David Perry · David Warwick

Handbook of Thromboprophylaxis

Third Edition

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David Perry, MD
Addenbrooke's Hospital
Cambridge
UK

David Warwick, MD
Southampton University Hospital
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Editors
David Perry, MD, PhD, FRCPEdin, FRCPLond, FRCPath
Addenbrooke's Hospital
Cambridge,
UK

David Warwick, MD, BM, FRCS, FRCS(Orth), EDHS
Southampton University Hospital
Southampton,
UK

Contributors
Jennifer R Eads, MD
David Gozzard, FRCP, FRCPath, MB
Mohammed M Khan, MD
Alok A Khorana, MD
Timothy Nokes, MB BS, FRCP, FRCPath
Henry G Watson, MBChB, MD, FRCP, FRCPath

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Editor biographies

David Perry, MD, PhD, FRCPEdin, FRCPLond, FRCPath, is Consultant in Haemostasis, Thrombosis and General Haematology at Addenbrooke's Hospital, Cambridge, UK, an Honorary Lecturer at the University of Cambridge, and Co-Director of the Haemophilia Comprehensive Care Centre. Prior to joining the staff at Addenbrooke's Hospital, he was Senior Lecturer in Hemostasis and Thrombosis at the Royal Free and University College Medical School (Royal Free Campus), London, UK. His interests include the molecular genetics of hemostasis and thrombosis, the rare inherited bleeding disorders, and the management of patients with venous thromboembolic disease, particularly in relation to pregnancy. He has published widely in the area of hemostasis and thrombosis. He is a member of the British Committee for Standards in Haematology Task Force on Haemostasis & Thrombosis, a member of the steering group for UK National External Quality Assessment Service (Blood Coagulation), and chairs the Specialist Advisory Group for Haemophilia Molecular Genetics for UK National External Quality Assessment Service. His other interests include medical education – he is examiner for the Royal College of Physicians, Edinburgh and the Royal College of Pathologists, and is the current lead physician for pathology education at Addenbrooke's Hospital.

David Warwick, MD, FRCS, FRCS(Orth), is a Consultant Orthopaedic Surgeon at University Hospitals Southampton, UK. He also runs a specialized practice for patients with hand and wrist problems in Wessex and is a professorial fellow of the University of Southampton. Professor Warwick obtained his doctorate from the University of Bristol in 1995 through original research and dissertation on deep vein thrombosis and total hip replacement, and in 1998 was awarded a Hunterian Professorship at the Royal College of Surgeons, UK. His current research interests include electrical stimulation in the prevention of venous thromboembolism (VTE). Professor Warwick has won awards and prizes for his work on VTE, and has sat on several thrombosis committees, including Chairman

of the International Surgical Thrombosis Forum Guidelines Committee. He is currently Section Editor for *Annals of Royal College of Surgeons* and serves on the Editorial Board of the *Bone and Joint Journal*. He has also reviewed for journals including *Thrombosis and Haemostasis*, *Hip International*, and *Clinical Orthopaedics*. In his research interest of VTE, he has published numerous papers in peer-reviewed journals and has written several book chapters. Professor Warwick recently authored the orthopedic section of the IUA Consensus Statement on the prevention and treatment of VTE, published in *International Angiology* in 2013. Professor Warwick has been invited to lecture and present at numerous international, national, and regional meetings. He also acted as an expert witness for the UK Parliamentary Select Committee on '*The Prevention of Venous Thromboembolism (VTE) in Hospitalised Patients*' in December 2004, which examined barriers to effective VTE thromboprophylaxis and strategies that could be used to improve therapy in UK hospitals. He was a member of the Guideline Development group which produced the NICE guidelines for VTE prophylaxis in the UK.

Abbreviations

AAOS	American Academy of Orthopedic Surgeons
ACCP	American College of Chest Physicians
ACT	Activated clotting time
AEs	Anti-embolism stockings
ALL	Acute lymphoblastic leukemia
APS	Antiphospholipid syndrome
APTT	Activated partial thromboplastin time
ART	Assisted reproductive therapy;
ARTEMIS	Arixtra for ThromboEmbolism prevention in Medical Indications Study
ASCO	American Society of Clinical Oncology
AT	Antithrombin
BMI	Body mass index
CI	Confidence interval
CrCL	Creatinine clearance
CT	Computed tomography
CVL	Central venous lines
CYP	Cytochrome P450
DM	Diabetes mellitus
DOACs	Direct oral anticoagulants
DoH	Department of Health
dRVVT	Dilute Russell viper venom time
DVT	Deep vein thrombosis
ECT	Ecarin clotting time
ENDORSE	Epidemiologic International Day for the Evaluation of Outcomes Research
ENOXACAN	ENOXAparin in CANcer
ESMO	European Society of Medical Oncology
F1+2	Prothrombin fragment 1+2
FRONTLINE	Fundamental Research in Oncology and Thrombosis
GCS	Graduated compression stockings

GECS	Graduated elastic compression stockings
HIT	Heparin-induced thrombocytopenia
HRT	Hormone replacement therapy
ICS	International Concensus Statement
IBD	Inflammatory bowel disease
INR	International normalized ratio
IVC	Inferior vena cava
IVDU	Intravenous drug user
IVF	In vitro fertilization
IPC	Intermittent pneumatic compression
L-Asp	L-Asparaginase
LMWH	Low-molecular-weight heparin
MBBRACE-UK	Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK
MEDENOX	Incidence of VTE in the MEDical patients with ENOXaparin
MI	Myocardial infarction
m-TP	Mechanical thromboprophylactic
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NR	Not recommended
NYHA	New York Health Association
NZATT	New Zealand Air Traveller's Thrombosis study
od	Once daily
OHSS	Ovarian hyperstimulation syndrome
PAARKA	Prophylactic Anti-thrombin Replacement in Kids with ALL treated with Asparaginase study
PAI	Plasminogen activator inhibitor
PE	Pulmonary embolism
PEP	The Pulmonary Embolism Prevention study
P-gp	P-glycoprotein
p-TP	Pharmacologic thromboprophylaxis
PGP	Pelvic girdle pain with reduced mobility
PNH	Paroxysmal nocturnal hemoglobinuria
PPI	Proton pump inhibitor

PREVENT	Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilised Patients
PRIME	Prophylaxis in Internal Medicine with Enoxaparin
PT	Prothrombin time.
QALY	Quality-adjusted life-years
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomized controlled trial
RECORD	Rivaroxaban: The Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism program
RR	Risk reduction
SCI	Spinal cord injury
SIGN	Scottish Intercollegiate Guidelines Network
SLE	Systemic lupus erythematosus;
T1/2	Half-life
TAT	Thrombin-antithrombin
TEDS	Thromboembolism deterrent stockings
THE-PRINCE	Thromboembolism Prevention in Cardiac or Respiratory Disease with Enoxaparin
THR	Total hip replacement
THRIFT	Thromboembolic Risk Factors Trial
TKR	Total knee replacement
tPA	Tissue type plasminogen activator
UFH	Unfractionated heparin
VFP	Venous foot pump
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

Chapter 1

Introduction

David Perry

The third edition of the *Handbook of Thromboprophylaxis* reviews the role of anticoagulants in clinical practice and the expanding role of the direct oral anticoagulants (DOACs).

There is an increasing awareness of the risks of venous thromboembolic disease, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE). In the UK, this was highlighted by the publication of the Health Committee's report on the Prevention of Venous Thromboembolism in Hospitalised Patients in 2005 [1], the Department of Health (DoH) Independent Working Group report on the Prevention of Venous Thromboembolism in Hospitalised Patients [2] in 2007 and the National Institute of Health and Clinical Excellence (NICE) guidelines on 'Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to Hospital' published in 2010 [3].

The House of Commons Health committee reported in 2005 that 25,000 people in England die from preventable hospital-acquired venous thromboembolism (VTE) every year [1]. This was recognized as a major health issue and within the UK a VTE risk assessment is a National Quality Requirement within the NHS Standard Contact for 2014/2015 and it sets a threshold of a 95% rate of inpatients undergoing risk assessment each month. All providers of NHS-funded acute care including both Foundation and non-Foundation trusts must provide this data collection. Currently, 96% of all admissions to NHS-funded acute care received a VTE risk

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assessment in Quarter 2 for 2014/2015 [4]. What constitutes best practice in VTE prevention is summarized in a series of statements from NICE [5].

1. All patients, on admission, receive an assessment of VTE and bleeding risk using the clinical risk assessment criteria described in the national tool.
2. Patients/carers are offered verbal and written information on VTE prevention as part of the admission process.
3. Patients provided with anti-embolism stockings have them fitted and monitored in accordance with NICE guidance.
4. Patients are re-assessed within 24 hours of admission for risk of VTE and bleeding.
5. Patients assessed to be at risk of VTE are offered VTE prophylaxis in accordance with NICE guidance.
6. Patients/carers are offered verbal and written information on VTE prevention as part of the discharge process.
7. Patients are offered extended (post-hospital) VTE prophylaxis in accordance with NICE guidance.

The field of anticoagulation has changed significantly with the introduction of new agents with fixed dosing and no requirement for monitoring. In this handbook, we address the role of thromboprophylaxis in a wide spectrum of patients and provide evidence-based guidelines to aid in their management

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Chapter 2

Overview of anticoagulants

David Perry

Historically anticoagulation involved the use of heparin and its derivatives or warfarin. However, the past few years have seen the introduction of a number of novel direct oral anticoagulants. These drugs are of interest as they require no laboratory monitoring, are relatively easy to use as they have a fixed dose and have demonstrated equivalence and in some cases superiority to warfarin, in the prevention of cardioembolic stroke in individuals with non-valvular atrial fibrillation, in deep vein thrombosis (DVT) prevention in patients undergoing hip and knee replacement surgery and in the treatment of DVT and pulmonary embolism (PE).

This chapter provides an overview of the currently available anticoagulant drugs, their licensed indications, their effects upon the standard laboratory tests and in addition provides guidelines on the management of patients undergoing invasive procedures.

Warfarin

Warfarin is a vitamin K antagonist [VKA] that inhibits γ-carboxylation of Factors II, VII, IX, and X [+ Proteins C, S and Z]. Warfarin has a half-life of 35–45 hours. The other common vitamin K antagonists (VKAs) include:

- Acenocoumarol with a half-life of 8–24 hours; and
- Phenprocoumon with a half-life of 5–6 days.
- Tecarfarin is a novel oral VKA that has been engineered so that it is not metabolized through the Cytochrome P450 [CYP]

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pathway. Tecarfarin is metabolized by esterases (mainly human carboxylesterase 2) to a single major metabolite, in rats, dogs, and humans. Tecarfarin is not significantly metabolized by CYP450 enzymes and for these reasons it has a decreased potential to interact with drugs that inhibit CYP450 enzymes. This drug may be of value for the treatment of patients with mechanical and prosthetic heart valves, as well as those with renal dysfunction.

- Phenindione is an inandione derivative but is now rarely used due to a high incidence of adverse events including skin rashes and abnormal liver function tests. Phenindione has a half-life of 5–10 hours.

The use of VKAs is complicated by a narrow therapeutic index and an unpredictable dose-response relationship, giving rise to bleeding complications or insufficient anticoagulation. The inter-individual variability observed with an individual's response to a VKA is in part due to the genetic variability arising from mutations in the *CYP2C9* and *VKORC1* genes. Mutations in *CYP2C9* have been linked to decreasing activity in metabolising VKA leading to a prolonged half-life and over-anticoagulation [1]. Conversely, mutations in the *VKORC1* gene have been linked to a decrease in requirements for warfarin [1]. An algorithm has been proposed to prevent over- or under-anticoagulation taking into account these two genes [2].

The *VKORC1* gene encodes the VKORC1 enzyme – a small transmembrane unit of the endoplasmic reticulum – and is primarily transcribed in the liver. Various polymorphisms and mutations within the *VKORC1* gene have been reported. The polymorphisms are associated with a reduction in the levels of VKORC1 and therefore a reduction in the amounts of warfarin that an individual requires to achieve a stable international normalized ratio (INR). Mutations within the *VKORC1* gene have been associated with a reduction in the levels of all the vitamin K-dependent clotting factors and are a rare cause of an inherited bleeding disorder [3].

Heparin

Several forms of heparin are available for therapeutic use.

Unfractionated heparin

Unfractionated heparin (UFH) is a sulphated polysaccharide with a molecular weight range of 3000–30,000 Da. It binds to the plasma serine protease inhibitor (SERPIN) antithrombin (AT) causing a conformational change in its structure and an acceleration of its inhibitory activity. UFH has both anti-IIa (thrombin) and anti-Xa activity.

Heparin binds to AT through a high affinity pentasaccharide binding site, which is present in ~one-third of heparin molecules. Maximal anti-IIa activity is dependent upon the binding of heparin to both thrombin and heparin. Heparin molecules <18 saccharide units lack the necessary chain length to form a bridge between the two molecules and so short chain heparin molecules have primarily anti-Xa inhibitory activity.

UFH binds to a number of plasma proteins, which accounts for the variable intra-individual anticoagulant response. While historically UFH was used for thromboprophylaxis, it is rarely used for this indication today. It is used primarily for patients who are at high risk of bleeding but in whom efficient anticoagulation is required. UFH has a short half-life and in addition can be efficiently reversed with the use of protamine sulphate. UFH is also used as an anticoagulant for patients on cardio-pulmonary bypass. UFH is commonly monitored by means of the activated partial thromboplastin time (APTT) test and occasionally by the anti-Xa assay.

Low molecular weight heparin

The LMWHs are primarily inhibitors of factor Xa but they also have some anti-IIa activity. The anti-Xa:IIa ratio varies from LMWH to LMWH preparation. LMWHs (of which there are a number) are prepared from UFH and are enriched for short-chain heparin molecules and so have primarily anti-Xa activity. LMWHs have a molecular weight range of 1000–10,000 Da with a mean range of 4500–5000 Da.

LMWHs have more predictable pharmacokinetics than UFH due to reduced binding to plasma proteins and so can be given once daily without (in the majority of individuals) any need for laboratory monitoring.

LMWHs are excreted through the kidneys and so may accumulate in patients with impaired renal function. The LMWHs may be monitored, if necessary, by means of an anti-Xa assay.

Synthetic pentasaccharide: fondaparinux and idraparinux

Fondaparinux is a synthetic pentasaccharide Xa-specific inhibitor identical to that found in LMWH and UFH. It is given subcutaneously and has a half-life of 17–21 hours. Fondaparinux is renally excreted and so may accumulate in patients with impaired renal function. Fondaparinux may be monitored, if necessary, by means of an anti-Xa assay.

Idraparinux, a specific Xa inhibitor, is a hypermethylated derivative of fondaparinux and binds to antithrombin with a strong affinity that accounts for its long half-life of 80–130 hours, which means the drug only requires weekly administration. However, although the drug is effective it may be associated with an increased risk of bleeding. Idrabiotaparinux is similar to idraparinux but contains a biotin group, which allows its anticoagulant activity to be rapidly reversed with avidin.

Danaparoid

Danaparoid is a mixture of heparan sulphate, chondroitin sulphate, and dermatan sulphate. Danaparoid has an anti-Xa elimination half-life of ~25 hours but the thrombin generation-inhibiting activity is eliminated with a half-life of ~7 hours. Danaparoid is excreted through the kidneys and so may accumulate in patients with impaired renal function. Danaparoid has an anti-Xa:anti-IIa activity ratio of 20 compared with ~2.5 for the LMWHs and 1 for UFH.

Danaparoid is not widely used and is usually reserved for individuals with heparin-induced thrombocytopenia (HIT) but in whom anticoagulation is required or in patients who develop other allergic reactions to LMWHs eg, skin rashes.

Direct IIa (thrombin) inhibitors

Bivalirudin

Bivalirudin is a 20 amino acid synthetic peptide that is a potent, reversible, direct inhibitor of thrombin. Bivalirudin binds to the catalytic site and the anion binding exosite of both circulating and clot-bound thrombin. This reaction is reversible as thrombin slowly cleaves the bivalirudin. It has a half-life of ~25 minutes if renal function is normal.

Dabigatran

Dabigatran is an oral, direct thrombin inhibitor with a high affinity (but reversible binding) for thrombin (factor IIa). Dabigatran also inhibits thrombin-induced platelet aggregation. Dabigatran etexilate is a prodrug that is converted into the active metabolite dabigatran with a low bioavailability. The intestinal absorption of dabigatran etexilate is pH sensitive and therefore its absorption is reduced in individuals receiving proton pump inhibitors.

Licensed indications

Dabigatran is licensed for thromboprophylaxis in patients undergoing hip and knee replacement surgery, for the treatment of DVT and PE and for the prevention of cardio-embolic stroke in patients with non-valvular atrial fibrillation. The dosing regimes for dabigatran are in Table 2.1 [4].

Direct oral Xa inhibitors

Currently two oral factor Xa (FXa) inhibitors are in common use – rivaroxaban [5] and apixaban [6]. A third oral FXa inhibitor, edoxaban, was recently approved. In the US, edoxaban is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (patients with creatinine clearance ≤95 mL/min), and for the treatment of DVT and PE following 5 to 10 days of initial therapy with a parenteral anticoagulant. In the EU, edoxaban was approved in June 2015 for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more risk factors (such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack). In addition, it received approval for the treatment of DVT and PE, and prevention of recurrent DVT and PE in adults following initial use of parenteral anticoagulant for at least 5 days. The recommended dose of edoxaban is 60 mg taken orally once daily (30 mg once daily in patients with creatinine clearance 15 to 50 mL/min, patients who weigh less than or equal to 60 kg, or patients who are taking certain concomitant P-gp inhibitor medications).

Surgery	Dabigatran dosing	Comments
Elective knee replacement surgery	Age >18 yrs <75 yrs. Commence dabigatran 110mg 1–4 hrs following surgery followed by 220 mg once daily 12–24 hours later for 9 days. Patients >75 yrs OR patients receiving amiodarone or verapamil. The dabigatran dose is reduced to 75 mg 1–4 hrs following surgery followed by 150mg once daily 12–24 hours later for 9 days	1. PPI inhibitors: Dabigatran requires an acidic environment for absorption and therefore, its absorption is reduced in individuals receiving PPIs. 2. Drugs affecting the P-gp pathway: i. Dabigatran etexilate is a substrate for P-gp although dabigatran is not and as a result its absorption can be altered by P-gp inducers or inhibitors during its passage through the gut enterocyte. Once dabigatran etexilate is absorbed and converted from the prodrug to the active drug, it is no longer susceptible to P-gp inhibitors. P-gp inhibitors such as amiodarone, verapamil, itraconazole, ketoconazole, diltiazem, ritonavir and tacrolimus will increase the plasma concentrations of dabigatran. ii. P-gp inducers such as rifampicin will decrease plasma dabigatran levels. St John's Wort and carbamazepine are similarly likely to affect plasma dabigatran levels. 3. Dabigatran has a T1/2 of 12–17 hrs with ~80% of the drug excreted renally. Therefore: a. CrCL <30 mL/min: dabigatran should be avoided. b. CrCL >50– ≤80 mL/min: no dose adjustment is necessary c. CrCL 30–50 mL/min: the recommended dose of dabigatran is 300 mg taken as one 150 mg capsule twice daily. However, for patients with high risk of bleeding, a dose reduction of dabigatran to 220 mg taken as one 110 mg capsule twice daily may be considered.
Elective hip replacement surgery	Age >18 yrs <75 yrs. Commence dabigatran 110 mg 1–4 hrs following surgery followed by 220 mg once daily 12–24 hours later for 27–34 days. Patients >75 yrs OR patients receiving amiodarone or verapamil – the dose of dabigatran is reduced to 75 mg 1–4 hrs following surgery and then 150mg once daily 12–24 hours later for 27–34 days	
Treatment of DVT or PE and prophylaxis of recurrent DVT and/or PE	Age >18 yrs <80 yrs. Dabigatran 150 mg twice daily following at least 5 days' treatment with a parenteral anticoagulant. Age >80 years OR receiving treatment with verapamil – dabigatran 110 mg twice daily following at least 5 days' treatment with a parenteral anticoagulant. The lower dose of dabigatran 110 mg twice daily may be considered in patients aged 75-80 yrs with moderate renal impairment [CrCL >30–<50 mL/min] or at increased risk of bleeding.	
Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation	Age >18 yrs <80 yrs dabigatran 150 mg twice daily. Age >80 yrs OR receiving treatment with verapamil – dabigatran 110 mg twice daily. The lower dose of dabigatran 110 mg twice daily may be considered in patients aged 75-80 yrs with moderate renal impairment [CrCL >30–<50 mL/min] or at increased risk of bleeding.	

Table 2.1 Dosing regimens for dabigatran. For additional information consult the dabigatran summary of product characteristics. CrCL, creatinine clearance; DVT, deep vein thrombosis; PE, pulmonary embolism. P-gp, P-glycoprotein; PPI, proton pump inhibitor; T1/2, half-life.

Rivaroxaban

Rivaroxaban is an oral, direct factor Xa inhibitor that inhibits prothrombinase-bound factor Xa, free factor Xa and clot-bound factor Xa. The majority of rivaroxaban [90–95%] is protein bound. Rivaroxaban is cleared from the plasma by the kidneys and in the feces:

- One-third of rivaroxaban is excreted unchanged by the kidneys
- One-third is metabolized by the liver [via CYP3A4-dependent and CYP3A4-independent pathways] and excreted into the feces
- One-third is metabolized to inactive metabolites which are then excreted by the kidneys.

The maximum inhibition of FXa occurs 1–4 hours after ingestion. Rivaroxaban has a half-life of 7–11 hours.

Licensed indications

See Table 2.2 for licensed indications.

Apixaban

Apixaban is an oral factor Xa inhibitor that inhibits prothrombinase-bound factor Xa, free factor Xa and clot-bound factor Xa. The majority of apixaban [87–93%] is protein bound with a half-life of 8–15 hours. The renal clearance is approximately 27%.

Licensed indications

See Table 2.3 for licensed indications.

Laboratory tests in patients on direct oral anticoagulant agents

The effects of the direct oral anticoagulant agents (DOACs) on routine hemostatic laboratory tests are summarized below. In general, the routine measurement of dabigatran, rivaroxaban, or apixaban levels is not indicated although assays for these drugs are available (Table 2.4). The data are also summarized in Table 2.5.

Surgery	Rivaroxaban dosing	Comments
Elective knee replacement surgery	Age >18 yrs Commence rivaroxaban 10 mg once daily 6–10 hrs after surgery and continue for 14 days.	1. No dose adjustment is needed for the elderly. 2. Rivaroxaban has a T½ of 7–11 hrs and one-third is excreted by the kidneys. Therefore: a. CrCL <15 mL/min: rivaroxaban is contraindicated b. 15–29 mL/min: i. Use with caution in patients undergoing hip and knee replacement surgery. ii. In patients with DVT or PE reduce the dose of rivaroxaban to 15 mg twice daily for 21 days and then1 5 mg once daily. iii. In the prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation the dose of Rivaroxaban should be reduced to 15 mg once daily. c. 30–49 mL/minute – no dose adjustment necessary. d. 50–80 mL/minute – no dose adjustment necessary. 3. Drug interactions: potent inhibitors of the CYP3A4 pathway and inhibitors of the P-gp pathway eg, ketoconazole [and related preparations] or ritonavir – can lead to an increase in the plasma concentration of rivaroxaban and therefore, to an increased risk of bleeding. Rivaroxaban is not advised in such cases. 4. Potent inducers of CYP3A4 such as rifampicin can lead to a decrease in mean rivaroxaban levels and to a decreased efficacy. Similarly other inducers of CYP3A4 such as phenytoin, carbamazepine and St John's Wort may also lead to reduced rivaroxaban levels and rivaroxaban should be avoided in such cases.
Elective hip replacement surgery	Age >18 yrs Commence rivaroxaban 10 mg once daily 6–10 hrs after surgery and continue for 35 days.	
Treatment of DVT or PE and prophylaxis of recurrent DVT and/or PE	Age >18 yrs Commence treatment with rivaroxaban 15 mg twice daily for 21 days then reduce the dose to 10 mg twice daily.	
Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation	Age >18 yrs Commence rivaroxaban 20 mg once daily.	

Table 2.2 Licensing indications for rivaroxaban. For additional information consult the summary of product characteristics. CrCL, creatinine clearance; DVT, deep vein thrombosis; PE, pulmonary embolism; P-gp, P-glycoprotein; T1/2, half-life.

Surgery	Apixaban dosing	Comments
Elective knee replacement surgery	Age >18 yrs Commence apixaban 2.5 mg once daily 12–24 hrs after surgery and continue for 10–14 days.	1. No dose adjustment is needed for the elderly although increasing age may increase the hemorrhagic risk. 2. Renal impairment: a. CrCL <15 mL/min: apixaban is contraindicated b. 15–29 mL/min: i. Use with caution in patients undergoing hip and knee replacement surgery. ii. Use with caution in patients with DVT or PE iii. In the prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation and age >80 yrs or weight <60 kg – the dose of apixaban is reduced to 2.5 mg twice daily. 3. Drug Interactions: i. Strong inhibitors of CYP3A4 and P-gp. Apixaban is not recommended in patients receiving concomitant systemic treatment with itraconazole, voriconazole and posaconazole, and HIV protease inhibitors (eg, ritonavir). These drugs may increase apixaban exposure by twofold. ii. Apixaban is not recommended for the treatment of DVT and PE in patients receiving strong CYP3A4 and P-gp inducers (eg, rifampicin, phenytoin, carbamazepine, St John's Wort) as these may lead to a reduction in apixaban levels and potentially, therefore, a reduction in efficacy.
Elective hip replacement surgery	Age >18 yrs Commence apixaban 2.5 mg once daily 12–24 hrs after surgery and continue for 32–38 days.	
Treatment of DVT or PE and prophylaxis of recurrent DVT and/or PE	Age >18 yrs i. Commence apixaban 10 mg orally twice daily for the first 7 days followed by 5 mg orally twice daily. ii. For the prevention of recurrent DVT and/or PE following completion of 6 months of treatment for DVT or PE, the dose of apixaban is 2.5 mg twice daily.	
Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation	i. Age >18 yrs apixaban 5 mg taken orally twice daily ii. Age > 80 yrs or weight <60 kg – the dose of apixaban is reduced to 2.5 mg twice daily.	

Table 2.3 Licensing indications for apixaban. For additional information consult the summary of product characteristics for apixaban. CrCL, creatinine clearance; DVT, deep vein thrombosis; PE, pulmonary embolism; P-gp, P-glycoprotein.

	Direct IIa inhibitor
	Dabigatran
PT	The PT is relatively insensitive to dabigatran. Although the PT will prolong with increasing concentrations of dabigatran, at trough dabigatran levels it can be normal. A normal PT, therefore, does not exclude the presence of dabigatran. The PT is less sensitive to dabigatran than the APTT. Factor assays based upon the PT will underestimate the factor level in the presence of dabigatran.
APTT	The APTT response curve flattens as the concentration of dabigatran increases above 200 ng/mL and the APTT is, therefore, relatively insensitive to the plasma concentrations of dabigatran that are likely to be encountered in clinical practice. The APTT can be used with most reagents for urgent determination of the relative intensity of anticoagulation due to dabigatran but it cannot be used to determine the drug level. Factor assays based upon the APTT will underestimate the factor level in the presence of dabigatran.
TT	The thrombin time is very sensitive to the effects of dabigatran and displays a linear dose-response curve over therapeutic levels but at high concentrations the actual clotting time may exceed the time that many instruments allow. A normal thrombin time excludes the presence of dabigatran.
Fibrinogen (Clauss)	Dabigatran may interfere with the Clauss fibrinogen assay and at high concentrations, fibrinogen levels may be underestimated. The effect is dependent upon the tests used in the assay.
ACT	The ACT shows a linear relationship with dabigatran with concentrations up to 250 ng/mL but is not specific for dabigatran.
ECT	Directly assesses the activity of thrombin in a plasma sample and displays a linear dose-response to therapeutic concentrations of dabigatran. However, the ECT is hampered by lack of standardization, different lots of ecarin, and limited availability.
Anti-Xa assays	Not applicable.

Table 2.4 The effects of the direct oral anticoagulant agents on routine hemostatic laboratory tests (continues overleaf).

Direct Xa inhibitors	
Rivaroxaban	**Apixaban**
i. The PT in patients receiving rivaroxaban varies significantly with differing thromboplastins and therefore individual labs need to determine the sensitivity of their PT for rivaroxaban. ii. INR: Conventional INR for monitoring patients on VKAs is not suitable for monitoring patients. Rivaroxaban INR: The possibility of developing a PT-based assay for rivaroxaban similar to the INR has been explored. Rivaroxaban has been assigned an ISI [$ISI^{Rivaroxaban}$] and the rivaroxaban 'INR' derived using a similar formula to that of the INR. The scheme is very similar to that proposed for the ISI^{Liver}. Factor assays based on the PT will underestimate the factor level in the presence of rivaroxaban .	The PT appears less sensitive to apixaban than rivaroxaban. A normal PT does not exclude significant levels of apixaban. Factor assays based upon the PT will underestimate the factor level in the presence of apixaban.
The APTT is sensitive to the anticoagulant effects of rivaroxaban and can lead to a prolonged APTT. With appropriate reagents, the APTT can be used for the urgent determination of the relative intensity of anticoagulation due to rivaroxaban (although the PT is usually more sensitive) but it cannot be used to determine the drug level. Factor assays based upon the APTT will underestimate the factor level in the presence of rivaroxaban.	The APTT is prolonged by the apixaban but less so than with rivaroxaban. There may be significant levels of apixaban in the plasma but only minimal prolongation of the APTT. Factor assays based upon the APTT will underestimate the factor level in the presence of apixaban.
No effect.	No effect.
Rivaroxaban appears to have minimal effect upon Clauss fibrinogen assays but at high rivaroxaban concentrations, may lead to a 10% reduction in fibrinogen levels.	No effect.
Supratherapeutic levels of rivaroxaban will prolong the ACT.	Supratherapeutic levels of apixaban will prolong the ACT.
No effect .	No effect.
Current data indicate that an anti-Xa assay appropriately calibrated correlates with apixaban.	Current data indicate that an anti-Xa assay appropriately calibrated correlates with apixaban concentrations.

Table 2.4 The effects of the direct oral anticoagulant agents on routine hemostatic laboratory tests (continued). ACT, activated clotting time; APTT, activated partial thromboplastin time; ECT, ecarin clotting time; INR, international normalized ratio; PT, prothrombin time.

	Dabigatran	Rivaroxaban	Apixaban
PT (INR)	↑	↑↑↑	↑↑
APTT	↑↑↑		↑
Thrombin time	↑↑↑↑	–	–
Fibrinogen (Clauss)	↓	–	–
PT-based factor assays	↓↓	↓	↓
APTT-based factor assays	↓	↓↓	↓↓
ACT	↑	(↑)	(↑)

Table 2.5 Summary of the data on the effects of the direct oral anticoagulant agents on routine hemostatic laboratory tests. ACT, activated clotting time; APTT, activated partial thromboplastin time; ECT, ecarin clotting time; INR, international normalized ratio; PT, prothrombin time.

Perioperative management of patients on direct oral anticoagulant agents

The management of patients on DOACs undergoing invasive procedures is becoming increasingly important [7]. The advised times to discontinue DOACs are summarized in the tables below (Table 2.6, Table 2.7, and Table 2.8). For patients at high risk of thrombosis bridging with a LMWH may be required.

Direct oral anticoagulant agents: summary of pharmacokinetic properties

Table 2.9 below summarizes the pharmacokinetic (PK) properties of dabigatran, rivaroxaban, and apixaban.

		Dabigatran dose	
eGFR	**Estimated half-life**	**High risk of bleeding**	**Standard risk of bleeding**
>80mL/minute	~13 hours	Discontinue 2 days before	Discontinue 24 hours before
≥50–<80 mL/minute	~15 hours	Discontinue 2–3 days before	Discontinue 1–2 days before
≥30–<50 mL/minute	~18 hours	Discontinue 4 days before	Discontinue 2–3 days before [>48 hours]

Table 2.6 The advised times for discontinuing dabigatran.

	eGFR			
	Normal	**60–90 mL/min**	**30–59 mL/min**	**15–29 mL/min**
Discontinue rivaroxaban	1 day	2 days	3 days	4 days

Table 2.7 The advised times for discontinuing rivaroxaban.

	eGFR		
		50–59 mL/min	**30–49 mL/min**
Discontinue apixaban	1-2 days	3 days	5 days

Table 2.8 The advised times for discontinuing apixaban.

	Dabigatran	**Rivaroxaban**	**Apixaban**
Prodrug	Yes	No	No
Frequency of dosing	Twice daily	Once daily	Twice daily
Effect of food	Delays absorption	Delays absorption	None
Bioavailability	6.5%	10 mg dose: 60–100% 20 mg dose: 66%	50%
Time to maximum inhibitory effect	1–3 hrs	2–4 hrs	2–4 hrs
Protein binding	25%	90–95%	87–93%
Metabolism	Predominantly by the kidneys	Predominantly through the liver	Predominantly through the liver
Half-life	12–17 hrs	7–11 hrs but may be longer in the elderly	8–15 hrs
Potential drug interactions	CYP3A4 P-gp inhibitors	CYP3A4 P-gp inhibitors	CYP3A4 P-gp inhibitors

Table 2.9 The pharmacokinetic properties of dabigatran, rivaroxaban, and apixaban. P-gp, P-glycoprotein.

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Chapter 3

Thromboprophylaxis in medical patients

David Perry

Introduction

Venous thromboembolic (VTE) disease is a significant cause of morbidity and mortality in hospitalized patients. The acutely ill or nonsurgical 'medical' patient represents approximately 60% of all hospital admissions in the UK and such patients are at high risk of VTE. Post-mortem data suggest that approximately 10% of deaths that occur in hospitals are due to pulmonary embolism (PE) [1–3].

In the absence of thromboprophylaxis, the incidence of VTE in the MEDical patients with ENOXaparin (MEDENOX) study [4] was 14.9% and for proximal deep vein thrombosis (DVT) alone 4.9% [5]. The incidence of VTE in the control arm of the Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilised Patients (PREVENT) trial was 4.96% and in the Arixtra® (fondaparinux) for ThromboEmbolism prevention in Medical Indications Study (ARTEMIS) 10.5% for all VTE [6].

Data from the large-scale Epidemiologic International Day for the Evaluation of Outcomes Research (ENDORSE) study have shown that 42% of medical inpatients are at risk of VTE but that less than half (40%) receive appropriate preventative treatment [7].

VTE is largely preventable and prophylaxis with low-molecular-weight heparins (LMWHs) has been shown to be well tolerated and cost-effective in numerous studies involving surgical patients. A large number of

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well-conducted, prospective, randomized trials have consistently demonstrated that the appropriate use of pharmacological thromboprophylaxis can significantly reduce the risk of VTE in medical patients [8]. There is accumulating evidence that use of thromboprophylaxis with LMWHs in this group of patients is both safe and effective. Three key trials involving medical patients – MEDENOX, PREVENT, and ARTEMIS – have shown a relative risk reduction of DVT of 50–65% with the appropriate use of thromboprophylaxis (LMWHs or fondaparinux).

A key issue that remains to be resolved, however, is the duration of thromboprophylaxis in medical patients. Data from trials involving surgical patients suggest that the risk of thrombosis persists for several weeks and such patients may require extended out-of-hospital thromboprophylaxis.

Risk factors and risk assessment models in medical patients

Hospitalized medical patients are often at increased risk of VTE because of the presence of one or more factors. These factors are outlined in Figure 3.1.

History of DVT or PE	Stroke
Family history of VTE	Prolonged immobility (>4 days)
Acute infection	Acute or chronic lung disease
Malignancy	Acute inflammatory disease
Age (>75 years)	Inflammatory bowel disease
Congestive heart failure	Shock
Paraproteinemia	Hyperhomocysteinemia
Behçet's disease	Dysfibrinogenemia
Nephrotic syndrome	Myeloproliferative disorders
Hypofibrinolysis	Age (>41 years)
Polycythemia	Sepsis (<1 month)
PNH	Heparin-induced thrombocytopenia
High-dose estrogen therapy	Congenital or acquired thrombophilia
Obesity (BMI ≥30 kg/m^2)	Varicose veins

Figure 3.1 Risk factors for venous thromboembolism in hospitalized medical patients. BMI, body mass index; DVT, deep vein thrombosis; PE, pulmonary embolism; PNH, paroxysmal nocturnal hemoglobinuria; VTE, venous thromboembolism.

Medical patients may also vary in their susceptibility to VTE. For example, a large pulmonary embolus may be asymptomatic in an otherwise healthy mobile individual but may prove fatal if a patient has a low cardiopulmonary reserve.

In light of these evidence- and consensus-based risk factors, a number of risk models have been proposed. A risk assessment model for medical thromboprophylaxis should ideally:

- identify medical patients who are at significant risk of VTE and who would, therefore, benefit from thromboprophylaxis;
- identify patients with contraindications to thromboprophylaxis or who would not benefit from thromboprophylaxis;
- allow transparent and simple decision making at the bedside; and
- be evidence-based.

A simplified risk assessment model was proposed by Cohen et al that can be applied to all medical patients (Figure 3.2) [9]. It revolves around the following two decisions:

1. 'Is the patient at increased risk of VTE?' If the answer is yes, they should be considered for thromboprophylaxis.
2. 'Is pharmacological thromboprophylaxis contraindicated?' If the answer is yes, other forms of thromboprophylaxis, such as mechanical thromboprophylaxis, should be considered. If the answer is no, pharmacological thromboprophylaxis is indicated.

This risk assessment model is applicable to all patients over the age of 40 years who have both evidence- or consensus-based acute medical illnesses and reduced mobility. It also takes into account patients' specific predisposing risk factors. Implementation of this simple risk assessment model would considerably increase the uptake of thromboprophylaxis in acutely medically ill patients and significantly reduce the burden of VTE.

Thromboprophylaxis clinical trials in medical patients

There have been three large prospective randomized placebo-controlled studies of LMWHs versus placebo performed in recent years. In 1999, the MEDENOX study [4] was published comparing enoxaparin in two doses (20 mg or 40 mg) with placebo. Subsequently, the PREVENT study [5],

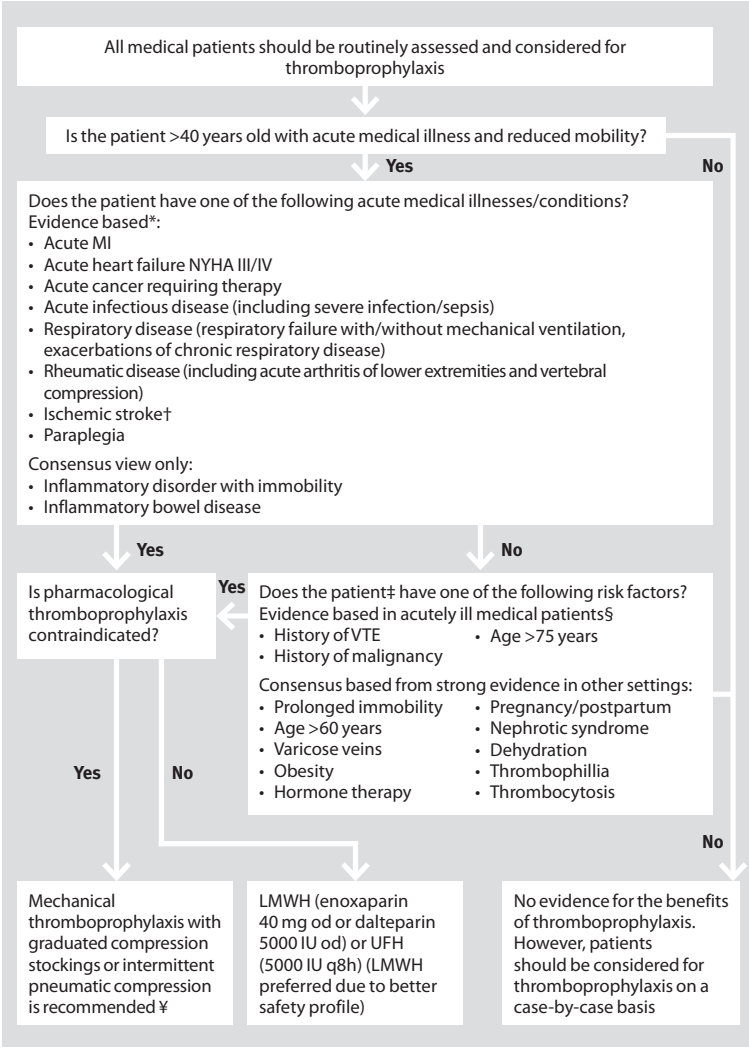

Figure 3.2 Risk assessment model for venous thromboembolism in medical patients.
*Equivalent to the evidence used by the American College of Chest Physicians for a Grade 1A recommendation (outlined in Chapter 4). †Note: the patient's risk of hemorrhagic transformation should be assessed before giving thromboprophylaxis. ‡Medical outpatients whose acute medical illness is not included in the risk assessment model should be considered for thromboprophylaxis on a case-by-case basis depending on the severity of their acute medical illness and their risk factors. §Evidence based primarily on subanalyses of the MEDENOX study. ¥Based on generalizations from randomized trials in other patient groups. LMWH, low-molecular-weight heparin; MI, myocardial infarction; NYHA, New York Health Association; od, once daily; UFH, unfractionated heparin; VTE, venous thromboembolism. Reproduced with permission from Cohen et al [9].

comparing dalteparin with placebo, and the ARTEMIS study, comparing the synthetic pentasaccharide fondaparinux with placebo, were published in 2004 and 2006, respectively. In addition, an analysis of combined data from the OASIS 5 and 6 trials comparing fondaparinux with a heparin-based strategy was published in 2008. A number of smaller trials have also compared LMWHs, primarily enoxaparin, with unfractionated heparins (UFHs) and have been analyzed in a meta-analysis [10].

The MEDENOX study followed 866 acutely ill medical patients for 14 days with bilateral ascending venography to determine the incidence of VTE and the efficacy of enoxaparin as treatment [4]. Two doses of enoxaparin were evaluated, 20 mg subcutaneously once daily and 40 mg subcutaneously once daily. The low dose produced results that were not significantly different from placebo, whereas the higher dose resulted in a 63% relative risk reduction in all VTE ($p<0.001$) and a 65% relative risk reduction ($p=0.04$) in proximal DVT. This significant reduction in the incidence of VTE was shown to be safe with no significant increase in major hemorrhagic adverse effects. Subgroup analysis of the MEDENOX study showed efficacy in all major clinical groups [11].

The ARTEMIS study assessed the incidence and treatment of VTE in 849 (425 patients in the fondaparinux group and 414 patients in the placebo group – 10 were not evaluated) acutely ill medical patients. The primary efficacy outcome was the incidence of VTE up to day 15 and treatment with fondaparinux was given in a dose of 2.5 mg subcutaneously once daily, similar to that used in high-risk surgical procedures. This study showed an incidence on a case-by-case basis depending on the severity of their acute medical illness and their risk factors.

The PREVENT study compared dalteparin 5000 IU subcutaneously once daily with placebo in 3706 acute medically ill patients. The cohort of acutely ill medical patients consisted of 52% with chronic heart failure and 30% with respiratory failure; the remaining patients had infection without septic shock, rheumatic disorders, or inflammatory bowel disease. The study used ultrasound (in contrast to the MEDENOX and ARTEMIS studies, which employed venography) to detect proximal venous thrombosis and was, therefore, unable to detect distal calf thrombosis unless the patient was symptomatic, probably resulting in an underestimation

of the true incidence of distal DVT. However, the incidence of proximal venous thrombosis in the placebo group was lower at 5%. The incidence of VTE in the treated group was 2.8% (p=0.0015), with a similar risk reduction in both asymptomatic proximal DVT and symptomatic DVT [12].

Mehta et al conducted an individual patient-level combined analysis of 26,512 patients with ST- and non-ST-segment elevation acute coronary syndromes from the OASIS 5 and 6 trials, who were randomized to fondaparinux 2.5 mg daily or a heparin-based strategy (dose-adjusted unfractionated heparin or enoxaparin) [13]. This showed that fondaparinux was superior to heparin in reducing the composite of death, myocardial infarction or stroke, at 7.2% versus 8.0% and a hazard ratio of 0.91. The risk of death alone was also significantly reduced with fondaparinux versus heparin, at 3.8% versus 4.3% and a hazard ratio of 0.89, as was the risk of major bleeding, at 3.4% versus 2.1% and a hazard ratio of 0.9. Overall, patients receiving fondaparinux had a significantly more favorable clinical outcome than patients in the heparin arm, at a hazard ratio of 0.83 [13].

The magnitude of the risk reduction is broadly consistent across all three of these studies and equates approximately to the 50–65% relative risk reduction seen in the incidence of VTE following high-risk orthopedic surgery, such as elective primary hip and knee replacement surgery. A meta-analysis comparing heparin – both UFH and LMWH – with placebo as thromboprophylaxis in medical patients [10] found a significant reduction in DVT and pulmonary embolus when using heparin, and a non-significant increase in hemorrhage. Another meta-analysis also compared LMWH with UFH and showed a trend of improved efficacy of LMWH over UFH in the treatment of DVT. More importantly, it showed a significant reduction in major hemorrhage in LMWH compared with UFH; therefore, while both treatments are efficacious, LMWH is the safer. However, all three of the above prospective randomized trials demonstrated the safety of pharmacological thromboprophylaxis in general in acutely ill medical patients.

The safety of LMWH was evident in the Thromboembolism Prevention in Cardiac or Respiratory Disease with Enoxaparin (THE-PRINCE) study [14], which was a multicenter, randomized, open, parallel-group

study that compared subcutaneous enoxaparin 40 mg subcutaneously once daily with UFH 5000 IU three times daily for the prevention of VTE in patients with heart failure or severe respiratory disease. There was no difference in efficacy between the two treatment groups, although bleeding events were less frequent in patients receiving enoxaparin (1.5%) than in the UFH arm (3.6%). Similar results were found in the Prophylaxis in Internal Medicine with Enoxaparin (PRIME) study [15], which compared the safety and efficacy of enoxaparin with UFH in 959 patients hospitalized as a result of acute medical illness and with at least one additional risk factor for VTE.

A meta-analysis of the safety of thromboprophylaxis in acute medical illness [16] evaluated data from 2346 patients. Similar rates of major bleeding (about 1%) were observed in patients given enoxaparin, UFH, or placebo. The incidence of minor bleeding was comparable in the enoxaparin and placebo groups but significantly higher in the group receiving UFH compared with enoxaparin. These data are in contrast to the meta-analysis conducted by Mismetti et al [10], which reported a significantly lower rate of major bleeding in medical patients receiving LMWH [10].

The combined results of these various trials highlight that medical patients are at high risk of VTE when immobilized with acute medical illnesses, and this risk can be reduced by the use of pharmacological prophylaxis with LMWH. The magnitude of the risk reduction with LMWH is similar to that seen in high-risk orthopedic surgery using a comparable dose of UFH. Lower doses of LMWH do not appear to be more efficacious than placebo. As a result of the evidence provided by analysis of these studies, a number of national and international guidelines for the use of pharmacological thromboprophylaxis in medical patients have become available. Medical thromboprophylaxis is a Grade 1 recommendation in the American College of Chest Physicians (ACCP) guidelines [17] and is recommended by the Scottish and Intercollegiate Guideline Network (SIGN) [18] and NICE [19].

NICE recommends that pharmacological thromboprophylaxis is offered to general medical patients who have been assessed as being at an increased risk of VTE. This can be in the form of fondaparinux, LMWH, or UFH. This should start as soon as possible after risk assessment and should continue

until the patient is no longer at increased risk of VTE [19]. These guidelines all recommend the use of pharmacological thromboprophylaxis in acutely ill medical patients in whom there is no contraindication.

Who should not receive thromboprophylaxis?

While there is now substantial evidence that pharmacological thromboprophylaxis with LMWH in medical patients who are at high risk of VTE significantly reduces this risk and is not associated with significant adverse effects, a number of barriers to the implementation of medical thromboprophylaxis have been identified, including the need for a simple, widely applicable, risk assessment model. Other issues include concerns over the applicability of the available data to all medical patients. However, the introduction of the risk assessment model described earlier should enable all medical patients to be evaluated for risk.

A number of medical conditions exist that can complicate the treatment of a patient, including:

- recent surgery;
- intra-cranial bleeding in the previous 12 months;
- thrombocytopenia (platelet count $<75 \times 10^9$/L);
- a known bleeding disorder;
- significantly impaired liver function (INR >1.4);
- impaired renal function with a creatinine clearance of <30 mL/min;
- uncontrolled hypertension;
- active or a history of gastrointestinal bleeding;
- effective anticoagulation and therefore removing the need for thromboprophylaxis; and
- lumbar puncture or spinal/epidural anesthesia within the previous 4 hours or planned in the next 12 hours.

In addition, the use of antiplatelet agents or non-steroidal anti-inflammatory drugs may also raise concerns about bleeding with the concomitant use of a LMWH. Conversely, advancing age, active cancer, previous DVT, obesity with a body mass index (BMI) of more than 30 kg/m^2, active inflammatory infections, stroke with hemiplegia, chronic heart or respiratory failure, or hormone therapy, may place these patients at a greater risk of developing VTE than patients recruited into the clinical trials.

If contraindications to the use of pharmacological thromboprophylaxis in the acutely ill medical patient do exist, mechanical thromboprophylaxis with graduated compression stockings (GCS) or intermittent pneumatic compression (IPC) should be considered [17].

Which drugs?

Historically, UFH was the first drug to be employed for thromboprophylaxis but its use has been almost entirely superseded by the use of LMWHs or fondaparinux due to comparable efficacy, fewer side effects, and more predictable pharmacokinetics. An unresolved issue is the optimal duration of thromboprophylaxis in medical patients and although studies have shown a reduced risk of VTE with extended use this is associated with an increased risk of bleeding [23].

Direct oral anticoagulants for the prevention of venous thromboembolism in medical patients

Two studies have evaluated the role of direct oral anticoagulants (DOACs) for medical thromboprophylaxis and in both cases safety has proven to be a concern. The ADOPT trial compared an extended course of apixaban to a standard course of enoxaparin in medical patients and reported a non-significant decrease in VTE-related mortality but a significant increase in major bleeding risk [20]. The MAGELLAN trial [21] compared an extended course of rivaroxaban against a standard course of enoxaparin in hospitalized medical patients and showed that rivaroxaban was non-inferior at day 10 and superior at days 30–35 in relation to VTE prevention but clinically significant bleeding rates were increased in the rivaroxaban arm at both day 10 and days 30–35 [22,23]. DOACs are not, therefore, currently recommended for medical thromboprophylaxis.

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Chapter 4

Introduction to thromboprophylaxis in surgical patients

David Warwick

Achieving a balance

The venous thromboembolism (VTE) risk associated with surgery varies according to the procedure being performed, with some surgical procedures carrying little or no risk and others carrying a very high risk. Thromboprophylaxis is effective but is associated with expense, inconvenience and adverse effects. Therefore, it is necessary to make a balanced judgment for each patient. Three key aspects must be considered:

- patient risk;
- procedure risk;
- prophylactic method – efficacy, safety, cost and convenience.

When considering prophylaxis for surgical patients, there are two general approaches. In the first approach, the risk of VTE is estimated by summating the individual's predisposing factors (Figure 4.1) and the risk of surgical procedures (Table 4.1) [1–3]. Data on the risk of clinical thromboembolism (symptomatic thrombophlebitis, nonfatal pulmonary embolism [PE], fatal PE, and chronic venous change) are sparse; the risk is usually assumed from studies using venography or sonography as a surrogate (Table 4.1) [1–3]. Some more recent prophylaxis studies in joint replacement have been large enough to derive comparative data on symptomatic VTE as an outcome.

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The next step is to balance the efficacy of a prophylactic method against safety, cost and convenience. Prophylactic methods can be broadly divided into mechanical and pharmacological methods; each has relative advantages and disadvantages, which are empirically summarized in Table 4.2. Most of the data are derived from orthopedic studies, but the principles can be reasonably extrapolated to other surgical procedures. In the other approach, prophylaxis is routinely implemented to all patients belonging to each of the major target groups, such as those undergoing major general surgery or major orthopedic surgery.

Previous or personal history of VTE
Increasing age (>60 years at particular risk)
Prolonged immobility (>4 weeks before or after surgery)
Recent myocardial infarction or stroke (paralysis)
Central venous catheter in situ
Cancer (including treatment)
Obesity (BMI ≥30 kg/m^2)
Varicose veins with associated phlebitis
Severe infection
Inflammatory bowel disease
Dehydration
Known thrombophilias
Use of HRT/estrogen-containing hormonal contraception

Figure 4.1 Individual risk factors for surgical patients. BMI, body mass index; HRT, hormone replacement therapy; VTE, venous thromboembolism. Adapted from © National Institute for Health and Care Excellence, 2010. All rights reserved. NICE [3].

Procedure	Venographic DVT (%)	Symptomatic DVT (%)	Fatal PE (%)
Hip replacement	60	4	0.4
Knee replacement	65	4–10	0.2
Hip fracture	60	4	2?
Polytrauma	55	?	?
Cancer surgery	30	?	??
Spinal surgery	35	?	?
Major gynecological surgery	20	–	–

Table 4.1 Surgical procedures and risk. DVT, deep vein thrombosis; PE, pulmonary embolism. Adapted from © Schattauer Publishers, 2013. All rights reserved. Nicolaides et al [2].

Guidelines

It is wise for each surgical department to follow established guidelines which combine common sense and experience with evidence. These guidelines should ensure the routine and automatic provision of prophylaxis, yet allow flexibility when required by individual patient circumstances. This should give the patient the benefit of best practice and give the hospital protection against risk [4].

The 9th American College of Chest Physicians (ACCP) [1] and the International Concensus Statement (ICS) [2] generally recommend either mechanical or pharmacologic prophylaxis, depending on the procedure

Method	Efficacy	Safety	Convenience	Cost
Mechanical				
Stockings	+	+++	++	£
Foot pumps	++	+++	+	£££
IPC	++	+++	+	£££
Pharmacological				
Warfarin	+++	+	+	££
LMWH	+++	++	++	££
Pentasaccharide	+++/ ++++	+	++	£££
Aspirin	+/–	+	++++	£
Unfractionated heparin	++	+	++	£
Oral anti-Xa/anti-thrombin	++++	++	++++	££

Table 4.2 Currently available prophylaxis in surgery. IPC, intermittent pneumatic compression; LMWH, low-molecular-weight heparin.

Thromboprophylaxis type	Patient type (excluding day case)
Mechanical (GCS, IPC, foot impulse devices)	All surgical patients
LMWH	Gynecological, cardiac*, thoracic, urological, neurosurgical†, vascular if one or more patient-related risk factors present, otherwise mechanical alone
LMWH or fondaparinux	Elective hip replacement, hip fracture‡, knee replacement, continue for 4 weeks if one or more patient-related risk factor

Table 4.3 Summary of NICE guidance on thromboprophylaxis in surgical patients. GCS, graduated compression stockings; IPC, intermittent pneumatic compression; LMWH, low molecular weight heparin. *If no other anticoagulant is being used. †Excepting unsecured lesions (ruptured cranial or spinal vascular malformations). ‡Continue for 4 weeks even if no patient-related risk factors present. Adapted from © National Institute for Health and Care Excellence, 2010. All rights reserved. NICE [3].

and whether the patient is at risk for bleeding complications. The National Institute for Health and Care Excellence (NICE), which serves both the English and the Welsh health services recommends mechanical prophylaxis (compression devices or anti-embolism stockings) for all surgical patients regardless of the type of procedure being performed [3]. For high-risk patients or those with additional risk factors, additional anticoagulation with low-molecular-weight heparin or fondaparinux is advised (Table 4.3). More recent guidelines from NICE also support the newer oral agents in orthopedics (apixaban, rivaroxaban, and dabigatran). Finally, although the Scottish Intercollegiate Guidelines Network guidelines have different recommendations for each type of surgery, they note that attention must be paid to identifiable risk factors, such as bleeding and thrombosis [5]. Whilst aspirin is not recommended as a form of thromboprophylaxis by NICE or the ICS, it is now recommended by the ACCP in lower risk joint replacement supporting previous advice from the American Academy of Orthopedic Surgeons [6].

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Chapter 5

Thromboprophylaxis in orthopedic surgery

David Warwick

The risk in orthopedic surgery

Some orthopedic procedures probably carry no material risk of thrombosis (eg, hand and wrist surgery), whereas others carry a particularly high risk (eg, hip fracture surgery). Total hip replacement, total knee replacement and hip fracture have been the most widely studied procedures. The rate of fatal pulmonary embolism (PE) without prophylaxis is probably around 0.2% for total hip replacement and total knee replacement, and is probably higher for hip fracture. The symptomatic deep vein thrombosis (DVT) rate for total hip replacement is around 4%. It may be higher for total knee replacement, although the similarity between postoperative and thrombotic swelling or calf pain confounds diagnosis. The frequency of chronic venous insufficiency, an important longer-term outcome, is unknown but is likely to be raised in those with symptomatic DVT.

Guidelines in orthopedic surgery

Guidelines have much in common although there are differences. The 2012 9th American College of Chest Physicians (ACCP) [1–3], The National Institute for Health and Care Excellence (NICE) [4], and International Concensus Statement (ICS) [5] all recommend a risk assessment and a balanced approach to thrombosis and the potential for prophylaxis-associated bleeding. A combination of mechanical and chemical prophylaxis is

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supported. The ACCP and American Academy of Orthopedic Surgeons (AAOS) guidelines [6] support aspirin in hip and knee surgery whereas NICE and ICS recommend against aspirin. The AAOS, ICS, and ACCP allow mechanical methods alone for total hip replacement, total knee replacement, and hip fracture if there is high bleeding risk and low thrombosis risk.

Mechanical prophylaxis

Because bleeding is of concern to surgeons and anesthetists, mechanical methods, particularly graduated compression stockings (GCS), are widely used. The stockings should be carefully woven and fit well and must remain in place. There are few data on their efficacy after orthopedic surgery, but a meta-analysis of studies from other surgeries suggests that they have a modest benefit [7]. Intermittent pneumatic compression (IPC) devices (above or below the knee) are effective, particularly after knee surgery. Foot pumps rhythmically empty the plantar venous plexus of the foot and flush out the deep leg veins. They work best without the simultaneous use of graduated stockings and with the leg flat or slightly hanging down to enhance the preload required to prime the foot plexus. Compliance and expense are issues for all mechanical methods; they are not suitable for, nor is there much evidence in favor of, extended-duration prophylaxis. Portable devices are now available which may address some of the issues around compliance and extended duration use.

Pharmacological methods

Warfarin

Death from PE in patients taking warfarin is exceedingly rare; the drug is nearly as effective as LMWH in reducing venographic DVT. It is supported by the ACCP, ICS and AAOS. As an oral agent, it can be delivered beyond hospital discharge to protect against the risk of late-onset venous thromboembolism (VTE). The point of commencing warfarin and the duration of warfarin therapy varies between guidelines. A more recent study found that 6 weeks of low-dose warfarin, given to a target international normalized ratio of 1.5–2.5, for patients undergoing total hip arthroplasty led to VTE rates similar to that seen with LMWH and high-dose warfarin, with relatively low bleeding rates [8].

Although warfarin (Coumadin) is still widely used in North America, it is not proposed by NICE and is regarded as obsolete in much of Europe because of the narrow window of safety, the need for regular coagulation monitoring, the delayed lead-time to effect, and the potential interaction with drugs or alcohol. NICE states that oral anticoagulants such as warfarin are less effective than unfractionated heparin (UFH) or LMWH and significantly increase the risk of bleeding [4]. It may not be as safe and efficacious in real clinical practice as it is in a well-controlled clinical trial.

Fondaparinux

Fondaparinux is a synthetic pentasaccharide that specifically inhibits factor Xa. It has a 100% bioavailability, is not metabolized and is renally excreted. The half-life is 15 hours, allowing once-daily administration. The drug is not readily reversed and is contraindicated in patients with renal impairment. NICE, ACCP and ICS support fondaparinux as an alternative to LMWHs within its licensed indications.

Fondaparinux has been compared with the LMWH enoxaparin in over 7300 hip replacement, knee replacement and hip fracture patients. The overall VTE rate at 11 days after surgery (venographic DVT plus symptomatic DVT or PE) was reduced from 13.7% with enoxaparin to 6.8% with fondaparinux (odds reduction 55.2%; 95% confidence interval [CI] 45.8–63.1, $p<0.001$) [9]. A meta-analysis of 15 articles comparing newer anticoagulants with enoxaparin, including four studies with fondaparinux as the comparator, found that fondaparinux had a lower incidence of any DVT, nonfatal pulmonary embolism, or death from any cause (risk ratio [RR], 0.50; 95% CI, 0.39, 0.63), but fewer bleeds were seen with enoxaparin (RR, 1.27; 95% CI, 1.04, 1.55) [10].

Some of this advantage in VTE (and disadvantage in bleeding) may be explained by a different timing schedule from that used with low-molecular-weight heparin (LMWH), as fondaparinux was given in closer proximity to surgery. Furthermore, the apparent advantage of fondaparinux was established for asymptomatic event rates rather than for symptomatic rates [11].

In the international, multicenter, nonrandomized, open-label, prospective, intervention EXPERT trial, 5704 patients undergoing major orthopedic

surgery of the lower limb were given a daily subcutaneous injection of 2.5 mg fondaparinux for 3–5 weeks postoperatively, of whom 1631 had a neuraxial or deep peripheral nerve catheter [12]. The last fondaparinux dose was given 36 hours before catheter removal, with the next dose administered 12 hours after catheter removal. The rate of symptomatic VTE at 4–6 weeks after surgery was 0.8% in catheter patients and 1.1% in patients without a catheter, which was below the predetermined margin of noninferiority, while the overall rate of major bleeding was 0.8%, with no significant differences between patients with and without a catheter.

Consequently, fondaparinux was shown to be safe and effective not only after major orthopedic lower limb surgery, but also when the drug is discontinued for 48 hours to allow catheter removal

Aspirin

Aspirin is superficially attractive as it is familiar and cheap. The Pulmonary Embolism Prevention (PEP) study examined over 17,000 hip fracture and arthroplasty patients randomly allocated to placebo or aspirin [13]. The death rate was identical in each group. The risk reduction for DVT and PE (in a post-hoc analysis) was only approximately 30% (50% less than is expected from LMWH); the reduction in symptomatic VTE was matched by an increase in bleeding events [13].

Jameson analyzed 108,584 patients from the National Joint Registry for England and Wales who received either aspirin or LMWH as sole pharmacological prophylaxis after joint replacement. The pulmonary embolism rate was the same between the treatment groups and the 90-day mortality rate was only slightly higher in the aspirin group [14].

Whilst the 8th ACCP Guidelines and NICE recommended against aspirin, the 9th ACCP Guidelines have changed their opinion, giving a clear recommendation for prophylaxis in patients undergoing total hip or knee arthroplasty or hip replacement surgery though one panel member believed that aspirin monotherapy should not be included as an option [1]. The AAOS similarly support the use of aspirin with mechanical devices based on a number of large series of low fatality and morbidity with this combination [5].

Low-molecular-weight heparins

LMWH is the most widely studied class of thromboprophylactic agents in orthopedics. The LMWHs can be administered once (Europe) or twice daily (North America), and no monitoring is required. They are superior to dextran and UFH and at least as effective as warfarin and mechanical pumps. Used carefully, significant bleeding complications are rare. Trials consistently show a risk reduction of around 60% compared with controls in major trauma, hip and knee replacement and hip fracture. There are also data to support their use in selected patients with knee arthroscopy or plaster casts.

All guidelines support the use of LMWH and the 9th ACCP Guidelines prefer them to other chemical agents. Either preoperative or postoperative chemical administration is recommended by ACCP and ICS whereas NICE prefers post-operative administration. The duration varies between guidelines. For example, the ACCP recommend that LMWHs are given for a minimum of 10–14 days in total hip replacement or total knee replacement or hip fracture surgery whereas NICE recommends prolonged (28–35 days) LMWH therapy in patients undergoing hip surgery and in those undergoing other orthopedic procedures if they have other risk factors for VTE [4].

Direct anti-Xa inhibitors and direct thrombin IIa inhibitors

These drugs are administered orally and have a broad therapeutic and safety window; therefore, monitoring is not required. Unlike with LMWHs and fondaparinux, they avoid the need for regular injections, which can be troublesome in extended out-of-hospital prophylaxis for some patients after joint replacement, hip fracture, major trauma, or spinal injury. They also avoid the complex monitoring that is required for warfarin. The first dose is given after surgery and the medication can be continued for as long as the patient is at risk of VTE. The drugs are difficult to reverse. Presently, three are available: a direct thrombin inhibitor, dabigatran, and two anti-Xa inhibitors, rivaroxaban and apixaban, all of which have been recommended by NICE as an option for the prevention of VTE in adults having elective total hip replacement or elective total knee replacement surgery [15–17]. However, dabigatran and apixaban are approved for VTE prophylaxis only in Europe; in the USA, they are

only currently approved for stroke and systemic embolism risk reduction in patients with atrial fibrillation [18–21].

Dabigatran has an onset and offset of anticoagulant activity which are rapid and predictable. It is recommended that treatment is initiated 1–4 hours after surgery, with only half a dose on the day after surgery. Dabigatran can be given once daily, with the 150-mg dose for use in patients aged ≥75 years and in those with moderate renal impairment, and the 220-mg dose in all other patients. Studies have indicated that dabigatran achieves outcomes comparable to enoxaparin, with similar efficacy and a similar safety profile [22]. In the RE-MODEL randomized, double-blind trial, in which dabigatran 150 mg or 220 mg once daily was compared with subcutaneous enoxaparin 40 mg once daily in 1076 patients undergoing total knee replacement who were treated for 6–10 days and followed-up for 3 months, both doses of dabigatran were noninferior to enoxaparin on the combined end point of total VTE and mortality during treatment, and there was no significant difference in the incidence of bleeding events [23]. In the double-blind, randomized RE-NOVATE trial, dabigatran 150 mg or 220 mg once daily was compared with subcutaneous enoxaparin 40 mg once daily for 28–35 days in 3494 patients undergoing total hip replacement. Again, both dabigatran doses were non-inferior to enoxaparin for the combined end point of total VTE and death during treatment, and there was no significant difference in major bleeding rates [24]. Both studies also found no differences between the dabigatran and enoxaparin groups in terms of increases in liver enzyme concentrations and the incidence of acute coronary events [23,24]. The follow-up RE-NOVATE II trial (N=2055) examined only the 220-mg dose of dabigatran compared with enoxaparin 40 mg. The non-inferiority of dabigatran in terms of efficacy was also achieved in this study, and major VTEs occurred in 2.2% of those taking dabigatran versus 4.2% of those taking enoxaparin (p=0.03) [25].

Rivaroxaban: The Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD) program of four randomized, double-blind, Phase III studies of rivaroxaban demonstrated efficacy for thromboprophylaxis after total hip (RECORD1 and 2) or total knee arthroplasty (RECORD3 and 4). Treatment with

rivaroxaban significantly reduced the incidence of DVT and VTE compared with enoxaparin [26–29]. A pooled safety analysis of these studies, in which a total of 12,729 patients were randomized to oral rivaroxaban 10 mg once daily starting 6–8 hours after surgery or subcutaneous enoxaparin 40 mg once daily (RECORD 1–3) or 30 mg twice daily (RECORD4), showed that rates of bleeding and other surgical complications were similar in the rivaroxaban and enoxaparin treatment groups on both day 12 and during the full study duration [30].

Apixaban is the most recently approved agent, and its efficacy and safety were established in the three Phase III ADVANCE trials comparing apixaban 2.5 mg twice daily with enoxaparin 30 mg every 12 hours or 40 mg once daily in patients with total knee (ADVANCE-1 and -2) or hip replacement (ADVANCE-3). Patients with knee replacement received treatment for 10–14 days and patients with hip replacement received treatment for 35 days [31–33]. A pooled analysis of the ADVANCE-2 and -3 trials (N=8464) found that treatment with apixaban led to lower rates of major VTE than treatment with enoxaparin (0.7% vs 1.5%; $p<0.0001$ for non-inferiority and $p=0.001$ for superiority). Both groups had similar rates of major bleeding, myocardial infarction, stroke and patient death [34].

Edoxaban was approved in Japan in April 2011 for the prevention of VTE after major orthopedic surgery. Note, edoxaban has not undergone Phase III trials in US or EU for the orthopedic surgery indication.

Particular aspects of chemical thromboprophylaxis

Proximity of dosing and surgery

The closer to surgery that pharmacological prophylaxis is administered, the better the thromboprophylactic effect, but this also correlates with an increased risk of bleeding. In Europe, the datasheet recommends that LMWHs are given prior to surgery (eg, enoxaparin 40 mg once daily starting 12 hours pre-operatively), presumably so that there is an anticoagulant effect to counteract the thrombogenic factors during surgery (tissue thromboplastins and venous stasis). However, if the drug is given too long before surgery, plasma levels will be too low for any prophylactic effect; if given too close to surgery, then surgical bleeding can be

expected [35]. In the US, LMWHs are given after surgery at a higher dose and more frequently (eg, enoxaparin 30 mg twice daily). This may reduce the risk of surgical bleeding, but the intraoperative risk factors are not covered and thrombi may have begun to form during surgery [36]. The drug is now expected to be therapeutic rather than prophylactic. Prophylaxis with pharmacological agents such as LMWHs needs to be given close but not too close to surgery [37] – 'just in time'.
NICE guidelines recommend post-operative administration to ensure a safe interval from the surgical procedure [4].

Neuraxial anesthesia

Orthopedic patients will benefit from neuraxial (ie, spinal or epidural) anesthesia because of reduced mortality, enhanced analgesia and a weak thromboprophylactic effect. Initial European experience with LMWHs reassured that neuraxial anesthesia could be safely used in their presence, but the US FDA has raised concerns that spinal hematomata may occur. The American Society of Regional Anesthesia and Pain Medicine recommends not using neuraxial anesthesia and LMWHs within 10–12 hours of each other (24 hours if patients are receiving high doses of LMWHs) and to ensure that patients are not receiving other drugs (ie, nonsteroidal anti-inflammatory drugs) that might interfere with coagulation and therefore increase the risk of bleeding. The interval for pentasaccharides (eg, fondaparinux), with their longer half-lives, is likely to be longer [38].

Extended-duration prophylaxis

Earlier LMWH studies established that prophylaxis for 7–10 days (while the patient was in hospital) would reduce the venographic DVT rate by 60%. However, consistent evidence from several sources shows that half of symptomatic thromboses after knee replacement and two-thirds after hip replacement occur beyond the second week, usually when the patient has been discharged from hospital [39]. Several randomized trials have proven that the risk of thrombosis after hospital discharge in hip surgery can be reduced by two-thirds if LMWH is continued for at least 4 weeks. The advantage for extended prophylaxis in knee replacement is not as clear [40].

A meta-analysis by Huo et al found that extending the duration of LMWH for approximately 28–35 days after hip replacement reduced the risk of developing a DVT by 59–69% and knee replacement 62%. [41]. Therefore, it can now be reasonably concluded that venographic surrogates do reflect clinical reality; until these extended duration studies, this was only an assumption [41]. These studies show that the number to treat to prevent one symptomatic DVT or PE after hip replacement is 37; from this figure, the cost-effectiveness can be calculated. General cost savings with the use of extended-duration LMWH have been estimated to be anywhere from US$1600–1800 per patient and US$3834–5737 per event avoided [41]. However, a recent study conducted in Canada found that patients given extended-duration LMWH had only a non-significant gain in quality-adjusted life years compared with those not given extended prophylaxis, while the treatment costs per 1000 patients for the former group were much higher [42].

Discharge at 3 days after joint replacement surgery is common and minimally invasive, and day-case hip surgery is being designed. Therefore, systems need to be considered for administering and financing thromboprophylaxis after hospital discharge. The new oral agents offer a pragmatic solution to the administration of extended-duration prophylaxis. Portable mechanical devices are also available as an adjunct in those with higher risk of VTE or delayed weightbearing.

Recommendations for specific orthopedic procedures

Knee arthroscopy

In knee arthroscopy, symptomatic VTE without prophylaxis is very rare (<1%) [43,44], although venographic DVT frequencies from 3% to as high as 18% have been reported [45]. Studies have shown that prophylaxis with LMWHs appears to reduce the risk of VTE without major bleeding complications [46–52].

Guidelines vary: NICE recommend that LMWH prophylaxis be given to those undergoing knee arthroscopy if additional risk factors are present and if the surgery is complicated; ACCP recommend no thromboprophylaxis in patients unless there is a history of prior VTE [1,4];

ICS recommend no prophylaxis for therapeutic arthroscopy but routine prophylaxis for therapeutic arthroscopy.

The use of injectable prophylaxis raises pragmatic issues in case surgery such as knee arthroscopy. The new oral agents provide a pragmatic solution but data are required for safety and efficacy

Trauma

Polytrauma patients

Because of thromboplastin release, major surgical interventions and subsequent prolonged immobility, patients with multiple trauma are at particularly high risk of VTE. Systematic venography has shown a DVT frequency of 58% in these patients [53]. Prophylaxis with LMWHs is likely to reduce the frequency of VTE but is contraindicated in associated head injury, visceral injury and widespread soft tissue injury; however, it can be used in patients with spinal cord injury [2,54,55]. Mechanical methods are an attractive alternative, although these devices have practical limitations because concomitant lower limb injuries may preclude their application; the evidence base is limited to a few small studies [56].

Isolated lower limb trauma

Due to this group's extensive heterogeneity and limited evidence base, clear recommendations cannot be devised [57]. ACCP and NICE recommend a risk assessment with prophylaxis individualized to each injured patient; ICS recommends routine LMWH in the absence of contraindications.

Spinal surgery

There is a risk of VTE during spinal surgery; however, pharmacological prophylaxis carries a risk of bleeding around the spinal cord. A survey of neurosurgeons and orthopedic surgeons conducted in the United Kingdom found that neurosurgeons were more likely than orthopedic surgeons to give LMWH for prophylaxis, while orthopedic surgeons were more likely to use mechanical methods. In trauma cases, LMWH was the preferred prophylaxis method, and below-the-knee GCS was most frequently given in non-trauma cases [58].

For straightforward cases, the risk–benefit ratio supports no routine prophylaxis for spinal surgery except early mobilization, perhaps potentiated by mechanical methods [2]. For those with greater risk factors for VTE, pharmacologic prophylaxis may be added to mechanical methods once the risk of bleeding decreases and hemostasis is established [2].

Upper limb surgery

In upper limb surgery, there is a risk of VTE in shoulder surgery and major elbow surgery; these patients should have a risk assessment and prophylaxis considered; in hand and wrist surgery the risk is negligible [59].

Combined prophylaxis

Because VTE is provoked by a combination of altered blood flow and hypercoagulability, it appears sensible to combine the two for a complimentary if not synergistic effect. In those with a high risk of bleeding, a chemical can be delayed until the bleeding risk has declined before it is started. In thise with a high risk of thrombosis, the two can be combined. This approach is recommended by the AAOS, NICE, and ICS, supported by meta-analysis evidence [60].

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Chapter 6

Thromboprophylaxis in cancer surgery

David Gozzard and David Perry

The presence of cancer, overt or occult, is thrombogenic to the individual. This has been recognized from the time of Armand Trousseau who, in 1865 [1], stated: "I have long been struck with the frequency with which cancerous patients are affected with painful edema of the superior or inferior extremities, whether or not either was the seat of the cancer. The frequent occurrence of phlegmasia alba dolens with an appreciable cancerous tumor, led me to the inquiry of whether a relationship of cause and effect did not exist between the two". This observation is classically associated with pancreatic carcinoma, but other tumors, particularly adenocarcinomas, can also cause thrombosis. Trousseau correctly diagnosed it in himself scarcely 18 months later and died of stomach cancer in 1867 [2].

Pathophysiology

Mucinous adenocarcinomas secrete abnormally glycosylated mucins and mucin fragments into the bloodstream [3]. Such tumors, grown in tissue culture, produce a supernatant that is tumor-free but characteristically shows marked thrombogenic properties. It is this secretion of abnormal mucins that leads to the hypercoagulable state in some malignancies and the association with venous thromboembolism (VTE). There are many reported abnormalities within the coagulation pathways, but these are inconsistent between types of cancer. Some individuals have a shortening

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of the activated partial thromboplastin time; in others, a reduction in levels of protein C or antithrombin are reported. Platelet activation can occasionally occur in tandem with activation of inflammatory pathways. Recent evidence has shown that tumor-induced coagulation activation is intrinsically involved with tumor cell growth, angiogenesis and metastasis. Continuous treatment with heparin is usually required to prevent recurrent episodes of thrombosis, but oral anticoagulants (vitamin K antagonists) that also decrease thrombin production are often ineffective and are not recommended for use in patients with cancer [4–8].

Epidemiology

VTE is a common complication in patients with cancer and an important cause of morbidity and mortality. The development of VTE in the patient with cancer is associated with a reduced prognosis. A UK cohort study found that the incidence rate of VTE in patients with cancer was 13.9 per 1000 patient-years, versus 3.0 per 1000 patient-years in matched controls [9]. Nearly 13% of all patients with pulmonary embolism (PE) have cancer, and PE is the second-leading cause of cancer-related mortality [10,11]. The effect of VTE is worse in patients with localized disease [10,12].

Venography is the usual method of detection of VTE in clinical trials. However, the clinical relevance of venographically detected deep vein thrombosis (DVT) is unclear, and the prevalence of this complication in clinical trials is not necessarily representative of the overall cancer surgery clinical risk. @RISTOS was a prospective registry of 2373 consecutive patients undergoing cancer surgery in 31 Italian hospitals [13]. Fifty-two percent of patients underwent general surgery, 29% urological surgery and 19% gynecological surgery. A follow-up, as scheduled by study protocol, was obtained in nearly all patients. In-hospital prophylaxis was performed in 81.7% of patients and post-discharge prophylaxis in 30.7%. Results from the study were as follows [13]:

- The overall death rate was 1.7% and nearly half of these cases were due to VTE.

- A total of 50 patients (2.1%) were found to be affected by clinically overt VTE by the external Adjudication Committee (deep vein thrombosis [DVT], n=10; nonfatal PE, n=21; death, n=19).
- The incidence rate of VTE was 2.8% in general surgery cases, 2.0% in gynecological surgery and 0.9% in urological surgery.
- Forty percent of the VTE events occurred >21 days after surgery.
- The major risk factors for developing VTE were age ≥60 years, previous VTE, advanced cancer, duration of anesthesia ≥2 hours and ≥4 days of bed rest.

Antithrombotic agents in cancer thromboprophylaxis

The advent of low molecular weight heparins (LMWHs) in the late 1980s and their apparent safety profile provided a further agent in the armamentarium for thromboprophylaxis. It soon became clear that LMWHs (initially in combination with dihydroergotamine [DHE]) were at least as effective as low-dose unfractionated heparins (UFHs) [14] with a lesser incidence of bleeding and ease of administration, particularly as the newer LMWHs could be administered once daily. A recent review of the LMWHs has demonstrated that, as a group, they are an effective and safe alternative to UFHs [15]. The 9th American College of Chest Physicians (ACCP) guidelines recommend LMWHs as first-line treatment for patients undergoing abdominal or pelvic surgery for cancer who are at high risk for developing a VTE [16].

Two studies have compared the use of LMWH and UFH in patients undergoing craniotomy for malignant brain tumors [17,18]. All patients also received pneumatic compression devices as well as compression stockings. Both studies concluded that both heparin regimens were effective and safe and were associated with a low incidence of VTE when used in combination with intermittent pneumatic devices.

The ENOXAparin in CANcer (ENOXACAN) study group examined patients undergoing surgery for malignant disease and investigated the efficacy of enoxaparin 40 mg once daily beginning before surgery versus low-dose UFH [19]. The study was designed as a prospective, double-blind, randomized, multicenter trial with participating institutions from

ten countries. The primary outcome, VTE, was detected by mandatory bilateral venography and pulmonary scintigraphy, and the follow-up period was 3 months. Of the 631 evaluable patients, 104 (16.5%) developed thromboembolic complications; the frequency was 18.2% in the UFH group and 14.7% in the enoxaparin group. There was no difference in the bleeding events or other complications between the groups, nor was there difference in mortality at 30 days or 3 months [19].

The follow-up ENOXACAN II study compared the safety and efficacy of 1-week and 4-week regimens of enoxaparin prophylaxis versus placebo in 332 patients undergoing surgery for abdominal or pelvic cancer. Thromboprophylaxis with a LMWH for 4 weeks significantly reduced the incidence of thrombosis versus treatment for 1 week (VTE rate 4.8% vs 12%; p=0.02) [20].

A meta-analysis of 16 randomized controlled trials compared LMWH and UFH for perioperative thromboprophylaxis in a total of 11,847 patients undergoing surgery for cancer. There was no significant difference in mortality rates between patients receiving LMWH and those given UFH, at a relative risk of 0.90. There were also no significant differences in the occurrence of clinically suspected DVT, PE, minor bleeding or major bleeding, at relative risks of 0.73, 0.59, 0.88, and 0.84, respectively [21].

The clinical approach to cancer thromboprophylaxis

Surgeons' perceptions regarding the risk of thrombosis in patients with cancer undergoing surgery have been highlighted in the Fundamental Research in Oncology and Thrombosis (FRONTLINE) survey [22]. This survey of clinical approaches to thrombosis prevention in patients with cancer was undertaken in 2001. At that time, just over half of the respondents would routinely use thromboprophylaxis, usually heparin, in cancer surgical patients. An additional 43% would decide on a case-by-case basis. The majority of respondents reported using thromboprophylaxis in cancer surgical patients for the duration of their hospital stay, although 25% would continue treatment only for 5–10 days. Within the UK, a study of the attitudes of general surgeons to thromboprophylaxis produced virtually identical results [23]. A 2010 survey of members of the Society of Gynecologic Oncology of Canada found that 78% believed

that thromboprophylaxis should be used routinely for gynecologic cancer surgical patients [24].

Recommendations

Cancer surgery is high risk, and there are few recognized recommendations for the management of patients undergoing such surgery. The SIGN guidelines recommend UFH, LMWH or fondaparinux for cancer surgery thromboprophylaxis [25]. As noted above, the 9th ACCP guidelines recommend that high-VTE-risk patients undergoing abdominal or pelvic surgery for cancer have long-term (4-week) prophylaxis with LMWH (Grade 1B) [16], whilst patients with cancer confined to bed with an acute medical illness should have routine prophylaxis similar to other high-risk patients (Grade 1A) [26]. Routine prophylaxis should not be used in patients with cancer either with or without indwelling central venous catheters (Grade 2B) [27]. Prophylaxis with intermittent pneumatic compression (IPC) should be considered in high-risk cancer surgery. However, it has been reported that such prophylaxis is likely to fail in women undergoing surgery for gynecological malignancies [26]. Consideration should be given to the prolonged use of heparin thromboprophylaxis (up to 28 days) in patients undergoing major abdominal cancer surgery. There are several reasons why LMWH is often the preferred antithrombotic agent over UFH:

- Many of the LMWHs can now be given once daily. This frees up nursing time and is more convenient for home use.
- There is a lesser incidence of heparin-associated thrombocytopenia with LMWH than UFH. LMWH is less likely to be associated with antiplatelet antibodies than UFH.

The use of epidural or spinal regional anesthetic in itself is associated with a reduction in VTE. However, concerns have been raised about the possibility of spinal hematoma. This appears to have been more of a problem in the USA than in Europe and may be associated with the timing and dosage of LMWH.

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Chapter 7

Thromboprophylaxis in other types of surgery

David Gozzard and David Perry

Whereas the evidence base for surgical thromboprophylaxis has centered on elective orthopedic surgery and subsequently been adopted in cancer surgery, there is a good evidence base for the prevention of thromboembolic disease in other surgical specialties. This chapter will present the evidence base for four surgical specialties – neurological, urological, cardiothoracic and gynecological surgery – as well as for patients with mechanical heart valves. A common theme is the difference in elective versus emergency thromboprophylaxis.

Neurological surgery

Acute ischemic stroke is associated with a high incidence of venous thromboembolism (VTE) [1] and reflects the thrombogenicity of damaged neurological tissue. Whilst neurosurgeons are acutely aware of the propensity of their surgery to initiate VTE, surgery within the confines of the cranium or spinal column has always presented the dilemma of balancing the risk between the development of thromboembolism and the disastrous complication of compressive hemorrhage. Neurological surgery patients constitute one of the highest risk groups for postoperative thromboembolic complications.

Neurological surgery performed without thromboprophylaxis produces a rate of symptomatic deep vein thrombosis (DVT) of up to 15% [2]. The

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risk of developing DVT/VTE after traumatic cranial injuries has been less well evaluated, though studies have noted a wide prevalence range (4–25%), even in patients given prophylaxis [3,4]. Several specific risk factors have been identified that increase the risk of VTE: paralysis or paresis; a meningioma or malignant tumor; the presence of an indwelling venous catheter; a large tumor; age ≥40 years; surgery lasting >4 hours, and chemotherapy [4,5]. Both mechanical methods and low molecular weight heparins (LMWHs) have shown benefit in reducing VTE in neurosurgery, decreasing the risk by about 50% [5]. Postoperative prophylaxis with a LMWH does not seem to increase the risk of intracranial bleeding. However, there is no demonstrated benefit in pre-operative thromboprophylaxis. The customary duration of prophylaxis is 7–10 days, but this has not been scientifically determined [5].

Prophylaxis against VTE, DVT and pulmonary embolism (PE) is a patient safety issue, and options include graduated compression stockings/graduated compression elasticated stockings (GCS/GCES), intermittent pneumatic compression (IPC) stockings, low-dose unfractionated heparin (UFH) (5000 IU every 8–12 hours) and LMWH. The risks and benefits associated with different prophylaxis regimens used in the prevention of DVT and PE in neurological surgery procedures have been analyzed. Smith and co-workers found that the incidence of DVT was greater for cranial (3.0%) than spinal procedures (1.1%) [6], and although IPC devices provided adequate reduction of DVT/PE events in some cranial and combined cranial/spinal series, low-dose subcutaneous UFH or LMWH further reduced the incidence of PE, though not always of DVT [7]. Nevertheless, low-dose heparin-based prophylaxis in cranial and spinal series does carry a risk of postoperative hemorrhages [8–10]:

- 2.5% incidence rate in a cranial series;
- 0.5–2.3% in a combined cranial/spinal series; and
- 1.7% incidence rate in a spinal series.

Traumatic closed head injury is an area where evidence is sparse. Norwood et al concluded that LMWH could be safely administered 24 hours after a head injury complicated by intracranial hemorrhage without an increased risk of hemorrhage progression or new bleeding [11]. Although mechanical prophylaxis is effective against DVT and PE, the added efficacy of

low-dose heparin regimens has to be balanced against the risk of major postoperative hemorrhages and their neurological sequelae [12,13].

Despite the proven success of perioperative anticoagulant prophylaxis in reducing DVT rates, some neurosurgeons may be reluctant to use it because of the potentially serious consequences of even small intracranial bleeds, particularly when the patient has an injury that carries an increased risk of hemorrhage [14,15]. Studies have found that a combination of GCS and low molecular weight heparin (LMWH) started postoperatively significantly reduces the incidence of DVT compared with GCS alone [14].

A survey of 66 consultant neurosurgeons in Canada found that 60–90% regularly used some form of prophylaxis, depending on the procedure being performed [15]. For all forms of neurological surgery, the most preferred mechanical method of prophylaxis was IPC or, in the postoperative period, a combination of mechanical methods and LMWH, UFH, or both. Pharmacological prophylaxis was rarely administered in the perioperative period. There were wide variations in timing of when heparin prophylaxis was normally administered, even within procedures [15]. Careful management of anticoagulant thromboprophylaxis provides improved outcomes in the prevention of VTE, but there is still room for improvement.

Guidelines

The following are the 9th American College of Chest Physicians (ACCP) guidelines for thromboprophylaxis of patients undergoing neurological surgery [16].

The National Institute for Health and Care Excellence (NICE) recommends that all patients having neurological surgery be offered mechanical prophylaxis, and that those with one or more risk factors for VTE should also be offered LMWH or UFH. However, pharmacological thromboprophylaxis is contraindicated in patients who have ruptured cranial or spinal malformations, such as brain aneurysms, until the lesion has been secured [17].

Craniotomy

- Mechanical prophylaxis, preferably with IPC, should be used in patients undergoing craniotomy, rather than pharmacological prophylaxis (Grade 2C).
- Mechanical prophylaxis and pharmacological prophylaxis should be combined in high-risk craniotomy patients once adequate hemostasis is established and there is less risk of bleeding (Grade 2C).

Spinal surgery

- Mechanical prophylaxis, preferably with IPC, should be used in patients undergoing spinal surgery, rather than pharmacological prophylaxis (Grade 2C).
- Mechanical prophylaxis and pharmacological prophylaxis should be combined in high-risk spinal surgery patients (including those with cancer or those undergoing surgery with a combined anterior-posterior approach) once adequate hemostasis is established and there is less risk of bleeding (Grade 2C).

Major trauma

- Mechanical prophylaxis (preferably with IPC), LMWH or UFH should be used in patients with major trauma (Grade 2C).
- Mechanical prophylaxis and pharmacological prophylaxis should be combined in high-risk major trauma patients (including those with traumatic brain injury, acute spinal injury, or spinal surgery for trauma), if it is not contraindicated by lower-extremity injury (Grade 2C).
- Mechanical prophylaxis, preferably with IPC, should be used in patients with major trauma when LMWH or UFH use is contraindicated. When there is less risk of bleeding or heparin use is no longer contraindicated, pharmacologic prophylaxis can be added (Grade 2C).
- Use of an inferior vena cava filter is not recommended (Grade 2C).
- Periodic surveillance with venous compression ultrasonography is not recommended (Grade 2C).

Urological surgery

Thromboembolic events are regarded as the most important nonsurgical complications to occur in major urological procedures [18–21]. The incidence of DVT in urological surgery is considered to be broadly similar to that in general surgery. Older studies noted DVT rates of anywhere from 10% (in transurethral surgery) to 40% (in open prostatectomy), but changes in surgical care, earlier postoperative mobilization of patients and the introduction of various methods of thromboprophylaxis have since resulted in a decrease of the reported rates of thrombosis to 0.3–9.7% [22–24]. The use of LMWH was not shown to increase blood loss or the formation of pelvic lymphoceles [25]. Certain factors increase the risk of VTE in urological surgery patients. An open procedure has more risk than a transurethral one [26], whilst the risk with other factors (ie, increased age, general anesthesia, and duration of procedure) is similar to that of patients undergoing general surgical procedures. There is broad agreement that prophylaxis is required for open procedures and this comes down, at present, to surgeon-specific protocols based upon recognized published guidelines.

Guidelines

The 9th ACCP guidelines group urological surgery in the 'abdominal/pelvic surgery' category, along with gastrointestinal and gynecological surgery [16].

The Scottish Intercollegiate Guidelines Network (SIGN) guidelines include the following recommendations (see below) [27]. A guide to the SIGN grading system is provided in Figure 7.1. Meanwhile, NICE recommends that mechanical prophylaxis be offered, with LMWH also used in those with one or more risk factors for VTE [17].

Urological surgery

- The preferred method of prophylaxis in patients undergoing urological surgery is mechanical prophylaxis with IPC or GCS/GECS (Grade D).
- Those who have additional risk factors for VTE should be given a combination of mechanical prophylaxis and LMWH (Grade D).

Abdominal/pelvic surgery

- For patients at very low risk for VTE, no specific mechanical (Grade 2C) or pharmacologic (Grade 1B) prophylaxis is recommended other than early ambulation.
- For patients at low risk for VTE, mechanical prophylaxis, preferably with IPC, is recommended (Grade 2C).
- For patients at moderate risk for VTE not at high risk for bleeding complications, the use of LMWH (Grade 2B), UFH (Grade 2B), or mechanical prophylaxis, preferably with IPC, is recommended (Grade 2C).
- For patients at moderate risk for VTE who are at high risk for bleeding complications, mechanical prophylaxis, preferably with IPC, is recommended (Grade 2C).
- For patients at high risk for VTE not at high risk for bleeding complications, the use of LMWH (Grade 1B) or UFH (Grade 1B) is recommended, along with the addition of mechanical prophylaxis (preferably with GECS or IPC) (Grade 2C).
- For patients at high risk for VTE who are at high risk for bleeding complications, mechanical prophylaxis, preferably with IPC, is recommended. Once the risk for bleeding is diminished, pharmacological prophylaxis may be started (Grade 2C).
- For patients at high risk for VTE in whom the use of LMWH and UFH is contraindicated, fondaparinux, low-dose aspirin, or mechanical prophylaxis (preferably or IPC) is recommended (Grade 2C).
- Use of an inferior vena cava filter is not recommended (Grade 2C).
- Periodic surveillance with venous compression ultrasonography is not recommended (Grade 2C).

Cardiothoracic surgery

Cardiac surgeons recognize the increased risk of VTE following cardiothoracic surgery, but again face the quandary of balancing the accepted benefits of LMWH thromboprophylaxis with the perceived increased

Level/grade	Clarity and methodological strength of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies; high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2–	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies; eg, case reports, case series
4	Expert opinion
A	At least one meta-analysis, systematic review or RCT rated as: • 1++ and directly applicable to the target population, or a body of evidence consisting principally of studies rated as • 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results, or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+

Figure 7.1 Scottish Intercollegiate Guidelines Network grades of evidence. RCT, randomized controlled trials. Reproduced with permission from © Scottish Intercollegiate Guidelines Network (SIGN), 2010. All rights reserved. SIGN [27].

risk of bleeding. Several studies have confirmed the high rate of VTE, usually DVT, occurring after vascular surgery [28–31]. Rates from 1.3% for PE [29] to 14–20% for DVT [30,31] have been observed, with 84% of thromboses in one study being observed in the leg ipsilateral to the saphenous vein harvest site. Risk factors for DVT include male gender, obesity, hypertension, and hyperlipidemia [30]. A study by Ambrosetti et al found that the adoption of heparin prophylaxis until discharge predicted the absence of DVT after adjustment for immobility [32].

Guidelines

Below are listed the SIGN guideline recommendations [27].

- Patients undergoing thoracic surgery should be given mechanical prophylaxis with GECS or IPC). Those who are not at high risk for bleeding may be given LMWH or UFH in addition to mechanical prophylaxis (Grade D).
- Patients undergoing cardiac surgery should be offered mechanical thromboprophylaxis. Those who are not at high risk for bleeding may be given LMWH or UFH in addition to mechanical prophylaxis (Grade D).

The following are recommendations from the 9th ACCP guidelines [16].

Cardiothoracic surgery

- In patients undergoing cardiac surgery who have an uncomplicated postoperative course, mechanical prophylaxis, preferably with optimally applied IPC, is recommended (Grade 2C).
- For patients undergoing cardiac surgery who have one or more postoperative nonhemorrhagic complications, it is recommended that LMWH or UFH be added to mechanical prophylaxis (Grade 2C).
- For patients undergoing thoracic surgery at moderate risk for VTE but not at high risk for perioperative bleeding, LMWH (Grade 2B), UFH (Grade 2B) or mechanical prophylaxis with optimally applied IPC are recommended (Grade 2C).
- For patients undergoing thoracic surgery at high risk for VTE but not at high risk for perioperative bleeding, LMWH or UFH are recommended (Grade 1B). Mechanical prophylaxis with GCES or IPC should be added to pharmacological prophylaxis (Grade 2C).
- For patients undergoing thoracic surgery at high risk for major bleeding, mechanical prophylaxis, preferably with optimally applied IPC, is recommended. Once the risk for bleeding is diminished, pharmacological prophylaxis may be started (Grade 2C).

The NICE guidelines state that mechanical prophylaxis should be offered and LMWH used in patients with one or more VTE risk factors [17]. It is noted that patients who are already receiving an agent that provides prophylaxis may not need additional pharmacological prophylaxis.

Gynecological surgery

VTE is an important complication of major gynecological surgery, with rates of DVT, PE and fatal PE similar to those seen after general surgical procedures. Risk factors for the development of VTE in relation to gynecological surgery include malignancy, age >40 years, obesity, previous DVT, prior chemotherapy, and the use of an abdominal surgical approach [33,34]. Furthermore, in women with gynecological malignancies, venous compression by the tumor or venous intimal damage secondary to surgery or radiotherapy also increase the risk of VTE [35]. Finally, surgery in such individuals is often lengthy, with a slow postoperative recovery.

The 9th edition of the ACCP guidelines groups gynecological surgery in the 'abdominal/pelvic surgery' category, along with gastrointestinal and urological surgery. Therefore, the urological surgery guidelines mentioned above are also applicable to the gynecological surgery population.

In practice, most women undergoing gynecological surgery will receive once-daily LMWH (eg, enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) and GCS [36]. NICE recommends mechanical prophylaxis in all women undergoing gynecological procedures, with added LMWH if they have one or more risk factors for VTE [17].

Patients with mechanical heart valves

The management of patients with mechanical heart valves who require surgery is a common clinical problem.

Risk stratification for patients with mechanical heart valves

Patients with mechanical heart valves are at increased risk of thrombus formation, in addition to arterial thromboembolism, stroke, and systemic embolism [37,38].

Most estimates of arterial thromboembolic risk are derived from studies in which patients were receiving either no antithrombotic therapy

or treatment that is currently considered suboptimal. There are few data available on the risk of VTE in patients who have modern prostheses and have not received antithrombotic therapy over an extended time period. In the absence of such data, it is sensible to err on the side of caution when recommending anticoagulant treatment or thromboprophylaxis for such patients.

The 9th ACCP guidelines suggest the following risk stratification categories for perioperative thromboembolism in patients with a mechanical heart valve [39]:

1. High-risk patients include:
    - Mitral valve prosthesis
    - Older-generation (caged-ball or tilting disk) aortic valve prosthesis
    - A recent (<6 months) stroke or transient ischemic attack
2. Moderate-risk patients include:
    - Bileaflet aortic valve prosthesis and one or more of the following:
    - Atrial fibrillation
    - Prior stroke or transient ischemic attack
    - Hypertension
    - Diabetes
    - Congestive heart failure
    - Age >75 years
3. Low-risk patients (<4%/year) are those with a bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke.

Management (per the 9th ACCP guidelines)

In patients with mechanical heart valves, bridging therapy is recommended, with LMWH or prophylactic UFH preferable to intravenous therapeutic UFH. When the patient is stable, a vitamin K antagonist (VKA) can be given for long-term treatment [40].

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Chapter 8

Thromboprophylaxis in pregnancy

David Perry

Pregnancy is associated with an approximate 10-fold increased risk of venous thromboembolism (VTE) compared with non-pregnant woman and this risk may be higher in some women because of the presence of additional risk factors (Figure 8.1). Despite its low absolute risk, it remains a leading cause of maternal mortality in developed countries. In 2009–2012, 357 women died during, or within six weeks of the end of their pregnancy in the UK [1]. This represents a statistically significant decrease in the maternal mortality rate, which is now 10.12 per 100,000 maternities. This decrease is predominantly due to a reduction in deaths due to direct (obstetric) causes. Thromboembolic disease was historically the leading direct cause of maternal death in the UK in the years 2003–2005 but fell to fourth position between 2006 and 2008, and this was attributed to the identification of at-risk women in pregnancy and the use of pharmacological thromboprophylaxis. However, thrombosis and thromboembolism is again the leading cause of direct maternal deaths in the UK (Table 8.1).

The risk of VTE increases throughout pregnancy and is highest in the immediate post-partum period but no longer statistically significant after 6 weeks. Although historically thromboprophylaxis is continued until 6 weeks following delivery the risk of VTE may extend past this but the absolute risk from 6 to 12 weeks is small. Antenatal deep vein thrombosis (DVT) is more common than pulmonary embolism (PE), is usually proximal, and affects the left leg in 70% of cases due to compression of

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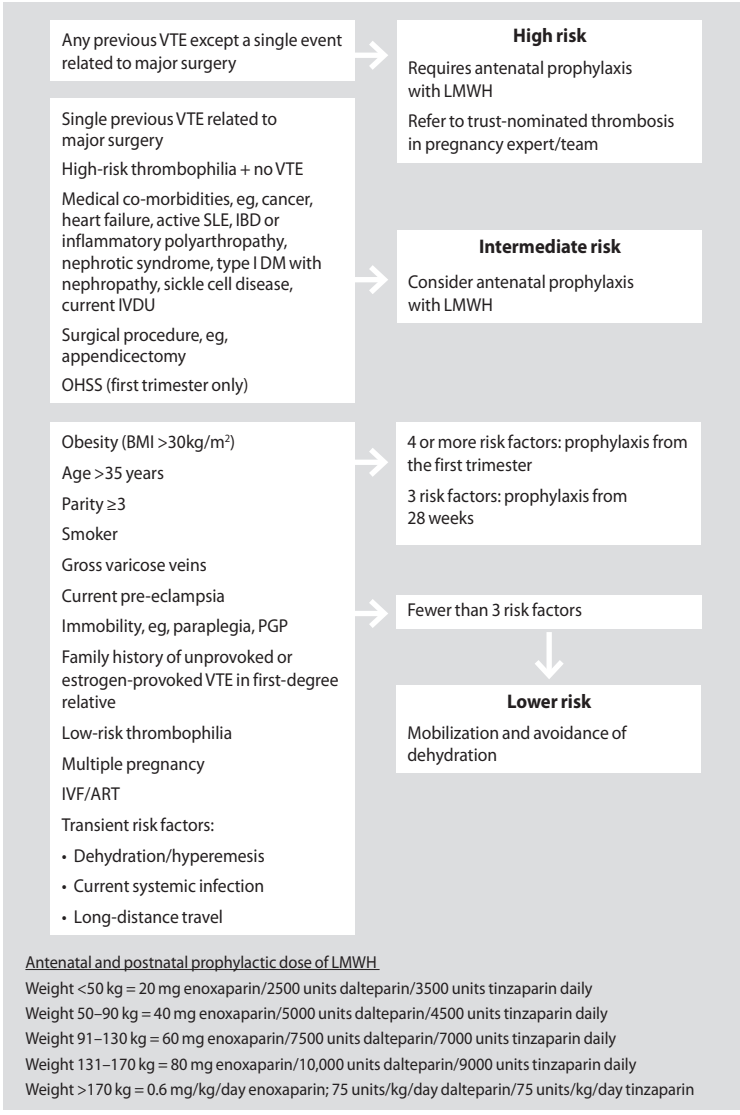

Figure 8.1 Antenatal thromboprophylaxis risk assessment and management (to be assessed at booking and repeated if admitted). ART, assisted reproductive therapy; BMI, body mass index; DM, diabetes mellitus; IBD, inflammatory bowel disease; IVDU, intravenous drug user; IVF, in vitro fertilization; LMWH, low-molecular-weight heparin; OHSS, ovarian hyperstimulation syndrome; PGP, pelvic girdle pain with reduced mobility; SLE, systemic lupus erythematosus; VTE, venous thromboembolism. Reproduced with permission from © Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBBRACE-UK), 2014. All rights reserved. MBBRACE -UK [1].

Dates	Number of deaths from thrombosis and thromboembolism	Rates per 100,000 maternities
2003–2005	41	1.94
2006–2008	18	0.79
2009–2011	30	1.26
2010–2012	26	1.08

Table 8.1 UK maternal deaths from thrombosis and thromboembolism 2003–2012. Part of this has been attributed to the known association of maternal obesity with thrombosis and the rising rates of obesity in the pregnant population. It should be noted, however, that the change in death rate from thrombosis and thromboembolism between 2006–08 and 2010–12 is not statistically significant.

the left common iliac vein by the right common iliac artery. Most fatal antenatal VTE events occur in the first trimester and therefore prophylaxis for women with a previous VTE should begin in early pregnancy. Following delivery, PE is more common than DVT.

The UK guidelines published by the Royal College of Obstetricians and Gynaecologists (RCOG) in 2015 [2] and endorsed by The National Institute for Health and Care Excellence (NICE), recommend that all women undergo a VTE risk assessment either before or in early pregnancy to establish if they would benefit from pharmacological thromboprophylaxis [2]. This assessment should be repeated if a woman is admitted to hospital or develops other related problems, which might independently increase her risk of VTE during pregnancy or at the time of delivery. Women at very high risk of VTE, including those with previous confirmed VTE, are on long-term anticoagulants for recurrent VTE, or who have metal heart valves require pre-pregnancy counseling with a clear, prospective management plan. The RCOG guidelines are in general similar to those published by the American College of Chest Physicians (ACCP) in 2012 [3].

Risk factors for venous thromboembolic disease in pregnancy

Risk factors for venous thromboembolic disease (VTED) in pregnancy can be separated into:

1. pre-existing maternal risk factors;
2. obstetric risk factors; and
3. new onset/transient risk factors, as summarized in Tables 8.2 and 8.3.

Pre-existing	Tick	Score
Previous VTE (except a single event related to major surgery)		4
Previous VTE provoked by major surgery		3
Known in high-risk thrombophilia		3
Medical comorbidities, eg, cancer, heart failure, active SLE, inflammatory polyarthropathy or IBD, nephrotic syndrome, type I DM with nephropathy, sickle cell disease, current IVDU		3
Family history of unprovoked or estrogen-related VTE in first-degree relative		1
Known low-risk thrombophilia (no VTE)		1*
Age (>35 years)		1
Obesity		1 or 2**
Parity ≥3		1
Smoker		1
Gross varicose veins		1
Obstetric risk factors		
Pre-eclampsia in current pregnancy		1
ART/IVF (antenatal only)		1
Multiple pregnancy		1
Cesarean section in labor		2
Elective cesarean section		1
Mid-cavity or rotational operative delivery		1
Prolonged labor (>24 hours)		1
PPH (>1 liter or transfusion)		1
Preterm birth <37 weeks in current pregnancy		1
Stillbirth in current pregnancy		1
Transient risk factors		
Any surgical procedure in pregnancy or puerperium except immediate repair of the perineum, eg, appendicectomy, postpartum sterilization		3
Hyperemesis		3
OHSS (first trimester only)		4
Current systemic infection		1
Immobility, dehydration		1
TOTAL		

Table 8.2 The Royal College of Obstetricians and Gynaecologists risk factors for venous thromboembolic disease in pregnancy and the puerperium. *If the known low-risk thrombophilia is in a woman with a family history of VTE in a first-degree relative postpartum thromboprophylaxis should be continued for 6 weeks. **BMI ≥30 = 1; BMI ≥40 = 2. ART, assisted reproductive technology; DM, diabetes mellitus; IBD, inflammatory bowel disease; IVDU, intravenous drug user; IVF, in vitro fertilization; OHSS, ovarian hyperstimulation syndrome; PPH, postpartum hemorrhage SLE, systemic lupus erythematosus; VTE, venous thromboembolism. Adapted from © the Royal College of Obstetricians and Gynaecologists (RCOG), 2015. All rights reserved. RCOG [2].

As the absolute risk of VTE in pregnancy is low, risk stratification is essential to establish which women will benefit from thromboprophylaxis. The VTE risk following delivery whilst higher, is of a shorter duration (6 weeks) and there is, therefore, a lower threshold for post-partum thromboprophylaxis. The risk factors for VTE in pregnancy and the puerperium are summarized in Tables 8.2 and 8.3. The puerperium is commonly defined as the time from the delivery of the placenta until 6 weeks thereafter.

The RCOG guidelines stratify women on the basis of their individual risk factors and the recommendations for thromboprophylaxis are based upon these (Figures 8.1, 8.2, and 8.3). However, regardless of their risk

Major risk factors (OR >6): presence of at least one risk factor suggests a risk of postpartum VTE >3%
Immobility (strict bed rest for ≥1 week in the antepartum period)
Postpartum hemorrhage ≥1000 mL with surgery
Previous VTE
Pre-eclampsia with fetal growth restriction
Thrombophilia: • Antithrombin deficiency* • Factor V Leiden (homozygous or heterozygous) • Prothrombin G20210A (homozygous or heterozygous)
Medical conditions: • Systemic lupus • Heart disease • Sicke cell disease
Blood transfusion
Postpartum infection
Minor risk factors (OR >6 when combined): presence of at least two risk factors or one risk factor in the setting of emergency cesarean section suggests a risk of postpartum VTE of >3%
BMI >30 kg/m^2
Multiple pregnancy
Postpartum hemorrhage >1 L
Smoking >10 cigarettes/d
Fetal growth restriction (gestational age + sex-adjusted birth weight <25th percentile)
Thrombophilia: • Protein C deficiency • Protein S deficiency
Pre-eclampsia

Table 8.3 The American College of Chest Physicians guidelines: risk factors for venous thromboembolic disease in pregnancy and the puerperium. Adapted from © American College of Chest Physicians (ACCP), 2012. All rights reserved. ACCP [3].

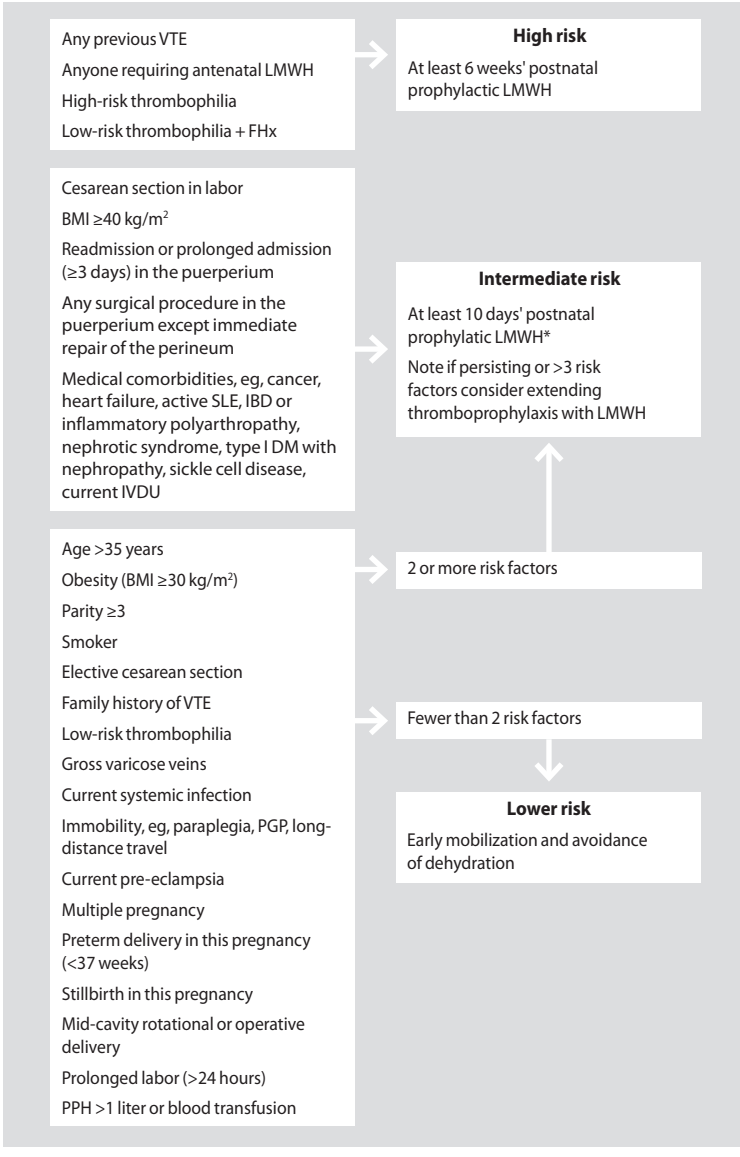

Figure 8.2 Postnatal thromboprophylaxis risk assessment and management (to be assessed on delivery suite). BMI, body mass index; DM, diabetes mellitus; IBD, inflammatory bowel disease; IVDU, intravenous drug user; LMWH, low-molecular-weight heparin; PGP, pelvic girdle pain with reduced mobility; PPH, postpartum hemorrhage; SLE, systemic lupus erythematosus; VTE, venous thromboembolism. (See Figure 8.1 for antenatal and postnatal prohylactic dose of LMWH). Reproduced with permission from © Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBBRACE-UK), 2014. All rights reserved. MBBRACE -UK [1].

Risk	Antenatal assessment*	Post-natal assessment**
High risk	**Risk factors:** • Any previous VTE event except when related to major surgery	**Risk factors:** • Previous VTE • Antenatal thromboprophylaxis • High risk thrombophilia[2] • Low risk thrombophilia and a family history
	Management: • Antenatal thromboprophylaxis with a LMWH	**Management:** • At least 6 weeks post-natal thromboprophylaxis with a LMWH
Intermediate risk – 1	**Risk factors:** • Hospital admission • Single DVT related to major surgery • High risk thrombophilia but no VTE • Medical comorbidities[1] • Ovarian hyperstimulation syndrome – 1st trimester	**Risk factors:** • Cesarean section in labor • BMI ≥40 kg/m^2 • Readmission or prolonged admission (≥3 days) in the puerperium • Any surgical procedure in the puerperium except immediate repair of the perineum • Medical comorbidities[1]
	Management: • Consider antenatal thromboprophylaxis with a LMWH	**Management:** • 2 or more risk factors: at least 10 days' postnatal thromboprophylaxis • If persisting for >3 risk factors: consider extending the period of thromboprophylaxis
Intermediate risk – 2	**Risk factors:** • Obesity (BMI >30 kg/m^2) • Age >35 yrs • Parity ≥3 • Smoker • Current pre-eclampsia • Gross varicose veins • Immobility, eg, paraplegia • Family history of unprovoked or estrogen-provoked VTE in a first-degree relative • Low-risk thrombophilia • Multiple pregnancy • IVF or assisted conception	**Risk factors:** • Obesity (BMI >30 kg/m^2) • Age >35 yrs • Parity ≥3 • Smoker • Elective cesarean section • Gross varicose veins • Immobility, eg, paraplegia • Family history of VTE • Low-risk thrombophilia • Multiple pregnancy • Current pre-eclampsia • Pre-term delivery in this pregnancy (<37 weeks) • Stillbirth in this pregnancy • Mid-cavity rotational or operative delivery • Prolonged labor (>24 hrs) • PPH >1L or blood transfusion

Figure 8.3 Assessment of risk (continued overleaf).

	Management: • 4 or more of the above risk factors present from the 1st trimester: antenatal thromboprophylaxis with a LMWH from the first trimester **Management:** • 2 or more risk factors: at least 10 days' postnatal thromboprophylaxis	**Management:** • 2 or more of the above risk factors: at least 10 days' postnatal prophylaxis with a LMWH • If persisting or >3 risk factors: consider extending the period of thromboprophlaxis
Lower risk	<3 risk factors from the above list **Management:** • Mobilization and avoidance of dehydration	<2 risk factors from the above list **Management:** • Mobilization and avoidance of dehydration

Figure 8.3 Assessment of risk (continued). [1]Medical comorbidities include: cancer, heart failure, active systemic lupus erythematosus, inflammatory bowel disease or inflammatory polyarthropathy, nephrotic syndrome, Type 1 diabetes mellitus with nephropathy, sickle cell disease, and current intravenous drug user. [2]Antithrombin deficiency. Heterozygosity for the factor V Leiden mutation. *See Figure 8.1; **See Figure 8.2. BMI, body mass index; LMWH, low-molecular-weight heparin; PPH, postpartum hemorrhage; VTE, venous thromboembolism.

of VTE, immobilization of women during pregnancy, labor, and the puerperium should be minimized and dehydration should be avoided.

Women on long-term anticoagulation

A number of women wishing to become pregnant may be on long-term anticoagulation with warfarin. Women should be counseled about the risks of these agents to the fetus in early pregnancy and advised to stop their oral anticoagulant therapy and change to a therapeutic low molecular weight heparin (LMWH) as soon as pregnancy is confirmed, ideally within 2 weeks of the missed period and before the sixth week of pregnancy. In such cases the recommendations are adjusted dose LMWH or 50 [2] or 75% [3] of a therapeutic dose of LMWH rather than a prophylactic dose.

The direct oral anticoagulants (DOACs), eg, rivaroxaban, apixaban, and dabigatran are increasingly prescribed for the management of VTED but they are not licensed for use in pregnancy. As the safety of these drugs in early pregnancy is unclear it may be prudent to switch such women to a LMWH in advance of a pregnancy.

Thrombophilia in pregnancy

Inherited prothrombotic abnormalities refer primarily to:

- antithrombin deficiency;
- protein C deficiency;
- protein S deficiency;
- heterozygosity or homozygosity for the factor V Leiden mutation (p.Arg534Gln or R506Q); and
- Heterozygosity or homozygosity for the prothrombin 20210G>A (G20210A or c.*97G>A) gene variant.

However, as the Factor V Leiden mutation and the prothrombin gene variant are relatively common in the population (5% and 2%, respectively) compound heterozygosity for combinations of these mutations is not uncommon.

Heritable thrombophilia is found in 20–50% of pregnancy-related VTE. The high-risk defect is primarily type 1 antithrombin deficiency in which there is a parallel reduction in both antithrombin antigen (the levels of the protein) and its activity. However, women who are homozygous for the factor V Leiden mutation or the prothrombin gene variant and with a family history of VTE, should be considered for antenatal thromboprophylaxis with either prophylactic LMWH or intermediate dose LMWH (eg, dalteparin 5000 units sc every 12 hours or enoxaparin 40 mg sc every 12 hours) and for 6 weeks following delivery [3].

Women with asymptomatic antithrombin, protein C or S deficiency or who are homozygous for the factor V Leiden mutation, the prothrombin gene variant or compound heterozygotes but with no family history of VTE, should be considered for antenatal thromboprophylaxis. They should receive 6 weeks' postnatal thromboprophylaxis even in the absence of any additional risk factors [2].

Antiphospholipid syndrome

The antiphospholipid syndrome (APS) is characterized by the occurrence of venous or arterial thromboses or of specific pregnancy-related problems. The latter are:

- an otherwise unexplained fetal death at ≥10 weeks gestation of a morphologically normal fetus;

- one or more premature births before 34 weeks of gestation because of eclampsia, pre-eclampsia, or placental insufficiency; and
- three or more embryonic (<10 weeks gestation) pregnancy losses unexplained by maternal or paternal chromosomal abnormalities or by maternal anatomic or hormonal causes.

In such situations screening for antiphospholipid antibodies is indicated and if positive, the tests should be repeated 12 weeks later. Screening for antiphospholipid antibodies involves:

1. Lupus anticoagulant screening using two different methodologies – classically an activated partial thromboplastin time (APTT)-based method, eg, the silica clotting time and a dilute Russell viper venom time (dRVVT)-based method in which Russell Viper venom is used to selectively activate factor X. Two different methodologies are required as no single test will identify all lupus anticoagulants due to their heterogeneous nature.
2. Screening for immunoglobulin G/M (IgG/IgM) anti-beta2-glycoprotein I antibodies and IgG/IgM anti-cardiolipin antibodies by an enzyme linked immunoassay (ELISA).

Antiphospholipid antibodies are sometimes detected because of a coagulation disturbance or connective tissue disorder in the absence of a history of thrombosis or obstetric problems, ie, in otherwise asymptomatic individuals. The risks of VTE in women with a persistent lupus anticoagulant and/or anti-cardiolipin and/or anti-beta2-glycoprotein 1 antibodies are small but unpredictable and it is not unreasonable to consider this as an acquired risk factor for VTE in pregnancy. The ACCP guidelines recommend that women who fulfil the criteria for APS should receive antepartum LMWH thromboprophylaxis combined with low dose aspirin over no treatment at all [3].

Monitoring of low molecular weight heparins in pregnancy

The LMWHs have predictable pharmacokinetics, and routine monitoring is not normally indicated. If necessary, eg, in women with impaired renal function, then an anti-Xa assay is employed. However, whilst anti-Xa levels provide a guide as to the concentration of the LMWH present in

the plasma they provide little or no evidence on their efficacy in relation to the prevention of thrombosis. However, lower doses of LMWHs will be required in women with significantly impaired renal function (creatinine clearance <30 mL/min and in some case <20 mL/min) as these drugs are cleared through the kidneys.

Commencing thromboprophylaxis

Table 8.3 summarizes the risk factors in pregnancy and in addition when to commence treatment. Once antenatal treatment is initiated it should continue until delivery unless a specific risk factor is removed or disappears. Post-partum thromboprophylaxis should be given as soon as possible after delivery, provided that there is no postpartum hemorrhage. The prothrombotic changes in pregnancy are maximal immediately following delivery and treatment with LMWH should, therefore, continue during labor. For women who are on therapeutic doses of LMWH, this should be reduced to a prophylactic dose 24–48 hours prior to delivery. This may necessitate a planned delivery and careful coordination with both the obstetricians and obstetric anesthetists. LMWH should be omitted on the day of a planned cesarean section or induction of labor.

Regional anesthesia

Women receiving antenatal thromboprophylaxis with a LMWH should be advised to discontinue the LMWH at the onset of labor. Epidural or spinal anesthesia should not be used until at least 12 hours after the last prophylactic dose of LMWH. When a woman presents whilst on a therapeutic regimen of LMWH, regional anesthetic techniques should not be employed for at least 24 hours following the last dose of LMWH. LMWH should not be given for at least 4 hours after the spinal/epidural catheter has been inserted or removed (or 6 hours if either insertion or removal were traumatic), and the cannula should not be removed within 10–12 hours of the most recent injection.

Pharmacological thromboprophylaxis in pregnancy: agents

Unfractionated heparin

While unfractionated heparin (UFH) has been shown to be effective as a thromboprophylactic agent, it is associated with more side effects (heparin-induced thrombocytopenia [HIT], osteoporosis, and allergic reactions) and possibly more bleeding complications than the LMWHs and is, therefore, used rarely in pregnancy. However, UFH has a shorter half-life than LMWH and there is a more complete reversal with protamine sulphate. It may be used, therefore, in women at high risk of bleeding but who require efficient anticoagulation. It is also used in some women with mechanical heart valves in pregnancy. UFH can be monitored by means of the APTT or a specific anti-Xa assay.

Low molecular weight heparins

LMWHs are the drugs of choice for antenatal thromboprophylaxis. They are effective, safer than UFH in pregnancy, and do not cross the placenta. In general, monitoring of anti-Xa levels is not indicated when LMWHs are used for thromboprophylaxis. Monitoring of anti-Xa levels in women at the extremes of body weight or with impaired renal function may be of value. Similarly in antithrombin deficiency, higher doses of LMWH and monitoring of anti-Xa levels may be necessary.

HIT is rare with the LMWHs but, in women receiving therapeutic anticoagulation with a LMWH, monitoring of the platelet count is recommended every 2 days for the initial 14 days of treatment. In other women, monitoring of the platelet count 1 week after starting treatment is recommended.

Allergic skin reactions to UFH and LMWH are rare but can occur. Switching to a different LMWH preparation or to a heparinoid (danaparoid) may be necessary.

Aspirin

Low-dose aspirin appears safe in pregnancy, although its use as a thromboprophylactic agent in this setting is not recommended. Aspirin is often combined with a LMWH in women with APS and recurrent miscarriage,

and is recommended for women at increased risk of pre-eclampsia in pregnancy [4].

Fondaparinux

Fondaparinux is a synthetic pentasaccharide which binds to antithrombin and has only Xa specificity. There is limited use of fondaparinux in pregnancy and evidence suggests that it crosses the placenta. The current ACCP guidelines advise against the use of fondaparinux in pregnancy limiting its use to those with severe allergic reactions to heparin (eg, HIT) and who cannot receive danaparoid [3].

Warfarin and vitamin K antagonists

Warfarin is generally avoided during pregnancy and especially during weeks 6–12 of gestation when major embryogenesis is occurring. It may be used in some women during the second trimester (ie, women with metal heart valves) but only after a careful evaluation of the risks and benefits. After delivery, the RCOG suggests that oral vitamin K anticoagulants may be considered although only after informing the patient of the need for regular blood monitoring in the first 10 days of treatment [2].

Danaparoid

Danaparoid is a heparinoid (containing heparan sulphate, dermatan sulphate, and chondroitin sulphate) that is used mostly in individuals with HIT or who develop a skin allergy to heparin. It is administered either subcutaneously or intravenously and is monitored by means of a specific anti-Xa assay.

Direct oral thrombin and Xa inhibitors

These drugs are not recommended for use in pregnancy [3].

Mechanical thromboprophylaxis

Mechanical thromboprophylaxis such as compression stockings reduce venous stasis and increase venous outflow but without any increase in bleeding risk. However, there are limited data on the value of graduated

compression stockings in pregnancy and much of the advice has been extrapolated from the surgical setting. The RCOG recommends the use of anti-embolism stockings (14–15 mmHg calf pressure) in all women who are hospitalized and have a contraindication to LMWH, and in women who are hospitalized following cesarean section and considered to be at exceptionally high risk of VTED who are in addition receiving LMWH.

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Chapter 9

Venous thromboprophylaxis in children

Timothy Nokes

Introduction

Prevention of venous thromboembolism (VTE) in children should initially involve a risk assessment of which there are few within the literature. There are no specific national protocols for assessing VTE risk in children. In England however there is a designated Department of Health VTE risk assessment tool for the adult population (>18 years), which may be extrapolated to pediatric cases (Figure 9.1) [1]. However, it should be understood that there are additional risk factors, which are particularly pertinent to the pediatric population, such as the significant influence of central venous lines (CVLs) and the use of L-Asparaginase (L-Asp) in acute lymphoblastic leukemia (ALL). There are two peaks in terms of VTE risk in children. Generally adolescents are at higher risk than younger children except for neonates, who are particularly prone to risk for VTE associated with CVLs, sepsis, congenital heart disease, surgery, and immobility (Figure 9.2) [2]. Some clinical groups have assessed their local pediatric VTE population, demonstrating that infants less than one year of age and adolescents comprise more than 70% of pediatric VTE [3]. The incidence of VTE in children is generally increasing, probably because of more complex treatment regimens and increasing use of CVLs. One pediatric hospital has demonstrated a significant rise of 70% over a seven-year period (2001–2007) from 34 to 58 cases per

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Risk assessment for venous thromboembolism					
Mobility – all patients (tick one box)	**Tick**		**Tick**		**Tick**
Surgical patient	☐	Medical patient expected to have ongoing reduced mobility relative to normal state	☐	Medical patient NOT expected to have significantly reduced mobility relative to normal state	☐
Assess for thrombosis and bleeding risk below			☐	**Risk assessment now complete**	☐

Thrombosis risk			
Patient-related	**Tick**	**Admission-related**	**Tick**
Active cancer or cancer treatment	☐	Significantly reduced mobility for 3 days or more	☐
Age >60 years	☐	Hip or knee replacement	☐
Dehydration	☐	Hip fracture	☐
Known thrombophilias	☐	Total anesthetic + surgical time >90 mins	☐
Obesity (BMI >30 kg/m^2)	☐	Surgery involving pelvis or lower limb with a total anesthetic +surgical time >60 mins	☐
One or more significant medical comorbidities (eg, heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases, and inflammatory conditions)	☐	Acute surgical admission with inflammatory or intra-abdominal condition	☐
Personal history or first-degree relative with a history of VTE	☐	Critical care admission	☐
Use of hormone replacement therapy	☐	Surgery with significant reduction in mobility	☐
Use of estrogen-containing contraceptive therapy	☐		
Varicose veins with phlebitis	☐		
Pregnancy or <6 weeks post-partum (see NICE guidance for specific risk factors)	☐		

Bleeding risk			
Patient-related	**Tick**	**Admission-related**	**Tick**
Active bleeding	☐	Neurosurgery, spinal surgery, or eye surgery	☐
Acquired bleeding disorders (such as acute liver failure)	☐	Other procedure with high bleeding risk	☐

Figure 9.1 Department of Health venous thromboembolism risk assessment model, 2010 (continues on the next page).

Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR >2)	☐	Lumbar puncture/epidural/spinal anesthesia expected within the next 12 hrs	☐
Acute stroke	☐	Lumbar puncture/epidural/spinal anesthesia within the previous 4 hrs	☐
Thrombocytopenia (platelets <75 x 10^9/L)	☐		
Uncontrolled systolic hypertension (230/120 mmHg or higher)	☐		
Untreated inherited bleeding disorders (such as hemophilia or von Willebrands Disease)	☐		

Figure 9.1 Department of Health venous thromboembolism risk assessment model, 2010 (continued). BMI, body mass index; hrs, hours; INR, international normalized ratio; mins, minutes; NICE, National Institute for Health and Care Excellence; VTE, venous thromboembolism. Reproduced with permission from © Department of Health, Crown Copyright, 2010. All rights reserved. NICE [1].

10,000 pediatric admissions [4]. Further studies are required to define accurately the highest risk groups in order to apply thromboprophylaxis to the most appropriate pediatric patients. As with all patient interventions, the benefits of introducing something like thromboprophylaxis should be assessed on an individual patient basis to realize the risk/benefit ratio [5].

The use of CVLs deserves further specific mention. CVLs increase the risk of VTE through various mechanical and biochemical effects including changes in venous flow, endothelial trauma, and the use of hyperosmolar infusions. Originally the PAARKA (Prophylactic Anti-thrombin Replacement in Kids with ALL treated with Asparaginase) study reported a significant risk for VTE as high as 22% associated with CVLs, particularly in association with L-Asp [6]. Subsequently, it became apparent that the risk was also related to their positioning and insertion techniques. The PAARKA study also identified that CVLs sited in the right internal jugular were associated with a lower risk for VTE and, that if essential, placement in the subclavian vein was safer by a cut-down rather than percutaneous technique. Such was the concern following the PAARKA study, that guidance suggested that CVLs should ideally not be placed in children during induction treatment for ALL whilst receiving L-Asp [6]. A small prospective study identified asymptomatic CVL-associated thrombosis in as many as 41 of 56 children with ALL, with four symptomatic VTE events

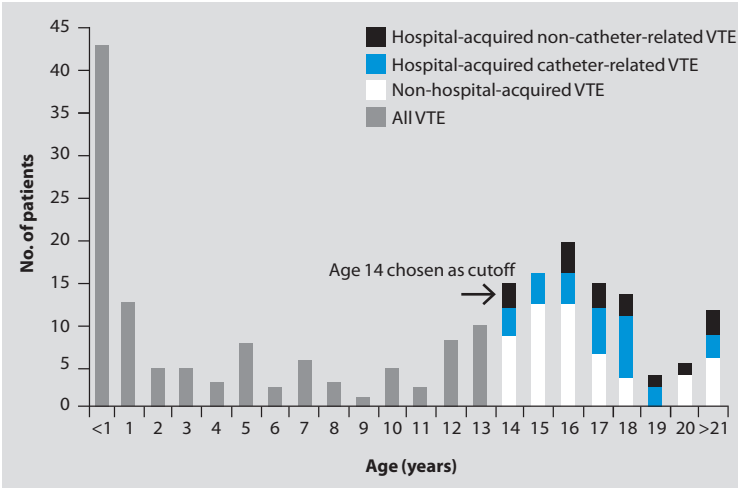

Figure 9.2 Histogram demonstrating bi-modal hospital-acquired venous thromboembolism (VTE) in pediatric and adolescent patients in The Children's Hospital of Philadelphia.

Raffini et al [2].

(7%). This study by Farrinasso [7] demonstrated symptomatic or severe thrombosis to be 18%, which was similar to the PAARKA study. Others have identified further patient and CVL-related risk factors in children and adolescents with all forms of cancer. In particular the use of peripherally inserted central catheters (PICCs) has been highlighted as an increased risk procedure [8]. Apart from L-Asp in ALL, other specific treatment regimens such as dexamethasone have been identified as a risk factor for VTE. Caruso [9] reported such in a meta-analysis of 1752 children, although this has not been replicated in other studies. The UK data give the risk for thrombosis associated with ALL as 3–5%, with two-thirds of these CVL-related and most of the remainder being cerebral venous sinus [10,11]. Although others have reported that half the VTE events occurring in patients with ALL, occur in the central nervous system. The overall risk for VTE in pediatric cancer patients is uncertain, but reported as between 2.2% and 14% for symptomatic events and up to 40% for asymptomatic events [12,13]. Approximately 30% of which is CVL-associated [14]. Both the malignancy itself and the cancer treatment are risk factors for VTE in pediatric patients as in adults. So pediatric cancer patients should definitely

be targeted for effective thromboprophylaxis acknowledging their associated high risk for VTE.

Risk for venous thromboembolism in specific clinical settings

Risk for VTE in children is apparent in other clinical situations; particularly high in the pediatric intensive care (ICU) environment [4,15]. In 2001, pediatric ICU centers in England and Wales reported no consensus regarding VTE thromboprophylaxis and proposed that simple empirical measures be formally implemented in critically ill children to reduce the risk of developing this 'important but under-recognized condition' [16]. This is recently highlighted in the PROTRACT study, which identified 87% of pediatric ICU patients as having at least one risk factor for VTE [17]. This prospective, multinational, cross-sectional study of 2484 children over four days, identified only 12.4% of these high-risk pediatric patients as receiving pharmacologic thromboprophylaxis (p-TP) and only 35% of those with risk sufficient to indicate the need for p-TP, actually receiving it. They also demonstrated that cyanotic congenital heart disease and spinal cord injury were the strongest predictors for use of all forms of thromboprophylaxis.

Single-center studies have also demonstrated increased VTE rates in children within other specific clinical settings, particularly trauma and major orthopedic surgery, as in adults. One recent paper reviewing the literature for VTE in children after trauma, identified that in children over 13 years of age, with more severe injuries, CVL in situ, and specific types of injury were factors that increased risk for VTE in children with trauma [18]. There have been a number of studies reviewing the risk for VTE in pediatric orthopedic and trauma settings documenting the increasing use of thromboprophylaxis [19–22]. The overall VTE rates varied considerably (0.25%, 2.1%, 0.17%, and 5.2%, respectively). One particular study relates a successful attempt at reducing the incidence of VTE in critically ill pediatric patients in an ICU following trauma within a pediatric trauma center, by introducing a clinical guideline for identifying those at most risk. This showed that there was a significant decrease in total and symptomatic VTE following implementation with

targeted p-TP [22]. Other areas of relatively high VTE risk in the pediatric population include complex cardiothoracic surgery [23] and inflammatory bowel disease [24,25].

Guidelines and recommendations

Guidelines have been proposed to establish risk and tailor thromboprophylaxis in various pediatric clinical situations, such as peri-operative [3] or alternatively for all pediatric inpatients (Figure 9.3) [2,26]. Mitchell [27] has reported a study involving retrospective test and prospective validation cohorts of patients treated on international childhood ALL protocols. Their hazard score included concomitant steroid and L-Asp, CVL, and thrombophilic abnormalities, identifying 5% of children with a 64.7% risk of thrombosis during induction therapy. However, in adjusted multivariate analysis the hazard ratio of thrombosis for the high-risk group had a wide confidence interval (CI) (8.22, 95% CI 1.85–36.53) and none of the French high-risk group of patients developed a thrombosis. Astwood and Vora [11] suggested that insufficient evidence exists to endorse the use of p-TP in the setting of ALL induction, acknowledging the risk for bleeding as well.

For all hospitalized patients less than 16 years old, simple preventative measures should be observed, such as maintaining adequate hydration (particularly peri- and post-operatively), early mobilization after surgery, and removal of CVLs as soon as they are no longer required. Maintaining the patency of CVLs is of utmost importance in all clinical settings. The use of unfractionated heparin (UFH) in children has been shown to be superior to saline in this respect, as well as reducing infections. However, the same has not been shown for continuous heparin infusion in peripherally placed percutaneous CVLs in neonates, suggesting the need for randomized controlled trials [28]. Consideration should also be given to temporary discontinuation of the combined contraceptive pill before elective surgery, particularly if other risk factors for VTE are present. Prophylactic anticoagulation in the form of low molecular weight heparin (LMWH) has also been shown to reduce catheter-related VTE in children receiving parenteral nutrition at home [29].

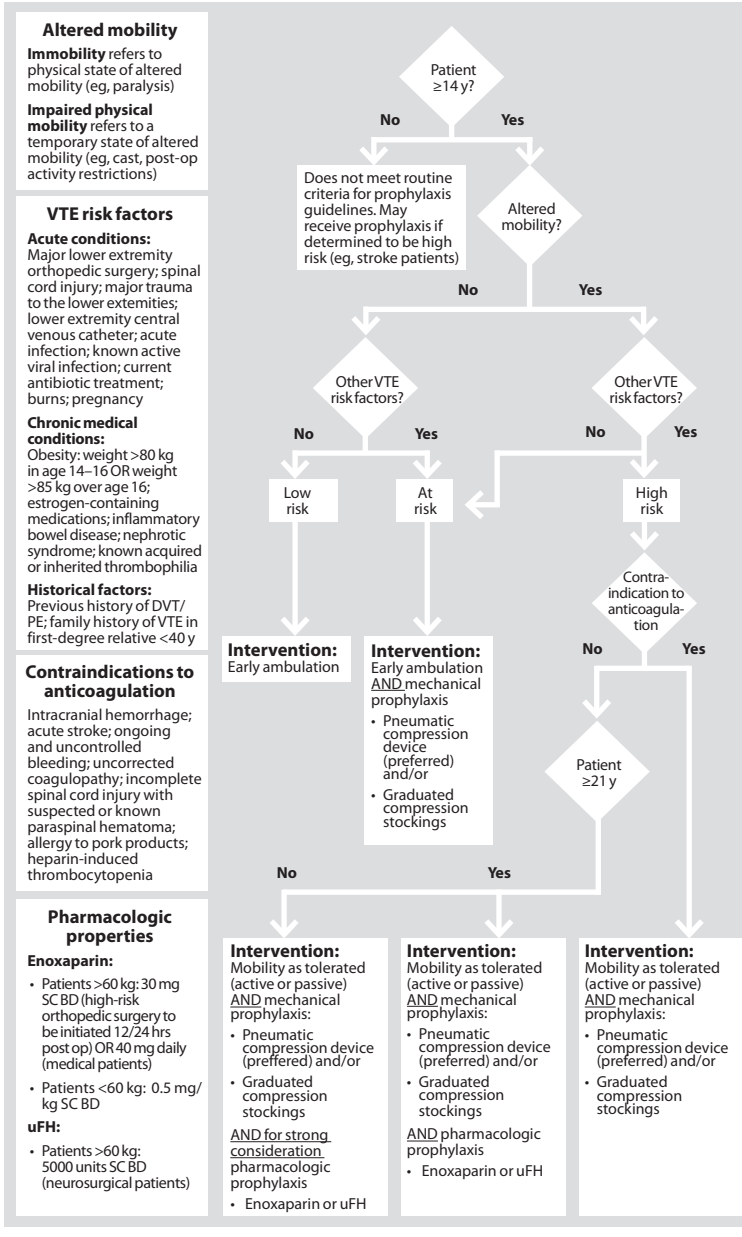

Figure 9.3 Example of guidelines for pediatric venous thromboembolism risk assessment and application of thromboprophylaxis. Reproduced with permission from © American Academy of Pediatrics, 2011. All rights reserved. Raffini et al [2].

Mechanical thromboprophylaxis

Mechanical thromboprophylactic (m-TP) measures should be considered, particularly when there is a contraindication to anticoagulants such as increased bleeding risk, or to compliment p-TP. Generally these devices increase venous return and therefore reduce stasis within the leg veins [30]. There is also some evidence that they may alter coagulation parameters, in favor of reducing clot production. The use of antiembolism stockings (AEs), intermittent pneumatic compression (IPC) devices and venous foot pumps (VFPs) have a limited evidence base in patients of all ages, by comparison to anticoagulation alternatives. There are even fewer data available for children and adolescents, where compliance may be a particular issue. Realistically, these methods of mechanical thromboprophylaxis can only be used in older or larger children of >40 kg in weight. Reductions in DVT associated with the use of mechanical thromboprophylaxis have been demonstrated in children [31]. However, no study has shown reductions in pulmonary embolism (PE) or all-cause mortality in any patient group apart from recently in adult immobile stroke patients [32]. This study showed a significant reduction in DVT and reduction in PE using IPC in bed-bound adult stroke patients, although the study was not powered to show the benefit of reducing PE. The uptake of all forms of thromboprophylaxis even in high-risk groups in children, is generally poor as demonstrated by the PROTRACT study already mentioned. However, this study in the pediatric infant/toddler unit setting did demonstrate relatively high levels of m-TP usage of nearly 24% in children greater than eight years of age.

The most important indication for the use of inferior vena cava (IVC) filters in both adults and children is the prevention of PE in patients with lower-limb VTE in whom systemic anticoagulation is contraindicated either on a temporary or long-term basis [33]. In children, clinical data on IVC filters are limited to case reports and small case series [34,35]. In one relatively large series, which reported on the placement of 24 filters in 20 children, there were no reported cases of PE following placement, although two patients did develop thrombosis around the filter. In this study, 23 of 24 filters were removed after a mean duration of 15 days. Further complications arose, related to difficulties in placement and removal of

the filter in four children. There are few reports on the use of permanent filters and in view of potential long-term side effects, including thrombosis and filter migration, children should probably only be considered for insertion of removable filters. In practice, although IVC filters are used in children, size is a significant limitation, for they are unlikely to be suitable for those weighing <10 kg. Indeed the ACCP guidelines state that children >10 kg with lower extremity VTE, should be considered for IVC filter (Grade 2C evidence [36]). Their placement may also be limited by a scarcity of appropriately trained and skilled operators [37].

Anticoagulants

With the increasing incidence of VTE events in children, there has also been a concurrent increase in the use of anticoagulants in those younger than 18 years. Children often metabolize drugs differently from adults and usually have a larger volume of distribution of many drugs including anticoagulants (especially the young), in whom there is rarely extensive testing during development. Dosing recommendations should ideally be derived from pharmacokinetic- and pharmacodynamic-based data and not simply extrapolated from adult dosing regimens. For this reason, medications for children are often based on weight or body surface area. Furthermore, the hemostatic system in neonates and infants differs from that of older children and adults, for instance lower plasma concentrations of anti-thrombin. Allowing for this difference between adults and children, younger children in particular may require relatively higher doses of LMWH, often with twice daily dosage and according to anti-Xa levels. Doses as high as 1.7–2.0 mg/kg may be required in neonates for treatment and longer-term prophylaxis for recurrent VTE. Furthermore, when using unfractionated heparin (UFH) in children less than two years, the APPT is less predictive so anti-Xa levels may be needed as well.

Low molecular weight heparin

Many antithrombotics such as LMWH are not licensed for use in children and therefore used ‘off-label’; however the Human Medicines Regulations 2012 does not prohibit the use of unlicensed medicines. It is recognized that the informed use of unlicensed medicines or of licensed medicines

for unlicensed applications ('off-label' use) is often necessary in pediatric practice. There is little doubt that using LMWH once daily is preferable to using UFH two to three times daily for p-TP in all patients. Although not licensed for children, its use over many years has established its safety and increasing efficacy for p-TP in children.

Pharmacologic thromboprophylaxis

As one might expect, there is a paucity of evidence supporting the use of p-TP for VTE prevention in children. Data and usage have therefore necessarily been extrapolated from trials in adults. There have however been a few small prospective studies investigating primary prophylaxis in the general pediatric setting [38]. Some data support the identification of inherited thrombophilic factors (particularly anti-thrombin [AT]) before using L-Asp in patients with ALL, so that targeted thromboprophylaxis could be applied [6,39]. The use of AT concentrate for primary prophylaxis in pediatric patients with ALL undergoing L-Asp therapy has increased. The PARKAA study, was an open-label, randomized, controlled extended Phase II trial of AT concentrate to prevent thrombosis during induction therapy in children with ALL [40]. There was a decreased incidence of asymptomatic thrombosis in the treatment group (37% versus 28%), which was not statistically significant. There was also no difference in laboratory parameters between the two groups. Another retrospective study compared prophylactic fresh frozen plasma (FFP) and cryoprecipitate to prevent thrombosis risk in children with ALL treated at two Canadian centers, one which gave these blood products based on AT and fibrinogen levels and another which did not [41]. There was no overall difference in the incidence of thrombosis at the two institutions and the investigators concluded that this form of thromboprophylaxis was not required. However, seven children with high-risk ALL, all of whom did not receive thromboprophylaxis, had a central nervous system thrombosis and the authors proposed that these blood products may be a cost-effective thromboprophylaxis in that sub-group. Owing to the inconsistent and low concentration of AT in FFP, it would seem sensible to use AT concentrate if anything, for these high-risk patients with ALL. In a separate study, AT levels were kept above 50 by supplementing AT concentrate in

112 children with ALL and 41 of those also received LMWH. Only 12.7% of the AT prophylaxis and none of the combined prophylaxis developed VTE events. The conclusion was that although encouraging, a prospective randomized trial is required. Other groups have found no benefit in identifying thrombophilic abnormalities [9,42]. Similar considerations have been postulated for adolescent patients undergoing major surgery, but no clear guidance has been published and therefore, similar to adults, thrombophilia testing in most clinical situations to assess risk for VTE, is generally not accepted. The Cochrane Collaboration have published a protocol for establishing effective prophylaxis for VTE in those patients receiving L-Asp, being treated for ALL, the final report is still awaited. The use of p-TP in some pediatric patients with ALL treated with L-Asp is also endorsed by recently published international clinical practice guidelines for prophylaxis of VTE in cancer patients [43]. In pediatric sarcoma patients undergoing major surgery LMWH has been shown to be effective for primary prophylaxis. In other groups, such as pediatric orthopedic surgery, the uptake of thromboprophylaxis has been low, particularly in those who have encountered no cases of pediatric VTE [44].

The use of low-dose oral warfarin for primary thromboprophylaxis in 62 pediatric oncologic patients with CVLs was investigated in a randomized controlled study [45]. Eighty percent of these children had international normalized ratios (INRs) in a lower than normal target range of 1.3–1.9 for more than 50% of the study period. As well as significant fluctuations in dose, unsurprisingly, none of the patients had the intended level of INR for the whole study period. They found that incidences of CVL-related VTE within the jugular vein (where CVLs were placed) were equally as frequent in the children on low-dose warfarin compared to those who were not. The actual asymptomatic VTE rate was 42% and often transient. There was an interesting positive association between VTE in the jugular vein and positive blood cultures.

The Cochrane Foundation reviewed the use of p-TP to prevent CVL-related VTE in children and identified a single study only, which was of sufficient quality. In this study (the only one of 17 studies within the systematic review, which was deemed to be eligible for assessment) LMWH was compared to the standard of care (UFH flush, or infusion of

approximately 3 U/kg/hour) in children with cancer and CVLs, demonstrating that there was no difference in the rate of VTEs between the two treatment arms [46]. However, while this study included 186 patients, only 51% and 50% of children had cancer in the LMWH and UFH treatment arms, respectively, and was underpowered to demonstrate a difference between LMWH and UFH. Specifically, the CIs for the risk of CVC-related thrombosis (symptomatic and asymptomatic events) were compatible with benefits of either LMWH (reviparin) or the control (RR for symptomatic thrombosis 1.03, 95% CI 0.21 to 4.93; RR for asymptomatic thrombosis 1.17, 95% CI 0.45 to 3.08). One patient, in the standard care group suffered a major bleeding event, while minor bleeding was found in 53.3% of patients in the reviparin arm and in 44.7% of patients in the standard care arm (major bleeding RR 0.34, 95% CI 0.01 to 8.26; minor bleeding RR 1.20, 95% CI 0.91 to 1.58). It was therefore concluded that good quality prospective, randomized studies are encouraged to try and answer this concern [39]. Another Cochrane report investigated the use of p-TP in cancer patients with a CVL in situ. This review identified 1291 children from six studies using a variety of anticoagulants and other hemostatic modalities but found no significant effects of such systemic treatments compared to no intervention in preventing symptomatic VTE in pediatric oncology patients with CVLs. The conclusion was that the meta-analysis was underpowered to demonstrate a benefit of any one strategy over others [47]. Indeed the ACCP guidelines have recommended against the use of routine p-TP in children with CVLs referring to grade 1B evidence, although low-dose UFH use is suggested to maintain patency of umbilical artery catheters. If the central or umbilical catheter remains in situ after therapeutic anticoagulation, then a prophylactic dose of LMWH should be given to prevent recurrent thrombosis, until the catheter is removed (grade 2C). However, in those children receiving long-term parenteral nutrition through a CVL, the use of warfarin (or another vitamin K antagonist) is suggested with grade 2C evidence [37]. Finally, a recent systematic review and meta-analysis of 3128 pediatric patients from 37 articles, found no evidence that any anti-thrombotic approach reduced CVL-associated thromboses. They concluded that an adequately powered multicenter trial is critically needed [48].

The new anticoagulants, both parenteral such as argatroban, bivalirudin, and fondaparinux and oral (DOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban, have favorable pharmacologic properties. All are approved for clinical use in adults and many are currently being investigated in children. Argatroban is the only new anticoagulant licensed for use in children so far. The role of these new anticoagulants as alternatives for children remains to be defined. However, a recent review of developments in pediatric VTE has stated that research has considerably improved the understanding of risk factors for hospital-acquired VTE and that investigation of safety of the DOACs in children is underway [49].

It is apparent that there is a real need for properly powered, randomized control trials to assess the need for primary p-TP in children in several clinical situations. What is also clear, is that children share many of the risk factors for VTE as adults, but the influence of some of these factors appears to be greater in children than in adults. Examples of this are the use of CVLs and of L-Asp in ALL. Until then, it would seem prudent to undertake a risk assessment of children admitted to hospital, if adolescent or neonatal children, and apply p-TP to those without a bleeding risk (and m-TP to those with a risk for bleeding). It seems reasonable to use LMWH for p-TP in children as this has been found to be safe in children in the past. It should however be noted that in young children metabolic pathways are not as well established as adults or even older children, and monitoring with anti-Xa assays may be required.

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Chapter 10

Thromboprophylaxis in cancer patients

Jennifer R Eads and Alok A Khorana

Introduction

The course of cancer is frequently complicated by the occurrence of thromboembolic disease. Typical presentations include venous thromboembolism (VTE), including deep vein thrombosis (DVT), pulmonary embolism (PE) and splanchnic vein thromboses, as well as arterial thromboembolism including stroke and myocardial infarction. VTE is highly consequential for cancer patients, particularly given a strong association with both short-term and long-term mortality [1,2]. In addition, VTE is paradoxically associated with both recurrent VTE and bleeding, as well as with a requirement for chronic anticoagulation and a significant consumption of health care resources. In a recent United States (US) study, cancer patients with VTE had a three-fold increase in hospitalizations and higher total health care costs than cancer patients without VTE (US$74,959 versus US$41,691 per patient, $p<0.0001$) [3]. In recent reports, VTE in cancer patients seems to be highly prevalent. For instance, in a retrospective analysis of patients treated with cisplatin-based chemotherapy at a major cancer center, 18.1% experienced thromboembolism – an "unacceptably high" burden [4]. This high prevalence seems to be driven by a combination of increased finding of incidental VTE due to improved computed tomography (CT) scan technology and newer, more thrombogenic anti-neoplastic drugs and regimens.

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The rise in cancer-associated VTE is especially concerning since there are several pharmacologic agents that are known to prevent this complication. Thromboprophylaxis in malignancy is associated with two particular challenges. First, despite the high prevalence, there is wide variation in risk amongst subgroups of cancer patients. Therefore, prophylaxis needs to be targeted to achieve an optimal risk/benefit ratio. Second, most oncologic care is now delivered in the outpatient setting and therefore VTE is also more likely in the outpatient setting [5]. Therefore, reducing the public health burden of VTE in malignancy requires appropriate risk assessment and a broad approach to both outpatient and inpatient prevention. This chapter focuses on risk assessment, outpatient and inpatient prophylaxis incorporating results of recent studies, and guideline recommendations in these settings. Thromboprophylaxis in the surgical cancer patient is discussed elsewhere (in Chapter 6).

Risk assessment

Despite cancer being an overall risk factor for the development of thromboembolic disease, not all cancer patients are at equal risk. Identification of patients at increased risk for VTE and most appropriate for prophylactic therapy is crucial, as both VTE and administration of anticoagulant therapy have significant implications. Development of VTE in cancer patients is associated with an increased mortality [1,2] – as such prevention of an event could impact survival. Administration of many chemotherapeutic agents also can result in the onset of thrombocytopenia, making administration of full-dose anticoagulants a challenge. Administration of prophylactic doses of these agents in patients at high risk for VTE would be preferable so as to decrease patient risk of developing anticoagulant-associated complications. To date, several risk factors for development of VTE have been identified [6–13]. These include patient-related, cancer-related, and treatment-related clinical factors as well as serum biomarkers [13–22], but none of these factors alone has demonstrated an improvement in physician predictability for the development of VTE in cancer patients. Individual risk factors for development of VTE in cancer patients are outlined in Table 10.1.

Patient-associated risk factors
Age (higher in older patients)
Race (higher in African American, lower in Asians)
Medical comorbidities
Obesity
Prior history of thrombosis
Varicose veins
Cancer-associated risk factors
Primary site of disease (gastric, pancreas, primary brain tumors, lung, renal, lymphoma)
Stage (higher in regional and advanced stage)
Cancer histology (higher for adenocarcinoma than squamous cell)
Tumor grade (higher for high-grade tumors)
Time after initial diagnosis (highest in first 3–6 months)
Treatment-associated risk factors
Chemotherapy
Anti-angiogenic agents (bevacizumab, sorafenib, sunitinib)*
Immunomodulatory agents (thalidomide, lenalidomide), particularly in combination regimens
Certain hormonal therapy agents (eg, tamoxifen)
Erythropoietin-stimulating agents
Transfusions
Central venous access devices
Inferior vena cava filters
Radiation
Major surgical resection
Biomarkers
Thrombocytosis (≥350,000/mm^3)
Leukocytosis (>11,000/mm^3)
Anemia (hemoglobin <10 g/dL)
Elevation in D-dimer
Prothrombin fragment F 1+2 (>358 pmol/L)
Elevation in soluble P-selectin (>53.1 ng/mL)
Factor VIII
Peak thrombin generation times
Tissue factor (antigen expression, circulating microparticles, antigen or activity)

Table 10.1 Risk factors for development of thrombosis in cancer patients. *Definitely associated with arterial thromboembolic events; unclear association with venous thromboembolism. Adapted from © Thieme Medical Publishers, 2014. All rights reserved. Gomes and Khorana [13].

Due to the lack of evidence that any one variable can predict for development of VTE in cancer patients, the 2013 American Society of Clinical Oncology (ASCO) VTE Guidelines recommend use of a risk score that considers multiple variables in making a treatment decision regarding thromboprophylaxis for cancer patients [23]. To date, only one multivariate risk score has been developed, evaluated in a follow-up cohort and externally validated [14,24]. Patients evaluated using this risk assessment model have demonstrated that cancer patients considered 'high risk' for developing VTE should receive thromboprophylaxis. Developed by Khorana and colleagues [14], this risk assessment score includes primary site of disease, pre-chemotherapy platelet and leukocyte count, hemoglobin level and/or use of erythropoietin-stimulating agents and body mass index. Points are assigned based on patient risk factors and a score calculated (Table 10.2).

Results of the development and validation cohort show VTE rates of 0.8 and 0.3% in the low-risk cohort (score=0), 1.8 and 2% in the intermediate-risk cohort (score=1–2), and 7.1 and 6.7% in the high-risk cohort (score≥3). When externally validated by the Vienna Cancer and Thrombosis Study (CATS) group, VTE rates were even higher at 1.5% in the low-risk group (score=0), 3.8 and 9.4% in the intermediate-risk group (score=1 and score=2, respectively), and 17.7% in the high-risk group (score=3) [24]. Overall, results of these studies provide evidence that VTE in cancer patients is much higher than we previously thought, particularly amongst high-risk patients, and provides a strong basis on which

Patient characteristics	Points
Site of cancer: • Very high risk (stomach, pancreas, primary brain malignancy) • High risk (lung, kidney, bladder, testicular, lymphoma, gynecologic malignancies)	2
Pre-chemotherapy platelet count ≥350,000/μL	1
Hemoglobin level <10 g/dL or use of erythropoietin-stimulating agents	1
Pre-chemotherapy leukocyte count >11,000/μL	1
Body mass index ≥35 kg/m^2	1

Table 10.2 Risk score for prediction of venous thromboembolism (VTE) in cancer outpatients. Assign points per parameter and sum, score=0 (low risk), score=1–2 (intermediate risk), and score ≥3 (high risk) for VTE. Adapted from © American Society of Hematology, 2008. All rights reserved. Khorana et al [14].

physicians may consider prophylactic anticoagulation for cancer patients. A subsequent trial of cancer patients treated as part of a Phase I consortium demonstrated that patients at intermediate risk for VTE also had elevated VTE rates and may potentially benefit from thromboprophylaxis [25].

Cancer patients with multiple myeloma are a population who are inherently at high risk for thrombosis. Additionally, many of the therapeutic agents used in the management of multiple myeloma are thrombogenic (in particular thalidomide- and lenolidamide-based regimens) and this is compounded when administered as part of a combination chemotherapy regimen (particularly with high-dose dexamethasone or doxorubicin) [11,26]. Nearly all patients are recommended thromboprophylaxis, which may include daily low-dose aspirin, low molecular weight heparin (LMWH) or warfarin [26]. Many individual risk factors, including clinical, myeloma-related and treatment-related factors have been identified that are used in determining what form of prophylaxis should be administered. Unlike for other malignancies, a specific algorithm using individual variables has been developed for patients with multiple myeloma by the International Myeloma Working Group. Individual risk factors and associated treatment recommendations are outlined in Figure 10.1. While this approach has not been validated in a prospective trial, it is considered standard by experts within the field. The Khorana risk assessment score is currently the only validated multivariable risk assessment tool for identifying cancer patients at increased risk for VTE [14,24]. This score meets criteria for a Level 1 clinical decision rule and has been integrated into thromboprophylactic guidelines by ASCO [23], the National Comprehensive Cancer Network (NCCN) [27] and the European Society of Medical Oncology (ESMO) [28] (Table 10.3) [29].

Outpatient thromboprophylaxis

Current management of most cancer patients involves administration of systemic chemotherapeutic agents, targeted therapies and immunomodulatory agents in the outpatient setting. Patients are often able to maintain at least a reasonable degree of their normal activity level (thereby decreasing the concern for VTE secondary to a sedentary lifestyle), yet these patients remain at high risk for VTE. Given this pattern

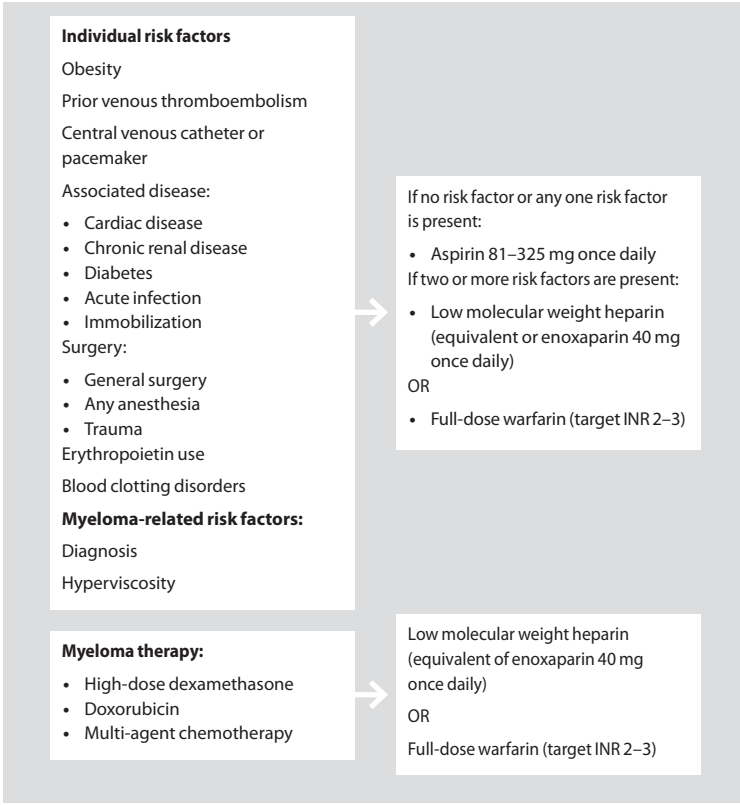

Figure 10.1 Risk assessment for patients with multiple myeloma receiving treatment: recommendations of the International Myeloma Working Group. Thromboprophylactic recommendations for patients with multiple myeloma according to individual, myeloma-related and myeloma therapy-related risk factors. INR, international normalized ratio. Adapted from Palumbo et al [26].

of outpatient treatment administration, it is not surprising that a significantly higher proportion of 17,000 cancer patients (78.3%) developed VTE as an outpatient as compared with 21.7% in the inpatient setting ($p<0.0001$) [5]. As such, identification of outpatients at greatest risk for VTE is crucial so as to allow for early institution of prophylactic therapy, particularly in patients at greatest risk.

Several randomized clinical trials have evaluated the role for thromboprophylaxis with two large studies evaluating patients with multiple tumor types. The PROTECHT study [30] randomized 1166 cancer patients

Patient Population	ASCO [23]	NCCN [27]	ESMO [28]
All cancer outpatients	Routine prophylaxis not recommended	Routine prophylaxis not recommended	Routine prophylaxis not recommended
Myeloma patients receiving IMiD-based regimens	Aspirin or LMWH for low-risk patients and LMWH for high-risk patients is considered	Aspirin for low-risk and LMWH or warfarin for high-risk patients is recommended	Consider LMWH, aspirin or adjusted-dose warfarin (INR~1.5)
'High-risk' outpatients	Consider LMWH prophylaxis on a case-by-case basis in highly select outpatients with solid tumors on chemotherapy	Consider patient conversation about risks and benefits of prophylaxis in Khorana score ≥3 population	Consider in high-risk ambulatory cancer patients. Predictive model may be used to identify patients clinically at high risk for VTE

Table 10.3 Recommendations for outpatient thromboprophylaxis per cancer panel guidelines. IMiD, immunomodulatory drug; INR, international normalized ratio; LMWH, low molecular weight heparin; VTE, venous thromboembolism. Adapted from © National Comprehensive Cancer Network, 2013. All rights reserved. Khorana [29].

with lung, gastrointestinal, pancreatic, breast, ovarian, and head and neck cancer in a 2:1 fashion to receive either nadroparin once daily for a maximum of 4 months or placebo. Of 1150 evaluable patients, thromboembolic events (either venous or arterial) occurred in 2.0% of the nadroparin group versus 3.9% in the placebo group. There was no significant difference in the bleeding risk in either of these groups. The second study SAVE-ONCO [31] randomized 3212 patients with lung, pancreatic, gastric, colorectal, bladder, and ovarian cancer to receive either semuloparin once daily for a maximum of 3 months or placebo. Venous thromboembolism occurred in 1.2% of the semuloparin group versus 3.4% in the placebo group. There was no significant difference in major or minor bleeding between the two groups. While each of these studies found a statistically significant difference between the treatment and placebo groups, the low event rates have precluded the use of these agents in clinical practice.

Several additional clinical trials have evaluated various thromboprophylactic regimens in targeted 'high-risk' populations such as pancreatic cancer, multiple myeloma and malignant glioma [32–36]. Overall results suggest that the incidence of VTE is significantly lowered by implementation of thromboprophylactic treatment in some of these high-risk populations. Integrating the validated Khorana risk assessment score into the larger thromboprophylaxis studies, a more validated assessment of 'high-risk'

cancer patients was conducted with a post-hoc analysis of results from both the PROTECHT [37] and SAVE-ONCO [38] studies. The risk assessment score identified 12% of patients in the PROTECHT study as 'high risk' with a score≥3. Amongst these patients, there was a significant difference in the incidence of VTE based on treatment with 11.1% and 4.5% of patients developing VTE in the placebo and nadroparin groups, respectively. Similarly, in the SAVE-ONCO study, patients identified as 'high risk' were found to have a higher incidence of VTE in the placebo group (5.4%) versus the semuloparin group (1.4%) (Figure 10.2) [29].

These two subgroup analyses suggest that while the institution of thromboprophylaxis in the general cancer population has little clinical benefit, high-risk groups do derive significant benefit and should be considered for prophylactic treatment.

Based on studies conducted thus far, the overall use of thromboprophylaxis for cancer patients shows no added clinical benefit when considering all cancer patients. A validated risk assessment score however seems to better define patients who may derive the most benefit. As such, ASCO [23], NCCN [27], and ESMO [28] have all acknowledged the importance of proper identification of high-risk patients and the use of a risk assessment

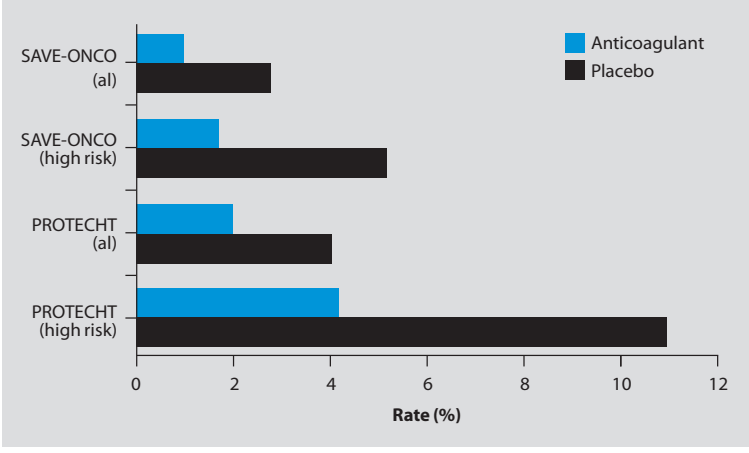

Figure 10.2 Assessment of results of thromboprophylaxis studies with inclusion of a risk assessment model. Rate of VTE in placebo and treatment groups amongst patients in the PROTECHT and SAVE-ONCO clinical trials with consideration of patients at high-risk for VTE (risk score≥3). VTE, venous thromboembolism. Adapted from © National Comprehensive Cancer Network, 2013. All rights reserved. Khorana [29].

score. Since trials investigating this population are still ongoing, outpatient prophylaxis is not mandated even in high-risk patients but offered as a consideration on a case-by-case basis for clinicians and patients.

Inpatient thromboprophylaxis

The role of thromboprophylaxis for cancer inpatients has become somewhat controversial recently. In general, it is well described that acutely ill medical patients are at increased risk for VTE and three large randomized clinical trials (MEDENOX [39], PREVENT [40], and ARTEMIS [41]) have demonstrated a clear benefit in favor of administration of thromboprophylactic therapy. As cancer patients are at increased risk for VTE compared with the general population and were included in these three trials, it is generally accepted that cancer inpatients should also receive thromboprophylactic therapy, and this is also reflected by summary recommendations from ASCO [23], NCCN [27], and ESMO [28] (Table 10.4). Appropriate agents for inpatient thromboprophylaxis and their doses are shown in Table 10.5. While inpatient thromboprophylaxis is recommended, there are no cancer-specific inpatient clinical trials. Recently, a pooled analysis of cancer patients from the three large randomized clinical trials reported that no significant benefit was observed in regard to reducing one's risk for VTE

Cancer panel	Recommendation
ASCO [23]	Patients with cancer should be considered candidates for VTE prophylaxis with anticoagulants (UFH, LMWH, or fondaparinux) in the absence of bleeding or other contraindications to anticoagulation*
NCCN [27]	Thromboprophylaxis for VTE is recommended for all hospitalized patients with cancer who do not have contraindications to such therapy, and the panel also emphasizes that an increased level of clinical suspicion of VTE should be maintained for cancer patients
ESMO [28]	Prophylaxis with UFH, LMWH or fondaparinux in hospitalized cancer patients confined to bed with an acute medical complication is recommended

Table 10.4 Recommendations for inpatient thromboprophylaxis per cancer panel guidelines. *Relative contraindications to anticoagulation include, among other conditions: active, uncontrollable bleeding; active cerebrovascular hemorrhage; dissecting or cerebral aneurysm; bacterial endocarditis; pericarditis, active peptic or other gastrointestinal ulceration; severe, uncontrolled or malignant hypertension; severe head trauma; pregnancy (warfarin); heparin-induced thrombocytopenia (heparin, LMWH); and epidural catheter placement. ASCO, American Society of Clinical Oncology; ESMO, European Society of Medical Oncology; LMWH, low molecular weight heparin; NCCN, the National Comprehensive Cancer Network; UFH, unfractionated heparin; VTE, venous thromboembolism.

Drug	Regimen
Unfractionated heparin	5000 units every 8 hours (5000 units every 12 hours also used but less effective)
Dalteparin	5000 units daily
Enoxaparin	40 mg daily
Fondaparinux	2.5 mg daily

Table 10.5 Acceptable thromboprophylactic regimens for cancer inpatients. Adapted from © American Society of Clinical Oncology, 2013. All rights reserved. Lyman et al [23]. Adapted from © Elsevier, 2014. All rights reserved. Carrier [42].

while receiving prophylactic therapy (relative risk 0.91, 95% confidence interval 0.21–4.0) [42]. These results are limited in that data are derived from a pooled analysis of a relatively small number of patients (n=374) and prospective studies evaluating thromboprophylaxis in cancer inpatients are needed. Studies in this population are difficult as nearly 32% of patients have contraindications to medical thromboprophylaxis [43]. Additionally, no standard risk assessment model is used in selecting which inpatients may benefit most from therapy. Development of an inpatient risk assessment tool and the conduct of a prospective study evaluating only high-risk cancer patients would be beneficial in furthering our understanding of the need to provide thromboprophylactic therapy to cancer inpatients.

Summary

- Cancer patients are at increased risk for VTE compared with the general population.
- In the outpatient setting, prophylactic use of anticoagulants is not generally recommended except for patients with multiple myeloma receiving immunomodulatory agents. Patients with a high-risk assessment score may be considered for thromboprophylaxis on a case-by-case basis.
- In the inpatient setting, it is recommended that cancer patients who are acutely ill or are undergoing surgery should receive thromboprophylaxis if they do not otherwise have a contraindication to therapy although further studies to optimize the risk-benefit ratio are needed.

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Chapter 11

Travel-related thrombosis

Mohammed M Khan and Henry G Watson

Introduction

Long distance travel is a recognized but low-level risk factor for venous thromboembolism (VTE). The first cases of VTE possibly associated with air travel were reported in 1951 [1]. Since then, relative and absolute risks of VTE have been studied in a number of observational and case-control studies. These studies have demonstrated an increased incidence of VTE associated with not only air travel, but also car and train travel [2]. Current evidence suggests the risk of VTE increases with duration of travel and is higher in those with pre-existing risk factors for thrombosis [3,4]. Studies examining the mechanism behind travel-related VTE have not shown any conclusive findings and there is a relative paucity of evidence to guide preventative strategies.

Incidence of travel-related venous thromboembolism

Deep vein thrombosis (DVT) following travel has been investigated prospectively in five studies [5–9]. In each of the studies, passengers at low or intermediate risk of thrombosis travelling for more than eight hours were included. In each case a diagnosis of VTE was excluded prior to travel by the use of a combination of methods including ultrasound or clinical risk assessment followed by D-dimer testing. Soon after travel the patients were reassessed by objective methods to exclude or diagnose

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DVT. Excluding the study by Scurr et al [5], which seems to be a statistical outlier with a rate of isolated calf vein thrombosis (CVT) of 12%, the incidence of all venous thrombosis was 40/2901 (1.4%). When isolated CVT was excluded, the incidence of DVT or pulmonary embolism (PE) was 16/2901 (0.5%). The incidence of symptomatic VTE was 10/2901 (0.3%). Two of the studies compared travellers with matched controls. Isolated CVT was detected in 24/1124 (2.1%) travellers compared with 11/1373 (0.8%) controls. DVT was demonstrated in 7/1124 (0.6%) travellers compared with 2/1373 (0.15%) in matched controls and symptomatic DVT was also more commonly observed in the flyers (0.18% vs 0.07%).

Case-control studies also support an association between travel and thrombosis [10–16]. In some of these studies, episodes of travel of as little as 'over 3 hours' were linked to an increased thrombosis risk, while in others an effect was only seen when periods of travel of 10–15 hours were considered [16].

Several retrospective studies have evaluated the association between flight duration and the development of early onset significant PE [3,4,17,18]. These studies show that early symptomatic PE is rare, with an incidence of 0.5 per million for all flyers and 1 in 115 million for those with a flight duration of less than 6 hours. An association between longer duration of travel and increased incidence of early onset PE was demonstrated, with a rate of 5 per million in those whose flight duration was greater than 12 hours. Most travellers who developed PE had pre-existing risk factors for VTE.

The absolute risk of symptomatic VTE has also been evaluated in approximately 9000 healthy employees of international companies who flew regularly. This study showed an absolute risk of VTE of 1 in 4600 for flights greater than 4 hours [19]. In this study, the period of time following the flight in which an excess of VTE was observed in the travellers was up to 8 weeks whilst in a large study of incoming flyers to Australia the period of excess risk of VTE in the travellers was only 14 days [20].

Mechanism of travel-related venous thromboembolism

Several studies have investigated the effect of air travel, or one of its aspects such as immobilization and hypobaric hypoxia, on blood coagulation. In these studies, markers of a prothrombotic state such as levels of thrombin-antithrombin (TAT), prothrombin fragment 1+2 (F1+2), D-dimer, tissue type plasminogen activator (tPA) and plasminogen activator inhibitor (PAI) have been measured in response to real or simulated travel conditions. Changes in the different parameters of thrombin generation and fibrinolysis before and after specific exposures have been determined in several studies. Table 11.1 summarizes these results. The majority fail to show any significant consistent change in markers of thrombin generation or fibrinolysis.

Thromboprophylaxis in long distance travel

There is a lack of robust data on the effectiveness of thromboprophylaxis in the context of travel-related thrombosis. Scurr et al [5] conducted randomized controlled studies assessing mechanical thromboprophylaxis with graduated below knee compression stockings during long-haul economy class flights. Study participants were all above the age of 50, had no prior history of VTE, and travelled for more than 8 hours. Of these participants, 10% of those who did not wear compression stockings developed asymptomatic DVT whilst none of the individuals who wore stockings developed DVT.

In the New Zealand Air Traveller's Thrombosis (NZATT) study cohort [7], DVT developed in 6/421 (1.4%) in those who used thromboprophylaxis (mechanical, pharmacological or both) and 3/466 (0.6%) of those who did not. Whilst there may be confounders, this study suggests such measures may have limited benefit in preventing travel-related thrombosis. Both the British Committee for Standards in Haematology (BCSH) and American College of Chest Physicians (ACCP) guidelines recommend compression hosiery only for individuals at increased risk of VTE [28,29].

With no evidence base to guide pharmacological prophylaxis use in long distance travel, recommendations are based on extrapolating from other clinical situations. An individual's thrombosis risk needs to

			Markers of thrombin generation		Markers of fibrinolysis		
Mechanism	**First author/year**	**Exposure**	**TAT**	**F1 + 2**	**D-dimer**	**tPA**	**PAI**
Immobility	Tardy 1996 [21]	8-hr bus trip	No difference versus controls	No difference versus controls	No difference versus controls		
	Stricker 2006 [22]	6 hrs of immobility		Lower after immobility	No change		
Hypobaric hypoxia	Bendz 2000 [23]	8 hrs of hypobaric hypoxia	Increased during exposure	Increased during exposure	No change		
			No controls	No controls			
	Toff 2006 [24]	Crossover: 8 hrs of hypobaric hypoxia/ 8 hrs of normobaric normoxia 2 wks apart	No difference in pre- versus post-levels for the different exposures	No difference in pre- versus post-levels for the different exposures	No difference in pre- versus post-levels for the different exposures	No difference in pre- versus post-levels for the different exposures	No difference in pre- versus post-levels for the different exposures
Air travel	Schobersberger 2002 [25]	Return long haul flight	No effect of travel		No effect of travel	Higher after travel	Lower after travel
	Boccalon 2005 [26]	11-hr flight	Lower after travel	Lower after travel	No effect of travel		No effect of travel
	Schreijer 2006 [27]	Crossover: 8-hr flight/ 8-hr movie marathon/ 8 hrs of daily activity	Higher after flight versus immobilization/ ambulant state				No effect of travel

Table 11.1 Studies evaluating the mechanism of travel-related thrombosis. F1+2, prothrombin fragment 1+2; PAI, plasminogen activator inhibitor; TAT, thrombin-antithrombin; tPA, tissue type plasminogen activator.

be assessed, taking account of pre-existing risk factors such as prior history of VTE, recent pregnancy, recent trauma and surgery, estrogen use, obesity and active malignancy. Furthermore, the duration of travel should also be considered. The individual's bleeding risk should be evaluated, and contraindications to anti-thrombotics need to be excluded. With regards to choice of pharmacological prophylaxis, anticoagulants such as low molecular weight heparin should be favored over antiplatelet drugs based on their superior efficacy in preventing venous thromboembolism in other clinical scenarios. The recent availability of dabigatran, rivaroxaban, and apixaban, all of which have been shown to be efficacious in the prevention of VTE in high-risk surgical settings, gives an alternative and possibly simpler option for the prevention of travel-related thrombosis on account of the oral as opposed to parenteral route of administration. Tables 11.2 and 11.3, respectively, show risk stratification for travel-related VTE, and interventions for the different risk groups according to travel time [28].

Risk group	Examples of venous thromboembolism risk factors
Low	None
Intermediate	All others, eg: • Up to 6 weeks post-partum • Previous unprovoked VTE no longer on anticoagulants • Previous travel-related VTE • Combinations of risk factors
High	Major surgery in previous 4 weeks Active cancer undergoing chemo-radiotherapy in the previous 6 months, awaiting surgery or chemo-radiotherapy, or in palliative phase

Table 11.2 Risk stratification of individuals prior to travel (British Committee for Standards in Haematology guideline, 2010). VTE, venous thromboembolism. Adapted from © John Wiley & Sons, Inc, 2010. All rights reserved. Watson and Baglin [28].

Duration of travel	<3 hours	3–8 hours	>8 hours
Low	Nil	Nil	Nil
Intermediate	Nil	Nil or stockings	Stockings
High	Nil	Stockings	Stockings +/– anticoagulant

Table 11.3 Intervention strategy based on individual risk and duration of travel (British Committee for Standards in Haematology guideline, 2010). Adapted from © John Wiley & Sons, Inc, 2010. All rights reserved. Watson and Baglin [28].

Individuals should also be advised to remain ambulant during their journey and perform calf muscle exercises regularly. Being seated next to the aisle may encourage passengers to be more mobile. Dehydration has not been shown to be associated with an increased risk of travel-related thrombosis [30]. As such, ensuring good hydration is unlikely to reduce the risk of VTE unless it increases mobilization on account of the need to urinate.

Summary

Long distance travel is a recognized common but weak risk factor for VTE. Flight times of three hours or more have been associated with VTE, with the risk increasing with longer duration of travel. The incidence for flights of four or more hours, in low/intermediate risk individuals, is approximately 1 in 4600. The risk of presenting with thrombosis may persist for up to eight weeks after a journey. The box below summarizes strategies to help prevent travel-related thrombosis.

Measures to reduce the risk of travel-related thrombosis

- Maintain mobility during journey
- Regular calf exercises
- If feasible, aim to sit next to the aisle
- Graduated below knee compression hosiery for individuals at moderate risk
- Consider pharmacological prophylaxis only for those individuals who are high risk for venous thromboembolism

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