovascular intervention, spinal cord/epidural stimulation, and extracorporeal limb perfusion. Functional electric stimulation for spinal cord injury was excluded.

3 Results

Thirty-one papers met criteria for inclusion and were grouped according to indication for use. Despite multiple devices, protocols and trial designs, inferences have been drawn. Table 1 details the studies, with numerical results data given where possible. Meta-analysis has not been performed.

4 Devices

4.1 Intermittent Pneumatic/External Compression

Six external compression devices were reported: five pneumatic (Circulator Boot, Circulator Boot Company, the AV Impulse, Novamedix Ltd, the DVT-30, Huntleigh Healthcare, the Art Assist 1000, ACI Medical, the ArterialFlow, DJO), and one which uses an external compressive band (FM220^{TM}, FlowMedic, Israel). Pressure settings varied from very low (55 mmHg in Circulation Boot) to high (120 mmHg in ArtAssist).

Table 1 Results of systematic review grouped according to indication

Device	Paper	Year	Setting/program	Subject profile	N (PAD/control)	Outcome measure	Outcome time period	Finding
Stable claudicants								
Circulator boot	Dillon [9]	1980	Combination of laboratory studies and case series	Claudicants, severe PAD non-reconstructable	29/6	Lab – subcutaneous pO_2, pulse volume, ABPI	40 mins	Oscillometry readings from the leg increased during therapy in normal and diseased limbs after one session, changes more pronounced after series of treatment. $TcPO_2$ increased in diseased limbs during treatment
						Clinical – ulcer healing, presence rest pain, ICD		
			Reclining, applied to whole leg. 55–80 mmHg applied in late diastole. One 40 min session for lab study,					22/25 severe legs benefitted clinically from therapy (claudication distance, ulcer healing, rest pain). Best results in 3–4 sessions/day for >1 week. Two stopped therapy due to pain
ArtAssist	Eze [10]	1996	Alternatively foot +/− calf, sitting position, 120 mmHg 10 s 2/min	Stable claudicants, SFA occlusion	10/22	Laser Doppler (great toe)	Mean of 6 IPC cycles	Flux (PAD/healthy) 288/428 % of baseline with combination IPC
						Duplex popliteal artery		Arterial flow (PAD/healthy) 150/273 % of baseline with combination IPC
								Combination IPC more effective than IPC calf/ft alone

ArtAssist	Delis [11]	2000	Recovery position, IPC foot, 1–120 mmHg, 4 s, 3/min, 5 mins on, 10 min rest, 5 mins on etc.	Claudicants (fontaine 2)	40/25	Duplex popliteal artery velocities and flow	Lab	Mean popliteal artery flow 211 % $p < 0.001$ in healthy, 151 % $p < 0.001$ in PAD Mean popliteal artery velocity 215 % $p < 0.001$ in healthy, 149 % $p < 0.001$ in PAD Post compression baselines of both were significantly higher than pre-compression
ArtAssist	Delis [12]	2000	Sitting position, IPC foot/calf/combination, 1–120 mmHg, 4 s, 3/min, 5 mins on, 10 min rest, 5 min on etc.	Claudicants (fontaine 2)	31/25	Duplex popliteal artery velocity and flow	Lab	IPC combination mean velocity 263 % ($p < 0.001$) in controls, 170 % ($p < 0.001$) in PAD IPC combination volume flow 278 % in ($p < 0.01$) controls, 174 % ($p < 0.001$) in PAD IPC combination was more effective than IPC foot or IPC calf in PAD
ArtAssist	Delis [13]	2000	Device versus no device. Sitting position, 1–120 mmHg, 4 s, 3/min, >4 h/day	Claudicants (fontaine 2) stratified for smoking and diabetes	25/12	ICD, ACD, ABPI rest and post-exercise, duplex popliteal artery flow	4.5 months treatment, follow-up at 12 months	No improvement in parameters for those randomised to no device Popliteal artery flow 136 % of week 0 baseline at 4.5 months IPC foot at 4.5 m – ICD 246 % baseline, AWD 206 % ($p < 0.001$ for both)

(continued)

Table 1 (continued)

Device	Paper	Year	Setting/program	Subject profile	N (PAD/control)	Outcome measure	Outcome time period	Finding
								ABPI (pe) significantly greater than control group at 4.5 and 12 m. Significant benefit over controls persisted at 12 m
ArtAssist	Delis [14]	2002	Sitting position, IPC calf/ft/combination, 1–120 mmHg, 4 s, 3/min, 5 mins stim, 10 min rest, 5 min stim etc.	Stable claudicants	22 IC, 36 bypass	Laser Doppler great toe	Minutes, unspecified	IPC increases limb skin blood flux in controls and claudicants
								IPC combination and IPC foot produced the biggest flux differences over IPC calf ($p < 0.004$)
ArtAssist	Ramaswami [15]	2005	Device versus no device	Stable claudicants (matched for smoking, diabetes)	15/15	ICD, AWD, ABPI	12 months	ICD compared to baseline (device/no device) at 4, 6 and 12 months was 237/102 %, 241/103 %, and 250/104 %
			Sitting, IPC foot + calf, 120 mmHg, 3/min, 1 h twice a day					AWD was 184/102 %, 196/105 %, and 201/106 % (difference $p < 0.01$ for all)
								No significant change in ABPI shown in either group

ArtAssist	Delis [16]	2005	Device versus no device	Stable claudicants (AWD 35–350 m)	20/21	ICD	17 months	ICD IPC at 5 months 197 % ($p < 0.005$), BMT no significant difference
			Sitting, IPC foot and calf, 1–120 mmHg, 4 s, 3/min, 3+ h/day			AWD		AWD IPC at 5 months 212 % ($p < 0.005$), BMT no difference
						ABPI (rest and post-exercise)		Resting ABPIs not changed either group
						US popliteal artery volume flow		pe-ABPI IPC higher at 5 months ($P < 0.005$), BMT no difference
						QoL (SF-36)		No significant resting artery flow volume changes either group
						Compliance		Improved quality of life in IPC group at 5 months, BMT unchanged
								All reported gains with IPC sustained 12 months after treatment
								85 % compliance with home IPC (defined as ≥2.5 h/day)
DVT-30	Morris [17]	2002	Supine, unilateral, thigh and calf, 60 mmHg, 10 s, 1/min	Stable claudicants	11/18	Duplex common femoral artery frequency	10 min	PAD subjects arterial frequency 94 %/129 % of baseline during compression/deflation. Controls 85 %/121 % of baseline
						Temperature limb		Hallux temperature changes −0.1 °C for controls and +2.2 °C PAD

(continued)

Table 1 (continued)

Device	Paper	Year	Setting/program	Subject profile	N (PAD/control)	Outcome measure	Outcome time period	Finding
AV impulse	Morgan [18]	1991	Seated, non-weight bearing, 100 mmHg, 3 s, 3/min	Claudicants	10/12	Doppler popliteal artery flow	Lab	Flow 193 % and 184 % of baseline in healthy and PAD ($p < 0.0001$ and $p < 0.03$)
								Increase reduced by supine position and limb cooling
								Flow increase more persistent in PAD
								Contralateral limb flow not affected
FM220 (IMC)	de Haro [19]	2010	Calf	Stable claudicants	14/16	ICD, AWD and ABPI (pre- and post- exercise)	3 months	ICD 185 %, ($p = 0.002$), ACD 176 % ($p = 0.002$), in IMC group, no significant changes in controls
			65 mmHg for 3 s, 3/min			Compliance		ABPI (pe) 197 % ($p = 0.003$) in IMC group, no significant changes in controls
								Changes sustained after 3 months
								Compliance with device 78 %
IPC (unspecified)	Anthonysamy [20]	2012	10 mins, settings not specified	Stable claudicants (fontaine 2)	15/0	Duplex popliteal artery peak systolic flow	Lab	Flow with IPC 175 % of baseline ($p < 0.05$)
NMES	Loubser [21]	1988	Unilateral, common peroneal nerve	Stable claudicants	8/8	BP, HR	60 min	BP and HR changes not significant for either group
			2 Hz, intensity to produce muscle contraction, 60 mins			Hallux photoplethysmographic waveform		Hallux photoplethysmographic waveform significant change in PAD, not control
						Skin temp		Skin temperature significant rise in PAD, not controls

NMES (Medicompex)	Tsang [22]	1994	NMES versus sham (TENS)	Stable claudicants, ABPI < 0.9, AWD < 500 m, peABPI drop > 30 mmHg	13/13 sham	Treadmill ICD/AWD	8 weeks	ICD with NMES 126 % of baseline ($p < 0.003$), control 122 %, at 8 weeks
			Popliteal and anterior tibial nerves, 8 Hz, 350 microsecs			ABPI,		AWD with NMES 134 % ($p < 0.004$), control 127 % at 8 weeks
						Ankle flexion fatigue index		Differences between control and IPC not significant after 4 weeks therapy cessation
								Neither group improved ABPI
								Fatigue index improved in both groups, NMES more than sham, but returned to baseline after treatment cessation
NMES (Medicompex)	Hudlicka [23]	1994	Unilateral, tibialis anterior and gastrocnemius muscles	Claudicants	12/12 sham	AWD	4 weeks	AWD with 4 weeks NMES 161 % baseline ($p < 0.05$), sham 102 % (ns)
			8 Hz, 330 microsecs, voltage to produce muscle contraction. 20 mins, 3/day, 28 days			ABPI		Fatigue index NMES 200 % baseline ($p < 0.05$), sham 111 % (ns)
						Ankle flexion fatigue index		ABPI did not change significantly in either group
EMS (MediCompex)	Anderson [24]	2004	EMS versus sham (TENS)	Stable claudicants, pe-ABPI < 0.8, AWD 50–350 m	15	Leucocyte activation, vascular permeability,	4 weeks	No evidence of activated neutrophils, increased vascular permeability, or increased cardiovascular event incidence
			Unilateral gastrocnemius			ICD/AWD		ICD EMS/sham 182 %/ 208 % of baseline ($p < 0.01$)

(continued)

Table 1 (continued)

Device	Paper	Year	Setting/program	Subject profile	N (PAD/control)	Outcome measure	Outcome time period	Finding
			250 microsecs, 100 V, 6 Hz, 20 mins. 3/day, 7/week			Compliance		AWD 250 %/163 % ($p < 0.05$)
								95 % compliance
EMS (Veinoplus)	Abraham [25]	2013	Gastrocnemius and soleus	Claudicants (Fontaine 2)	15	Duplex SFA,	Baseline, during, 10 mins after	Flow 240 % baseline with stimulation at 100 bpm ($p < 0.01$) but wide variation
			Rectangular pulse <25 micro C, 50 Vpeak, 1–250 Hz, max duration 240 microsecs, 20 mins increasing contraction rates 60–100 bpm	Most symptomatic leg		NIRS TcO_2		No change in NIRS or O_2Hb signal with stimulation
						O_2Hb		No induction of ischaemic pain
						(compared to treadmill test)		
Critical limb ischaemia								
Circulator Boot	Dillon [26]	1997	Reclining. Cardiosynchronous end-diastolic single chamber pneumatic compression boot, 55–80 mmHg	Limb lesions (peripheral arterial, venous, diabetic, and neuropathic disease)	1517	Healing rate	Variable	80.5 % healed or improved
						Relapse rate		Relapse rate of 21.6 %
								Smoking and distance of home from treatment centre sig affected healing rates
Circulator Boot	Dillon [27]	1997	Reclining. Cardiosynchronous end-diastolic single chamber pneumatic compression boot, 55–80 mmHg	CLI for limb salvage	2/0	Limb salvage	Variable	Limb salvage described in both PAD cases, also diabetes and osteomyelitis. Intensive treatment regime using injected antibiotics, soaks, dressings and boot Tx. Reversal of peripheral neuropathy loosely described

Circulator boot (then home programme)	Vella [28]	2000	No unified protocol.	CLI, non-reconstructable with ischaemic ulcers	98/0	Ulcer healing, ulcer size (static or smaller), amputation rate, mortality	Average 40 days	79 % "favourable outcome" (ulcer decrease in size, complete healing, revascularised)
			Circulator boot – 55–80 mmHg timed with end-diastole, 45 mins, 1–2/day					83 % limb salvage (15 major amputations, 2 deaths)
			Home boot – foot +/− leg, 100 mmHg 3 s, 3/min, 2–6 h/day, mean duration 8 weeks					Authors claim can be used to bridge to revascularisation or skin grafting
ArtAssist	Louridas [29]	2002	Not specified	CLI	25/0	Ulcer healing	Mean 3 month	26 % ulcers healed
						Rest pain		
						Amputation rate		Rest pain improved in 40 %
						Toe pressures		
						Mortality		58 % limb salvage
								Toe pressures improved $p = 0.03$
								Mortality rate 12 %
ArtAssist	Labropoulos [30]	2005	Foot and calf IPC. Semi-erect, 120 mmHg, 3 s, 3/min	CLI (fontaine 3–4)	20/0	Duplex flow volume popliteal, medial gastrocnemius, genicular collateral artery	5 IPC cycles	Popliteal – 205 % of baseline ($p < 0.01$)
								Gastrocnemial–170 % of baseline ($p < 0.01$)
						Laser doppler foot		Collateral – 156 % of baseline ($p < 0.01$)
								Laser Doppler flux increased significantly with IPC use ($p < 0.03$)
ArtAssist	Sultan [31]	2011	Upright. 0–120 mmHg, 4 s, 3/min, 2 × 3 h/day, 3 months	CLI (Rutherford ≥ 4)	171/0	Ulcer healing	3 months, repeated for 18 %	94 % clinical improvement (Rutherford 4 -- > 3), 30 % at 3 years
			Protocol repeated if of significant benefit			Limb salvage	Median F/U 13 months	Rest pain resolved in all over treatment period
						Mortality		

(continued)

Table 1 (continued)

Device	Paper	Year	Setting/program	Subject profile	N (PAD/control)	Outcome measure	Outcome time period	Finding
								94 % resolution of ulcers and limb salvage at 3.5 years, median amputation-free survival 18 months
						Doppler popliteal arterial flow		30-day mortality 0.6 %. All-cause survival 31 % at 4 years
						Toe pressure		Toe pressures 146 % of baseline ($p < 0.0001$), sustained at 12 m
						QoL		Popliteal artery flow 158 % of baseline ($p < 0.0001$), sustained at 12 m
						Cost-effectiveness		Regression showed DM, chronic renal failure, and hypercholesterolemia had no significant effect on limb salvage
								Cost per quality-adjusted life year for IPC was €2953
Arterial flow, DJO	Kavros [32]	2008	IPC calf, 85–95 mmHg, 2 s, 3/min, 3 × 2 h/day	CLI (non-reconstructable)-non-healing ulcer or amputation wound	24/24	Limb salvage, wound healing	18 m	58 % (IPC) vs 17 % (control) had complete healing and limb salvage ($p < 0.01$)

IPC (unspecified)	Montori [33]	2002	Home use, 6 h/day	CLI non-healing wounds	107/0	Wound healing, amputation rate	Median 6 m	Wound healing seen with 40 % patients $TcPO_2 < 20$, 48 % in osteomyelitis/active infection, 46 % in IDDM, 28 % with a previous amputation
								7 patients discontinued use due to pain
IPC (unspecified)	Beirne [34]	2009	Not specified	CLI	149/0	Limb salvage, mortality.	30 days, 90 days, 6 m intervals (mean 18 m)	72 % "Sustained clinical improvement"
						Limb digital pressure measurement		3 % amputation rate
								21 % mortality
NeuroTrac 3 TENS (Verity Medical, UK)	Seenan [35]	2012	TENS versus sham	Tourniquet induced ischaemic pain in healthy legs	13	Time to pain threshold, pain tolerance, total pain endurance	To maximal pain able to be endured	Time to pain threshold ($p < 0.05$), tolerance ($p = 0.002$) and total endurance ($p = 0.003$) increased with device compared to sham controls
			Unilateral			Reported pain (21-NRS, McGill Pain Questionnaire)		Reported pain lower with device compared to sham
			Gastrocnemius					
			200 msecs biphasic pulses, 120 Hz, in a continuous pattern					
Post revascularisation								
AV impulse	White [36]	1996	IPC foot. 50–200 mmHg, 3 s, 3/min. 7 post-operative days, 4–6 h/day	Post ischaemic leg reconstruction (femorotibial bypass)	5/5	Calf and ankle circumference	7 days	Significantly less swelling in experimental patients compared to controls, which peaked on day 5 (no figure given)
						Duplex femoral/popliteal venous velocity		Significant increase in experimental patients' femoral and popliteal

(continued)

Table 1 (continued)

Device	Paper	Year	Setting/program	Subject profile	N (PAD/control)	Outcome measure	Outcome time period	Finding
								venous velocities (no figure given)
								Cessation of treatment to less than 4 h per day led to recurrence of symptoms, oedema, and a worsening of ulcers
ArtAssist	Delis [14]	2002	Sitting position, IPC calf/ft/combination, 1–120 mmHg, 4 s, 3/min, 5 mins stim, 10 min rest, 5 min stim etc.	Infra-inguinal arterial revascularization	36/20	Laser Doppler great toe	Minutes, unspecified	IPC increases limb skin blood flux in controls and grafted arteriopaths ($p < 0.001$), although no difference between these groups
								IPC combination and IPC foot produced the biggest flux differences over IPC calf ($p < 0.004$)
Misc								
Galvanic electrical stimulation (Micro Z)	Peters [37]	1998	Device on diabetics, with and without impaired TcO_2 ft	Diabetics	11/8	Laser Doppler foot TcO_2 ft	1 day	No difference in fluximetry readings, either group
			Unilateral, 100 Hz (twin peak monophasic), delivered via a silver nylon mesh stocking, 4 × 60 mins. No muscle contraction	(Foot $TcO_2 < 40$ mmHg)				Oxygen perfusion rose with stimulation during first 5 mins ($p < 0.04$). No changes in controls. No significant difference from baseline after cessation of device

Galvanic electrical stimulation (Micro Z)	Peters [38]	2001	Device to placebo	Diabetics with foot ulcers	20/20	Healing rate	12 weeks	No significant differences in wound healing rate between groups
			50 V, twin peak monophasic pulses, pulse width 100 microsecs, delivered via a silver nylon mesh stocking. 8 h, delivered at night. Alternating 10 min 80 Hz, 10 min 8 Hz, 40 min no stimulation	(TcO_2 > 30 mmHg)		Complete wound healing		Device/sham total wound surface area healed 86.2 %/71.4 % (ns)
						Complications		Complete healing 13/7 subjects (ns)
						Compliance (>20 h/ week)		Time to complete healing 6.8/6.9 weeks (ns)
								One amputation, in sham group
								70 % device compliance

PAD peripheral arterial disease, *ICD* intermittent claudication distance, *AWD* absolute walking distance, *$TcPO_2$* transcutaneous oxygen, *SFA* superficial femoral artery, *IPC* intermittent pneumatic compression, *ABPI* ankle brachial pressure index, *pe* post-exercise, *US* ultrasound, *NIRS* near-infrared spectroscopy, *CLI* critical limb ischaemia, *DM* diabetes mellitus

All applied pressure anatomically to the calf, some additionally to the foot or thigh.

4.2 Electrical Stimulators

A mixture of transcutaneous electrical stimulators were reported. The Veinoplus™ (Adrem Tech, France) delivers electricity to the gastrocnemius muscle (1–250 Hz, 50 V, pulse width 240 ms), whilst the three NMES/TENS machines can operate at variable settings and be placed over muscles or nerves (Medicompex™, Medicompex SA, NeuroTrac ™ TENS, Verity Medical Ltd, TENS SM1, Schwa-Medico). The Micro-Z™, Prizm Medical Inc is a galvanic electrical stimulator (50 V, pulse width 100 μs, sub-threshold for sensation and muscle contraction). Direct current is applied to a specific body area by a conducting garment, with contact aided by an electrolyte solution.

5 Evidence by Indication

5.1 Intermittent Claudication (Also Described as "Stable Claudicants", or Fontaine Stage 2)

The immediate effect of IPC devices is to increase popliteal artery velocity (49–70 %) [11, 12] and flow (49–84 %) [10–12, 18, 20] when compared to baseline levels. When used for a prolonged period of time they have also been shown to improve popliteal artery flow by 3–36 % [13, 16]. Electrical stimulation of the gastrocnemius has been shown to increase superficial femoral artery flow by 140 %, although there were a wide range of flow changes in the small cohort study [25].

There were a wide variety of protocols, however over the course of 4.5–6 months IPC was shown to increase ICD (97–150 %) and AWD (84–112 %) by clinically significant distances, with the benefits persisting over 12 months [13, 15, 16]. External compression of the calf achieved an increase of 85 % and 76 % in ICD and AWD, which was significant when compared to negative controls, and sustained at 3 months [19]. NMES of the calf muscles, using the Medicompex, increased ICD and AWD by 82 % and 61–150 % over 4 weeks [23, 24], and 26 % and 34 % over 8 weeks [22]. These trials were small, but results were significant when compared to a sham device group.

Delis et al. showed an increase in quality of life at 5 months with IPC therapy, whilst the best medical therapy groups scores were unchanged [16]. These gains were sustained at 12 months post-treatment.

5.2 Critical Limb Ischaemia

Studies suggest that IPC reduces rest pain in 40–100 % [29, 31]. One trial evaluated the effect of high frequency TENS on the relief of laboratory-induced tourniquet ischaemic pain [35]. The blinded use of the TENS machine delayed the onset of pain, reduced pain levels, and increased endurance of pain over a period of several minutes. This was significant when compared to sham-placebo. However, the feasibility of clinical use of TENS in peripheral arterial disease does not appear to have been explored.

IPC treatment was shown to have ulcer healing rates of 26 % [29]. Vella et al. offer a 79 % "favourable outcome" at 40 days, a loose term which covers decreased ulcer size, complete healing, or improved sufficiently to allow revascularisation [28]. Blood flux to the skin of the foot, as evidenced by laser Doppler, was increased significantly over 5 IPC cycles in a cohort of 20 subjects [30].

IPC had an early limb salvage rate of 58–83 % at 1–3 months, and 58–94 % at 1.5–3.5 years [28, 29, 31, 32, 39]. Beirne et al. quoted an amputation rate of 3 % at 18 months, and a mortality rate of 21 %, but do not compare to controls [34].

No studies have reported the use of EMS or NMES in the management of CLI.

5.3 Post Revascularisation

Two IPC devices have been investigated for their utility in circulatory support after surgical revascularisation. Application to the foot for 7 days after femorodistal bypass in 5 subjects led to reduced swelling and increased haemodynamic parameters in the femoral and popliteal vessels over controls not treated with IPC [36]. No numerical data to support this is given, and conflicts of interest have not been declared. The 2002 paper looks at grafted arteriopaths (femoropopliteal and femorodistal bypass) approximately 18 months post-operation, and shows that a single treatment with IPC increases foot skin blood flux from baseline equally to controls, during device operation [14].

5.4 Galvanic stimulation - a special mention

There were few published clinical studies using galvanic electrical stimulation in peripheral arterial disease. Peter et al. investigated subjects who had impaired peripheral perfusion and microvascular insufficiency, as measured by laser Doppler and transcutaneous oximeter [37]. He demonstrated an increase in skin blood flux and oxygen tension in 11 diabetic patients with impaired microcirculation after 5 mins of stimulation, which dropped back to baseline after stimulation ceased. Another study of 40 randomised and controlled subjects looked at the healing of diabetic neuropathic foot ulcers when subjected to a nocturnal program of galvanic skin stimulation over 12 weeks [38]. There was no significant difference in wound healing rate, time to complete healing, or limb salvage between test and control groups.

6 Discussion

There is evidence to support the use of IPC in the management of intermittent claudication, with clinically important changes in treadmill distances seen with regular use. The greatest volume of published supporting research lies behind the ArtAssist device. The benefit of linking compressions to cardiac cycle, such as with the Circulator Boot, has not been shown to be clinically important at this point in time.

This review suggests that long term EMS or NMES can positively affect clinical parameters of symptomatic peripheral arterial disease. It remains to be seen how effective long term NMES is for treating symptomatic intermittent claudication, and if this is equivalent to supervised exercise training, or a useful adjunct. NMES may have additional benefits over exercise alone. There is evidence in animal models that changes in muscle stimulation can affect muscle fibre differentiation, although this has not been replicated in adult humans [40]. Nerve cross-union experiments have shown the ability of fast and slow twitch muscles to change their contraction times and metabolic activity, according to changes in innervation [40, 41]. Forst et al. showed a positive effect on diabetic microvascular disease, with NMES able to increase foot temperature, but this was blunted in cases of peripheral neuropathy [42]. High level evidence will only be provided by an adequately powered comparative clinical trial.

The evidence presented here suggests that IPC reduces pain and increases limb salvage in critical limb ischaemia, and that this would be directly applicable to the clinical management of these patients were revascularisation is not possible.

Electrical stimulation devices have evolved significantly since their initial introduction as a simple pair of electrodes attached to a generator box, with significant safety concerns – they had been known to cause burns at the interface site, or explode in the operating theatre [43]. They are decreasing in size and cost, some are portable and do not interfere with mobilisation. The duration and length of NMES protocol remains contentious, with some advocating three 20 min stimulation sessions per day, others 1 h continuous stimulation per day. However, results in these small studies do appear to be both beneficial and similar [44]. There is no general

consensus as to an ideal protocol, which may be best explored in a combination of laboratory and clinical trials.

TENS machines have been used in the management of pain, and are thought to work through a gating mechanism, effectively switching off downstream pain signals by providing an alternative stimulus. This can be used in the treatment of pain symptoms of any cause, and do appear to be effective in the short-term treatment of ischaemic pain. Conclusions beyond this are not supported by the literature.

There is little evidence to support the use of galvanic stimulation in this patient cohort.

7 Conclusion

There are many devices that are clinically relevant to the vascular specialist managing patients with peripheral arterial disease. A working knowledge of available devices, especially IPC and NMES, expands the range of therapies available for management of symptomatic disease, and may be of special benefit to those with limited exercise capacity. The use of IPC in non-reconstructable critical limb ischaemia is particularly useful for limb salvage.

Medical devices for the assistance in management of all forms of PAD are emerging as important non-invasive tools. If they are to cement their roles in this management strategy, more robust research in the form of randomised controlled studies will be required to add to their evidence base.

Declarations of Interest None declared

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Medico-Legal Aspects of Pulmonary Thromboembolism

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Abstract

Pulmonary ThromboEmolism (PTE) is an important disease for legal medicine. Because of their sudden lethal onset, generally medicolegal autopsies show few clinical information when PTE is the cause of death. During medicolegal autopsies, the autopsy operator must answer to important questions. For example, autopsy operator can need to assess the casual relationship between PTE and recent accident, such as trauma or long air travel. Furthermore, the autopsy operator needs to investigate the pathology of PTE as a cause of sudden cardiovascular death. It is relatively simple to confirm a fatal massive thromboembolus in the initial stage of thoracic investigations, but sometimes it might be difficult to distinguish this from postmortem clot. In such cases histopathological examination can help in the differentiation. Histological examination is also required for observation of chronological changes of the thrombi. Chronological evaluation is an important factor especially to determine whether the death coincides with the date of a specific accident/event or instead there is an earlier onset of PTE. In addition, histological sections sometimes show additional information, such as tumor fragments in cases of malignancy or small fragments of bone marrow in cases of active resuscitation, that can be useful in a medicolegal scenario. Furthermore, new diagnostic tools are arising, which they can be very helpful in the individuation of this frequently underdiagnosed disease. The goal of our work is to investigate these aspects through the review of the recent literature.

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Keywords
Autopsy • Pulmonary thromboemolism • Thromboembolus • Immunoistochemestry • Histological examination • Postmortem computed tomography (PMCT) • Postmortem computed tomography angiography (PMCTA) • Macroscopic examination

1 Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two aspects of the same disease known as venous thromboembolism (VTE). The term "Embolism" refers to the transport of material in the blood stream from its origin into the vascular system to a distant location from the starting point. Emboli may be formed by a variety of different endogenous and exogenous materials, for example, fat, air, amniotic fluid, but the most common embolic material consists of admixed fibrin, platelets and red blood cells, (thrombi), which can arise within the venous circulation when one or more of the three requirements of Virchow's triad occur: stasis of blood flow, injury to the endothelial lining, and hypercoagulability of blood components. Based on their composition, aetiology, origin and site of impaction, embolic events can be sub-classified in different ways, but the most practical method groups the embolic accidents according to the particular embolic material that is involved and the portion of the vascular system that is obstructed (Byard 2013). The prevalence of VTE has been documented to be different in different parts of the world: for example, it has been reported that the prevalence of VTE in Africans and Asians is not as pronounced as it is in the Caucasians (Sotunmbi et al. 2006). Approximately 200,000 new cases occur in the United States every year, including 94,000 with PE, resulting in an incidence of 23 per 100,000 patients per year-cases (Kroegel and Reissig 2003). Ethnicity play an important role (Dilley et al. 1998), in fact, there is strong evidence that the prevalence of venous thromboembolism varies significantly among different ethnic/racial groups, but the genetic, physiologic and/or clinical basis for these differences remain largely undefined. For example, there is strong evidence that African-American patients have a significantly higher incidence of first-time VTE after exposure to a provoking risk factor. African-Americans are more likely to manifest PE compared to other racial groups. The incidence of recurrent VTE is similar in African- American and Caucasian women who develop DVT, but significantly higher in African-American women diagnosed with PE (Hira et al. 2003). African-American men and Caucasian men have a similar incidence of recurrent VTE (Hooper et al. 2006). Hispanics have a significantly lower prevalence of VTE compared to Caucasians, but higher than Asians (Itakura 2005). Instead, Asians have a significant 3 5-fold lower incidence of symptomatic first-time idiopathic and secondary VTE, and this racial group has significantly lower incidence of cancer-associated VTE (White and Keenan 2009), even if in the recent years some studies revealed that the Japanese population show the same tendency for an increase of PTE. The reason is still unknown, but suggested causes include the Westernization of the diet and an increase in the elderly people in the population, in addition to an improvement in clinicians' awareness of PTE in Asian Countries. In fact, venous thromboembolism is a multifactorial disease, involving both environmental exposure as well as genetic and ambiental interactions. Concerning inherent hypercoagulability, some ethnic differences seem to exist between Asians and Caucasians (Ro et al. 2008). Abnormalities within the gene loci encoding for natural anticoagulants (antithrombin, protein C, and protein S) and for fibrinogen have been shown to be rather uncommon risk factors for VTE. In

patients of European ancestry, a common mutation within the gene of the coagulation factor V (FV) Leiden (G1691A) and one within the factor II (FII) gene (G20210A) have been shown to account for a large number of cases of thromboembolism (Fineschi et al. 2012). Neither Factor V Leiden nor the prothrombin G20210A mutation, which is the most common genetic mutation related to venous thrombosis in Caucasians, are found among Asians (Ro et al. 2008). So, ethnicity should be considered an important factor in the risk-stratification of patients with suspected VTE or patients at some risk for developing VTE (White and Keenan 2009). Environmental factors include obesity, psychiatric disease, advanced age, trauma, malignancy (Ro et al. 2008), immobilization, surgery, hospital or nursing home confinement, neurologic disease with extremity paresis, as well as some types of oral contraception and hormone replacement therapy (Kroegel and Reissig 2003). Particularly, Venous thromboembolism is a fatal complication and a frequent cause of death among patients which are hospitalized for remediable and often minor conditions. The risk of symptomatic pulmonary embolism is 22-fold higher in hospitalized patients than in healthy outpatients, because of an accumulation of multiple embolic factors related to hospitalization: trauma or venous catheter produce damages to the vessel wall; immobilization, anesthesia or paralysis contributes to venous stasis; the use of procoagulating drugs or a primary disease that induce hypercoagulability (malignancy) leads to hypercoagulability (Ro et al. 2003).

Clinically, PE may present as isolated dyspnea, pleuritic pain and/or hemoptysis, and circulatory collapse, but clinical history and examination can be notoriously misleading in reaching a diagnosis. In fact, based on postmortem studies, two-thirds of the patients with pulmonary emboli remain undiagnosed (Kroegel and Reissig 2003), but some authors report higher percentages, for example Steiner et coll demonstrated in their studies that the accuracy of antemortem diagnosis of DVT and PE is within the range of just 10–30 % (Steiner 2007). Autopsy is still regarded as the diagnostic gold standard. For example, an analysis conducted by Siragusa et al. on 11,000 autopsies showed that 316 of these had macroscopic pulmonary emboli; nevertheless, only 11 % of cases were diagnosed before death, while 32 % of the patients were diagnosed as died of myocardial infarction, 15 % of cerebrovascular disease and 14 % of pneumonia (Siragusa et al. 1996). Unfortunately, statistics from recent, larger autopsy studies are poor and, moreover, the results of such studies are often controversial. This is due to the declining rate of autopsies during the last decades and the different autopsy techniques that make difficult to compare results from different sources (Steiner 2007). Also with these limitations, PE represent, however, one of the most frequent missed diagnosis in sudden, unexpected death. This provides a setting for malpractice claims. For these reasons, deaths caused by pulmonary thromboembolism are often of forensic interest, because of a possible professional responsibility (Montisci et al. 2003). Lethal PTE is one of the most frequent topics for suspected medical malpractice, especially when dealing with patients originally affected by non-critical illnesses and suddenly killed by a non-prevented embolic event. The question which the forensic operator must answer about a lethal PTE is the following one: was lethal PTE an unpreventable complication or was it a consequence of medical malpractice? In fact, post-surgical PTE cannot be automatically labeled as a consequence of medical malpractice. The combination of correct prophylaxis, careful diagnostic monitoring and the correct therapy reduces the frequency of lethal PTE, but it does not completely erase this insidious pathology. In the hypothesis of a medical malpractice, only careful analysis by an experienced forensic pathologist can make a reliable distinction between an unpreventable complication and real medical malpractice. The aim of our work is to analyze the forensic aspects of this disease (Mobilia et al. 2014).

2 Macroscopic Examination of Pulmonary Thromboembolism

The prevalence of PE at autopsy (approximately 12–15 % in hospitalized patients) has not changed over three decades. The failure to diagnose the disease is due to the difficulty in identifying an often elusive source of an embolic event. Clinical and autopsy studies have found the source of thromboemboli in 50–70 % of cases (Elhammady et al. 2011). In the hypothesis of pulmonary thromboembolism as a cause of death, careful analysis by an experienced forensic pathologist is mandatory. Usually, the majority of emboli originate in the veins of the legs, at the level of the femoral and iliac veins (Van Beek et al. 2000), but also upper extremity venous thrombosis and thrombi in the superior vena cava (attributed to invasive procedures), have been shown, while cardiac origin of PE plays only a minor role (Prandoni et al. 1997). The postmortem examination for thrombosis of deep veins of the lower limbs typically is confined to the manual compression of the lower extremities with repeated upward compression (milking), for the identification of premortem clots, but this technique may be useless in case of inadequate pressure to the leg (for example in obese patients) or when the clot may already have migrated (Elhammady et al. 2011). For this reason, in medicolegal autopsy, detail examination by direct view of the bilateral leg deep veins (not only at the proximal thigh veins but also including the crural calf veins) is mandatory. Some studies demonstrated that carefully examination of leg deep veins has improved the detecting rate of the embolic remainders from 51 % (Murai et al. 2001) to over 90 % (Ro et al. 2006). Deep vein thrombosis of the lower extremity is usually classified into three types: iliac, femoral, and crural (Ro et al. 2003). Since these events usually produce an early venous obstruction with clinical symptoms such as flare swelling, clinical medicine focused on iliac and femoral type DVT. Crural type DVT is generally found in association with bilateral venous stagnation in cases of immobilization and it is clinically very insidious. Some studies demonstrated that among inhospital patients without prophylaxis, DVT is found in 24 % of cases involving medical or general surgical patients (Sakon et al. 2006) and 22 % following major orthopedic surgery (Fujita et al. 2000) and, among them, form three-quarters to two-thirds of these were crural type deep veins thrombi, that are asymptomatic. In summary, iliac type and femoral type DVT are clinically important and occur mainly with leg symptoms. In contrast, crural vein thrombosis is usually asymptomatic, and one-fifth of them contain the risk of proximal propagation, resulting in a potentially massive embolus that can lead to a sudden death. The crural deep vein consists of seven kinds of veins, i.e. the popliteal vein, the posterior tibial vein, the peroneal vein, the anterior tibial vein, the soleal vein, and the gastrocnemius vein. The soleal vein is especially important as an initial site of DVT resulting in massive PTE. This happens because soleal vein and soleal muscle are anatomically weak and susceptible to exposure to venous stagnation caused by prolonged sitting. It's very important for the autopsy prosector to investigate these aspects in every case of sudden death, particularly when the patient has one or more risk factors (Fig. 1). A detailed histopathological examination is mandatory to reach the correct diagnosis. The diagnosis of acute PTE is relatively simple, because it is possible to see a large emboli in the pulmonary system (Fig. 2). But diagnosis is not so simple in the case of chronic PTE. In the past, acute PTE and chronic PTE were considered different diseases, but now we know that they are the same disease. Generally, acute PTE is characterized by a large thromboemboli that could be fatal in a single attack. However, detailed histopathological examination of acute massive PTE revealed a significantly increased detecting rate for organized thrombi at more distal sites which proves they were latent, remaining from previous attacks, setting the chronic PTE. Therefore, sudden death cases by PTE were suggestive of a chronic repeated history that could be seen

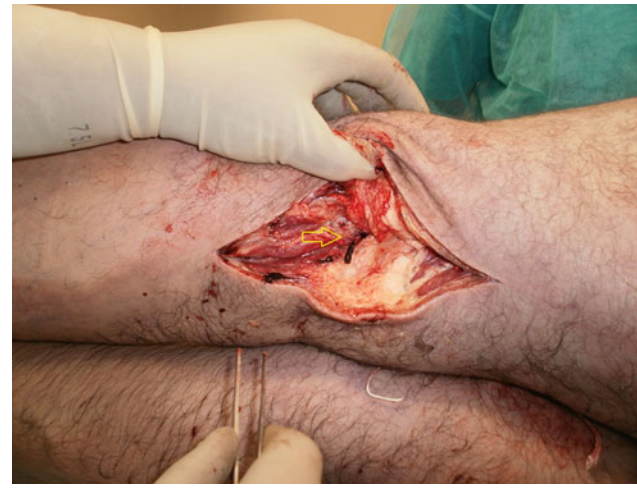

Fig. 1 Macroscopic findings: the origin of a thrombus in the popliteal vein (*arrow*)

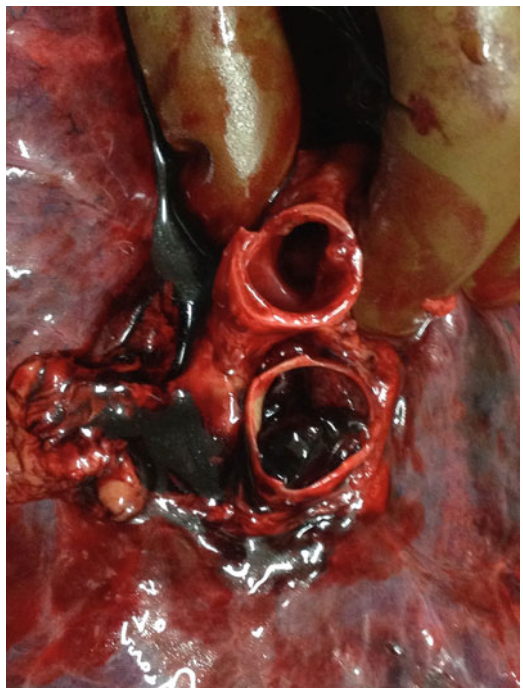

Fig. 2 Macroscopic findings: pulmonary embolism

upon autopsy. In a study by Dunnill et al., it was demonstrated that although massive embolism is usually unexpected, careful examination of fixed, inflated lungs at necropsy usually reveals that previous small emboli have occurred. These small emboli are 'herald' emboli and they are often undergoing organization in small conducting pulmonary vessels at the time of death (Ro et al. 2008). Occlusion of these pulmonary vessels has variable and transient clinical and pathophysiologic consequences, involving both mechanical and reflex effects of vascular occlusion with a consecutive perfusion defect and the release of vasoactive and other inflammatory mediators (Kroegel and Reissig 2003).

Usually, the starting point of emboli are leg deep veins, but autopsy operators must keep in minds that also other sites can be involved. For example, it is therefore important to examine the pelvic venous plexuses for thrombi, even if demonstration of pelvic vein thrombosis as the source of pulmonary thromboemboli is rare. Periprostatic or periuterine venous thrombosis are reported in literature. Of course, the diagnosis of thrombosis in these sites is most likely to be made only during postmortem examination. Other sites of clot origin may be suspected based on the clinical presentation (for example the atrial appendage of the right heart or the vessel wall at the tip of a venous catheter). Despite all, there is a group of patients for whom the site of clot origin is an enigma. The autopsy operator must keep in mind the pathways for emboli migration. These pathways may be, for example, the inferior vena cava or Batson's plexus through paravertebral veins (Elhammady et al. 2011).

Other autopsy finds that must be considered in the suspect of pulmonary embolism are cardiac and pulmonary findings.

Heart PTE-related mortality is considered to have a strong relationship with right ventricular dysfunction. As morphological changes with acute right ventricle failure due to volume overload, an enlargement of right ventricle was found in almost all the cases of PTE. In addition to the acute changes, right ventricular hypertrophy caused by continuous pulmonary hypertension was concomitantly observed in the most part of these subjects. These findings suggested that the patients had few subjective symptoms from the latent history of recurrent thromboemboli, and that the previous submassive PTE easily induced a pulmonary circulation disturbance resulting in right ventricular hypertrophy.

At the end, the most specific finding related to acute PTE at autopsy is the presence of thromboemboli in main pulmonary artery, which are easily found in routine autopsies with fatal PTE. Sometimes, it is possible to notice the marks of the venous valves that certificated the embolic sources. These emboli can be white or black emboli. Black emboli are easily found at the main pulmonary artery or at the segmental artery, while the white ones are usually found at the subsegmental artery or at the small elastic artery. White emboli are the remnants of fresh thrombi changed by the organizing process. These organized thrombi are useful for indication of latent past thromboemboli in patients subsequently examined in the forensic autopsy. However, detailed autopsies of cases of fresh massive thromboemboli could detect also organized thrombi in the same patient: Morpurgo and Schmid (1980) stated that 15 % of the PTE patients showed multiple infarctions occurring at different ages. Macroscopically, the more distal site at the pulmonary parenchyma appeared pale due to pulmonary circulatory ischemia. However, pulmonary infarction is an infrequent finding, because it occurs only in the 21 % of the cases with massive PTE. This can be due to dual perfusion of the pulmonary artery and the bronchial artery.

3 Microscopic Examination of Pulmonary Thromboembolism

Generally, pathologic features of thromboemboli must be estimated using histological sections stained by haematoxylin–eosin (H&E), trichromic stains (Masson, Azan, Mallory, PTAH, Van Gieson), Von Kossa for calcium salts and Perl's stain for hemosiderin to confirm the presence of iron (Fineschi et al. 2012). All these stains are fundamental for dating the embolic event. In fact, three phases of organization of the thromboembolus are known. The first phase (1st–7th day) starts with flowing blood on an eroded endothelium, this condition causes a platelet plug with deposition of fibrin in a layered fashion (Zahn's lines). In this phase, the thrombus is firmly attached to the vessel and there are not reactions between endothelium and thrombus; erythrocytes are preserved and agglomerated. It is possible to see initial pyknosis of white blood cells and also monocytes cells with enlarged nuclei. Precipitates of Calcium are observed in Von Kossa stain. After the first phase, the second one is characterized by endothelial budding and proliferative changes of the medial ring represented by penetration of fibroblasts. This phase usually lasts from 2nd to 8th week, and it is characterized by a predomination of macrophages containing hemosiderin and fibrinous transformation. The ribbons of fibrin change to a clot of white cells. The surface of the thrombus is covered by endothelium and scattered nuclear debris of white blood cells are observed. The third and last phase, from the eighth week, is characterized by a completely hyalinized thrombus with central sinuous cavities. Lately (older than 2 months), neo-formed larger vessels with fresh flowing blood are observed (Fineschi et al. 2009). As time goes by, if the subject survives, the thrombus become "organized". Organized thrombi are constituted by eccentric collagen or elastin elements that completely replace erythrocytes and fibrin, the main components of acute thromboemboli. The discovery of organized thrombi during histo-

pathological examination, especially in acute PE cases, suggests the previous occurrence of PE, and it is suggested by some authors that the frequency of organized thrombi might reflect the severity of recurrent PE (Ro et al. 2011). These histopathological advice provide very important suggestive information for physicians to predict acute PE at a preventable stage. Many studies demonstrated the frequency of recurrent PE. Dunnill (1987) stated that careful autopsy examination of patients with acute PE usually reveals small organized thrombi. Morpurgo (Morpurgo and Schmid 1980) reported that autopsy findings of multiple PE and pulmonary infarction are obtained in at least 15 % of PE cases (Ro et al. 2011), so further studies are needed to better understand the pathology of PE and discovery new diagnostic tool to monitor these patients which show high risk of thromboembolic events (Freiman et al. 1965).

Regarding the localization, it was demonstrated that fresh thromboemboli are more frequently located in the right lung than in the left one, and furthermore the lower lobes are mostly involved (Wagenvoort 1995). This is related to the flow distribution, which favors the right lung and the lower lobes. The highest frequency of organized thrombi is in the right pulmonary artery in the posterior basal lobe, even if it is possible to detect organized thrombi in the upper and middle lobes (Moser and Bloor 1993). Another aspect that autopsy operator must consider is that thromboemboli are usually trapped and organized at the bifurcation of the elastic artery (Morrell and Dunnill 1967), and that organized thrombi in the muscular artery arise as a consequence of fragmentation of previous PEs lodged in the proximal elastic artery.

To conclude, our message is to underline that autopsy confirmation of thrombi is fundamental for estimating the subclinical history of patients with recurrent PE, and it has an inestimable value for the diagnostic classification of family members of the deceased subject and to prevent other deaths.

4 Immunoistochemestry of Pulmonary Thromboembolism

As discussed above, PTE is an important disease for legal medicine for several reasons: it can be necessary to assess the causal relationship between PTE and recent accident, such as trauma, or it can be necessary to judge the medical practice in the cases of in-hospital PTE among patients who were treated for other diseases, or it can be necessary to investigate the pathology of PTE as a cause of sudden cardiovascular death. It is important, in a medico-legal contest, to know if a pulmonary embolus arose prior to, or subsequent to, some traumatic event. A major difficulty is that the embolus may be the most recent addition to an extending, older venous thrombosis. The best method to evaluate this condition is to examine and to try to date the residual thrombus (Fineschi et al. 2009). Historically, for the first time Iringer et al. (Irninger 1963) proposed histological aspects about forensic-histological age determination of thrombi. Subsequently, Leu et al. (Leu and Leu 1989) established representative findings in relation with thrombotic changes and chronological organization. In the last years, many interest are arising about the application of immunoistochemestry with the purpose to date the thrombus, because immunohistochemical markers are more sensitive and specific than conventional markers.

Immunohistochemistry (IHC) is a technique that combines anatomical, immunological and biochemical methods to identify discrete tissue components by the interaction of target antigens with specific antibodies tagged with a visible label. IHC visualize the distribution and localization of specific cellular components within cells and in the proper tissue context. A limitation of this method is that it is routinely used with tissues after fixation, and fixation chemically crosslinks proteins or reduces their solubility, and so it can mask target antigens during prolonged or improper fixation. The most common fixative is formaldehyde, a reagent that can be used for

immersion fixation for any length of time, depending on the level of fixation required. Fixed tissue samples are embedded in paraffin to maintain the natural architecture of the sample during long-term storage and sectioning for IHC. Formalin-fixed, paraffin-embedded tissues are usually sectioned into slices as thin as 4–5 μm for IHC diagnostic purpose.

Some studies (Fineschi et al. 2009, 2012; Nosaka et al. 2010, 2015) show that immunohistochemistry permits an objective age determination of the thrombus: the immunohistochemical detection of neutrophils and macrophages in venous thrombi could give significant information for age determination of venous thrombi. Furthermore, the dynamics of other types of cells and extracellular matrix, intrathrombotic collagen contents, and the appearance of hemosiderin-positive cells, myofibroblasts and neovessels are essentially involved in the formation and resolution of venous thrombi. Using histochemical and immunohistochemical techniques, it is possible to investigate these aspects in order to estabilish the thrombus age. Fineschi et al. (2009), for example, proposed immunohistochemical investigation of thrombus and embolus using polyclonal anti-fibrinogen antibodies, CD61, CD45, CD15, CD68. Nosaka et al. (2010), in their studies, evaluated intrathrombotic appearance of hemosiderin-positive cells as useful tool for thrombus age determination: in fact, macrophage recruitment is essential for thrombotic formation. Recruited macrophages can produce various cytokines and phagocytose red blood cells, and hemoglobin is converted into hemosiderin, that can be detected by Berlin blue staining. Hemosiderin- positive cells, myofibroblasts and neovessels were evaluated in these studies: hemosiderin-positive cells constantly appeared later than 5 days, while both myofibroblasts and neovessels were routinely detected at 10 days, demonstrating that these markers may be applicable for thrombus age determination (Nosaka et al. 2010). More recently, the same group showed that the immunohistochemical detection of cytokines and chemokines should be useful for determination of thrombus age. In fact, various kinds of bioactive molecules, such as cytokines and growth factors, are closely involved in the processes of formation and resolution of thrombi. They demonstrated the pathophysiological roles of cytokines such as IL-1, IL-6, TNFα, and IFNγ in the processes of thrombus resolution using genetically engineered mice. Particularly, IL-6 may be a key molecule in the formation and resolution of venous thrombi: thrombus resolution seem to be delayed in the absence of IL-6 through reduced matrix metalloproteinases (MMPs). IL-6 is a pleiotropic cytokine produced by many cells, including macrophages, T cells, fibroblasts, keratinocytes, and endothelial cells, and it seems to have detrimental roles in the thrombus resolution by suppressing intrathrombotic proteinases. However, further studies are necessary to confirm that immunohistochemical detection of intrathrombotic IL-6 would be applicable for thrombus age estimation (Nosaka et al. 2015).

To summarize, we state that the histological age determination of thromboses is an important task of PE and requires through knowledge of the general and specific pathology of VTE. Although further studies are needed, we believe that immunohistochemical study in venous thrombi could give information to determine the age of venous thrombi. However, the observed transformation of the thrombus by organization is suitable for a pathologically utilizable age determination. Furthermore, modern technologies are a valid aid to date the DVT phenomenon and the chronological changes of the thrombus.

5 New Postmortem Diagnostic Tools in Pulmonary Thromboembolism

In the last years, the detecting rate of venous thrombi in the cases of PTE has been increasing both in clinical and forensic medicine, due to the fact that the crural calf vein, including the intramuscular veins, can be more easily visualized by magnetic resonance imaging or ultrasonography than with the previous diagnostic techniques such as venography or computed tomography (Ro et al. 2011). These fundamental diagnostic tools can be performed after a lethal PE, for an

useful diagnostic aid in the evaluation of these patients, especially when there are problems to obtain permission for autopsy. Dedouit et al., for example, reported a case in which permission for autopsy was not obtained, but post-mortem computed tomography investigation was performed with the agreement of the patient's family in order to successfully ascertain the cause of death (Dedouit et al. 2006).

Postmortem computed tomography (PMCT) is routinely used in the forensic setting as supplemental investigation because of his capacity of provide significant data that can affect final conclusions. It is possible to integrate it with angiographic methods (postmortem computed tomography angiography, PMCTA and multiphase postmortem CT angiography, MPMCTA). These techniques allow the examination of the cardiovascular system, that is very useful in the field of forensic pathology. MPMCTA is an easily applicable technique that consists of the acquisition of one native scan and three different phases of angiography: an arterial phase, a venous phase and a dynamic phase. This technique allows the diagnosis of most cardiovascular pathologies because the native scan and the following injection of the contrast agent provide high diagnostic sensitivity similar to clinical CT angiography. MPMCTA is a powerful diagnostic tool in forensic investigations, and particularly for cardiovascular imaging purpose, even if artefacts and pitfalls have been recently demonstrated. The most important problem is that even if the Technical Working Group Postmortem Angiography Methods (TWGPAM) (Grabherr et al. 2011) proposed a method to perform postmortem angiography, this protocol does not specifically investigate the venous system of the arms and legs (legs are omitted from the protocol). But this diagnostic tool offers great possibility. It is well known that the majority of emboli originate in the veins of the legs, frequently at the level of the femoral and iliac veins, but it is difficult to identify during the autopsy other sources of emboli in the legs. In some specific but not infrequent situations (for example, when the vessels are located in poorly accessible anatomical areas of the body such as in distal thrombosis or when the vessels are small), identifying the exact location of the thrombus can be time consuming, difficult, and unsuccessful. Furthermore, obesity and patients with lower extremity oedema are others important limitations during the autopsy. Imaging through multiphase postmortem CT angiography can be very helpful in these cases. Recognition of a filling defect or inhomogeneous opacification allows the identification of the exact site of the suspected venous thrombus, making easier for the forensic pathologist to check the correct site in the venous system of the lower extremities and to identify the venous thrombus for subsequent histological examination (Pomara et al. 2014).

In conclusion, the combination of postmortem computed tomography angiography or multiphase postmortem computed tomography angiography with autopsy, histological, and immunohistochemical investigations may integrate the methodological approach to fatal cases in which there is a strong suspicion of PTE, helping the forensic pathologist to reach the correct diagnosis.

6 Discussion

Pulmonary ThromboEmolism (PTE) is an important disease in the field of legal medicine. During medicolegal autopsies, the autopsy operator must answer to important questions: for example, autopsy operator can need to assess the casual relationship between PTE and an accident, a trauma or a long air travel, or he must judge the medical practice in the cases of inhospital PTE. But it can be very difficult to answer to these questions, because generally medicolegal autopsies have poor clinical informations when PTE is the cause of death, due to the sudden lethal onset. Generally, it is very easy to recognize a fatal massive thromboembolus during the thoracic investigations, but the difficulties arise in the cases of multiple or organized thrombi, because they can involute, so it could be difficult to detect them macroscopically. In such cases histopathological examination can help in the

differentiation. Histological examination is necessary also for evaluation of chronological changes of the thrombi. Chronological evaluation is important especially to determine whether the event coincides with the date of a specific accident/operation (Ro et al. 2008). After the autopsy, the forensic operator must evaluate the patients' thrombotic risk factors: age, obesity, trauma, and inherent disease inducing hypercoagulability.

Regarding age, advanced age is an important risk factor, even if cases in young patients are reported (Matsumoto et al. 1994). As in adults, also in younger patients risk factors include immobility, injury, sepsis, chronic illness (including malignancy with chemotherapy), and recent surgery. Other factors that play a role in childhood are congenital heart disease, arteriovenous malformations, and central venous catheters, because these conditions can produce an interruption of laminar blood flow and damages to vessel endothelium. A high body mass index undoubtedly also has an effect on childhood thrombosis (Byard 2013).

Forensic research on PTE has recently focused on some specific situations, such as long distance travelers. Usually, the association between travel and the incidence of deep-vein thrombosis or pulmonary embolism is indicate with the terms "economy class syndrome" and "economy class stroke". These terms underline the association of thromboembolism and travel in the cramped conditions of the economy class, even if also business class travellers alike can be affected. As demonstrated in epidemiologic studies, flights of more than 8 h and especially in subjects at higher risk for this disease are at increased relative risk of thromboembolism. But thrombosis of travelers is not restricted only to flight travel: also after a long car or train journey it can occur. The risk of venous thromboembolism increases for prolonged immobilization in a confined space. Even if the literature emphasizes the risk of deep venous thrombosis and pulmonary embolism during air travel, some authors (Hitosugi et al. 2005; Margiotta et al. 2014) demonstrates that this risk is not only restricted to air transports. There are reported for example cases of pulmonary embolism after prolonged train, car or truck travels.

Despite all these new diagnostic tools, PE remain a difficult challenge for the pathologist. In 1954, De Bakey (Me 1954) published a review after critical evaluation of more than 375,000 postmortem cases and more than 3,000,000 clinical cases of PE and he concluded that there was great confusion over its true incidence. Fifty years later, Widimsky (Widimsky and Maly 2005) states: "The incidence of thromboembolic disease in the population is not precisely known". PE remains a commonly misdiagnosed condition with frequent errors: there is a tendency to underdiagnose and overdiagnose the disease. This condition is further made more confusing, on the one hand, by a steadily declining rate of autopsies with diminishing numbers of reports of cases of TE, and on the other hand, by progress in clinical diagnostic, prophylactic, and therapeutic approaches, that contribute to the decreased fatality rate due to earlier and better management (Steiner 2007). Guidelines for the prevention of PTE have been established and revised in many countries. For example, the latest 9th American College of Chest Physicians (ACCP) guideline on antithrombotic and thrombolytic therapy was published in 2012. These guidelines, according to the patients' thrombotic status, classify the patients into groups, and for each group it is suggested the more effective method (mechanical methods, antithrombotic therapy, use of intravenous filters) for prevention of thromboembolic events (Guyatt et al. 2012). These preventions are useful, but not sufficient to completely eradicate the risk of venous thromboembolism (Ro et al. 2003). However, early diagnosis and treatment of this state is possible and would be of great benefit in preventing fatal PTE (Ro et al. 2003): the majority of the patients had ealry symptoms related to VTE, like dyspnea, syncope and chest pain, and frequently these patients suffer for more than 1 day, before dying (Ro et al. 2011). Clinical awareness of subclinical PE at an early stage is an effective way to prevent sudden death by acute PE. So, a great attention is due to the patients that can have risk factors for PE because frequently it is possible to prevent this fatal condition.

7 Conclusions

In the last years, new diagnostic techniques and detailed clinical research studies revealed very important information about PTE and DVT. Neverthless acute massive PTE is still one of the most common life-threatening diseases. VTE is a preventable and treatable condition, so, mortality due to this condition should be held in high esteem and treated with deep caution. In many cases of sudden unexpected death, autopsy examination is the only method for elucidating the etiology. Forensic operators should take advantage of autopsy investigations for clinical contributions on prevention and treatment. Chronological evaluation is an important factor especially to determine whether the death coincides with the date of a specific accident/event or instead there is an earlier onset of PTE. In the hypothesis of a medical malpractice, only careful analysis by an experienced forensic pathologist can make a reliable distinction between an unpreventable complication and real medical malpractice.

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