Chapter 2

Common clinical indications for anticoagulation

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As discussed in Chapter 1, an anticoagulant is a substance that possesses the properties to limit clot formation and therefore can be used therapeutically to prevent or treat thrombotic disorders. In this chapter we discuss the common clinical conditions in which anticoagulation should be considered and the evidence available to justify the use of an appropriate antithrombotic therapy in these clinical settings.

Venous thromboembolism

Epidemiology

Venous thromboembolism (VTE) encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE). It is a common disorder with an incidence of 7.1 per 1000 person-years in developed countries [1,2]. VTE is more common in males and in black populations, and the incidence increases with aging. Furthermore, up to a fifth of patients with previous VTE have recurrences of VTE in the following 5 years [3].

PE, a life-threatening presentation of VTE, has a reported incidence of 6 cases per 10,000 person-years [4]. Notably, around 80% of cases of PE occur without any clinical signs [5]. It is also estimated that 1 in every 100 inpatient deaths is related to PE, making it one of the most common causes of preventable hospital mortality [6].

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Given that patients with VTE have a substantially increased risk of morbidity and mortality because of its complications (life-threatening PE and post-thrombotic syndrome) [7], when its presence is suspected patients should be carefully considered to ensure timely diagnosis and initiation of treatment. Common conditions associated with VTE are shown in Table 2.1. The imbalance between the activated coagulation cascade (both intrinsic and extrinsic pathways) and the fibrinolytic system is another predisposing feature that increases the risk of VTE.

It is worth mentioning that venous thrombi differ in site of formation and are rich in red cells compared with arterial thrombi, which are mainly platelet rich. Consequently, the antithrombotic effects of anticoagulants may vary substantially depending on thrombus location and these agents require a specific regimen for the clinical settings of venous thrombosis (eg, VTE) and arterial thrombosis (eg, acute coronary syndromes).

Anticoagulation in the prevention of venous thromboembolism

The incidence of VTE can be reduced significantly using prophylactic regimens in high-risk patients. Appropriate prophylaxis has been found to be cost-effective compared with the cost of managing established VTE cases [8].

Various prophylactic measures have been recommended in the prevention of VTE, including injections of low-dose unfractionated heparin (UFH), adjusted-dose UFH, low-molecular-weight heparin (LMWH), oral warfarin, external pneumatic compression, or gradient elastic stockings

Common conditions associated with venous thromboembolism
Post-trauma
• Post-surgical patients (major surgery lasting >30 min, orthopedic surgeries) • Previous deep vein thrombosis/pulmonary embolism • Prolonged immobilization (bed rest, paralysis of legs or plaster casts, long flights) • Malignancy • Obesity • Pregnancy, use of oral contraceptive pills • Advanced age • Other conditions: antithrombin III deficiency, protein C and S deficiency (eg, varicose veins, thrombocytosis, polycythemia rubra vera, systemic lupus erythematosus, nephritic syndrome, stroke and debilitating infections)

Table 2.1 Common conditions associated with venous thromboembolism.

alone or in combination. Prophylactic therapy in high-risk patients should be tailored carefully, assessing both individual risk(s) and therapeutic benefits. Nevertheless, in contrast to the management of developed thrombosis, prophylactic therapy is simple, carries minimal risks and, if warfarin is not used, does not require monitoring.

In a meta-analysis of trials (n=19,958) using parenteral anticoagulant thromboprophylaxis (UFH, LMWH, fondaparinux) in hospitalized medical patients, there was a significant risk reduction in PE (relative risk [RR] 0.43, 95% confidence interval [CI] 0.26–0.71) and fatal PE (RR 0.38, 95% CI 0.21–0.69) and a nonsignificant reduction in DVT (RR 0.47, 95% CI 0.22–1.00) [9]. There was no effect on all-cause mortality (RR 0.97, 95% CI 0.790–1.19), and, impressively, there was no significant increase in the risk of major hemorrhage (RR 1.32, 95% CI 0.73–2.37).

From another meta-analysis of randomized trials (n=16,000), perioperative use of prophylactic low-dose UFH reduced the incidence of DVT (odds ratio [OR] 0.3), symptomatic PE (OR 0.5), fatal PE (OR 0.4), and all-cause mortality (OR 0.8) compared with placebo in those undergoing general, orthopedic, and urological surgery [10]. In another analysis, there was an increase in the incidence of wound hematomas with low-dose UFH compared with placebo, although the incidence of major hemorrhage in these patients was not increased [11]. However, the use of UFH is limited due to its shorter half-life and the requirement for repeated injections and monitoring of the activated partial thromboplastin time (APTT).

Because of these limitations, there has been a major switch in clinical practice from low-dose UFH to LMWH (depolymerized UFH). This has both clinical and practical advantages: LMWH has a longer half-life, has higher bioavailability, and can be safely administered subcutaneously without the need for monitoring. In one meta-analysis, LMWH prophylaxis in patients undergoing general surgery showed a reduction of up to 70% in asymptomatic DVT and symptomatic VTE compared with no prophylaxis [12]. In a meta-analysis assessing the efficacy of individual anticoagulant agents, LMWH appeared to be more effective than UFH in the prevention of asymptomatic DVT (RR 0.47, 95% CI 0.36–0.62), without any increased risk of thrombocytopenia or hemorrhage [13], and it was also more cost-effective than UFH [14]. Similarly, meta-analyses of

head-to-head trials comparing LMWH and UFH prophylaxis in patients undergoing abdominal, hip, or knee surgery showed superior efficacy for LMWH in reducing VTE and deaths related to VTE with a good safety profile [15–17].

Hopes for a further improvement in parenteral management of thrombosis were associated with the introduction of the selective indirect factor Xa inhibitor fondaparinux. However, although the benefits of fondaparinux were demonstrated in patients with acute coronary syndromes, it has been found to have similar effectiveness and safety to the LMWH dalteparin in patients undergoing high-risk abdominal surgery [18].

Oral anticoagulants for thromboprophylaxis after surgery

Until recently, oral anticoagulants were not considered an option for thromboprophylaxis after surgery. Warfarin could not be recommended for VTE prevention due to its delayed onset of action, its narrow therapeutic range and the requirement for careful monitoring. The novel oral direct thrombin inhibitor ximelagatran achieved favorable results in initial trials but was removed from further development because of safety issues [19,20]. More recently, however, newer oral anticoagulants have been shown to be safe and effective for thromboprophylaxis after surgery (see Chapter 5).

Guidelines for prevention of venous thromboembolism

The risk of VTE is not homogeneous and depends on the presence of concomitant risk factors. The American College of Chest Physicians (ACCP) has published evidence-based clinical practice guidelines on VTE prevention following surgery and other medical conditions (Tables 2.2–2.4) [21].

Treatment of venous thromboembolism

A number of randomized trials have confirmed that in patients with lower-limb DVT, LMWH is superior to UFH in reducing mortality at 3–6 months and reducing the risk of hemorrhage [22]. Furthermore, a meta-analysis of trials comparing UFH and LMWH for the treatment of VTE showed no difference in the recurrence of VTE or PE, in minor or major hemorrhage, or in thrombocytopenia [23]. Furthermore, a 24% reduction in the risk

of total mortality was observed in patients treated with LMWH compared with UFH (RR 0.76, 95% CI 0.59–0.98). Treatment of PE with LMWH also appears to be safe, being at least as effective as UFH, and also cost effective, without the need for special laboratory monitoring [24,25]. LMWHs have also proved to be effective and safe options for the outpatient treatment of VTE [26–28].

Prevention of venous thromboembolism in non-surgical patients

Condition	Recommendations
Acutely ill hospitalized medical patients at increased risk of thrombosis	LMWH, LDUH, or fondaparinux (Grade 1B)
For acutely ill hospitalized medical patients at low risk of thrombosis, or who are bleeding or at high risk for bleeding	No prophylaxis (Grade 1B)
Acutely ill hospitalized medical patients at increased risk of thrombosis who are bleeding or at high risk for major bleeding	Mechanical thromboprophylaxis with GCS or IPC (Grade 2C)
Critically ill patients with no bleeding	LMWH or LDUH thromboprophylaxis (Grade 2C)
Critically ill patients, who are bleeding, or are at high risk for major bleeding	Mechanical thromboprophylaxis with GCS or IPC (Grade 2C)
Outpatients with cancer who have no additional risk factors for VTE*	No routine prophylaxis (Grade 1B)
Outpatients with solid tumors who have additional risk factors for VTE and who are at low risk of bleeding*	Prophylactic dose LMWH or LDUH (Grade 2B)
Outpatients with cancer and indwelling central venous catheters	No routine prophylaxis (Grade 2B for LMWH or LDUH, Grade 2C for VKAs)
Chronically immobilized persons residing at home or at a nursing home	No routine prophylaxis (Grade 2C)
Long-distance travelers at increased risk of VTE†	Frequent ambulation, calf muscle exercise, or sitting in an aisle seat if feasible; below knee GCS (Grade 2C)
Asymptomatic thrombophilia	No long-term daily use mechanical or pharmacologic thromboprophylaxis to prevent VTE (Grade 1C)

Table 2.2 Prevention of venous thromboembolism in non-surgical patients. These recommendations are from the American College of Chest Physicians evidence-based clinical practice guidelines. *Additional risk factors for venous thrombosis in cancer outpatients include previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenali domide. †Increased risk of VTE includes previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or known thrombophilic disorder). GCS, gradient compression stockings; IPC, intermittent pneumatic compression; LDUH, low-dose unfractionated heparin; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism. Data from Guyatt et al [21].

Prevention of venous thromboembolism in non-orthopedic surgical patients

Conditions	Recommendations
General and abdominal-pelvic surgery	
Very low risk for VTE*	No pharmacologic (Grade 1B) or mechanical (Grade 2C) prophylaxis
Low risk for VTE	Mechanical prophylaxis (Grade 2C)
Moderate risk for VTE (not at high risk for major bleeding)	LMWH (Grade 2B), LDUH (Grade 2B), or mechanical prophylaxis (Grade 2C)
Moderate risk for VTE (at high risk for major bleeding or with bleeding thought to have particularly severe consequences)	Mechanical prophylaxis (Grade 2C)
High risk for VTE (not at high risk for major bleeding)	LMWH (Grade 1B) or LDUH (Grade 1B). Plus mechanical prophylaxis (Grade 2C)
High-VTE-risk patients undergoing surgery for cancer (not at high risk for major bleeding)	Extended (4 weeks) LMWH (Grade 1B)
High-VTE-risk patients (at high risk for major bleeding or with bleeding thought to have particularly severe consequences)	Mechanical prophylaxis (Grade 2C)
High risk for VTE in whom both LMWH and UFH are contraindicated or unavailable (not at high risk for major bleeding)	Low-dose aspirin, fondaparinux, or mechanical prophylaxis (Grade 2C)
Cardiac surgery	
Uncomplicated	Mechanical prophylaxis (Grade 2C)
Hospital course is prolonged nonhemorrhagic surgical complications	Pharmacologic prophylaxis (LDUH or LMWH) and mechanical prophylaxis (Grade 2C)
Thoracic surgery	
Moderate risk for VTE (not at high risk for perioperative bleeding)	LDUH or LMWH (Grade 2B), or mechanical prophylaxis with IPC (Grade 2C)
High risk for VTE (not at high risk for perioperative bleeding)	LDUH or LMWH (Grade 1B). Plus mechanical prophylaxis (Grade 2C)
High risk for major bleeding	Mechanical prophylaxis (Grade 2C)
Craniotomy	
At very high risk for VTE (eg, those undergoing craniotomy for malignant disease)	Pharmacologic prophylaxis added once adequate hemostasis is established and the risk of bleeding decreases (Grade 2C)
Spinal surgery at high risk for VTE (including those with malignant disease or those undergoing surgery with a combined anterior-posterior approach)	Mechanical prophylaxis (Grade 2C), UFH (Grade 2C), or LMWH (Grade 2C)

Table 2.3 Prevention of venous thromboembolism in non-orthopedic surgical patients (continues opposite).

Prevention of venous thromboembolism in non-orthopedic surgical patients (continued)	
Major trauma	
Low risk for VTE	LDUH, LMWH, or mechanical prophylaxis (Grade 2C)
High risk for VTE (including those with acute spinal cord injury, traumatic brain injury, and spinal surgery for trauma)	Adding mechanical prophylaxis to pharmacologic prophylaxis (Grade 2C) when not contraindicated by leg injury
If LMWH and LDUH are contraindicated	Mechanical prophylaxis (Grade 2C) when not contraindicated by leg injury

Table 2.3 Prevention of venous thromboembolism in non-orthopedic surgical patients (continued). These recommendations are from the American College of Chest Physicians evidence-based clinical practice guidelines. *Based on Rogers and Caprini scores. LDUH, low-dose unfractionated heparin; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism. Data from Guyatt et al [21].

Prevention of venous thromboembolism in patients undergoing major orthopedic surgery
Total hip arthroplasty or total knee arthroplasty One of the following for a minimum of 10 to 14 days: LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH, VKA, aspirin (Grade 1B), or IPCD (Grade 1C)
LMWH is preferred to other agents for THA and TKA: fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH (all Grade 2B), adjusted-dose VKA, or aspirin (all Grade 2C)
Hip fracture surgery One of the following for a minimum of 10 to 14 days: LMWH, fondaparinux, LDUH, VKA, aspirin (Grade 1B), or an IPCD (Grade 1C)
LMWH is preferred to the other agents (fondaparinux, LDUH [Grade 2B]; adjusted-dose VKA or aspirin [Grade 2C])
Major orthopedic surgery: total hip arthroplasty, total knee arthroplasty and hip fracture surgery If receiving LMWH as thromboprophylaxis, to start either ≥12 hours preoperatively or ≥12 hours postoperatively rather than within ≤4 hours preoperatively or ≤4 hours postoperatively (Grade 1B)
Extend thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery (Grade 2B)
Use dual prophylaxis with an antithrombotic agent and an IPCD during the hospital stay (Grade 2C)
If increased risk of bleeding, use an IPCD or no prophylaxis rather than pharmacologic treatment (Grade 2C)
If patients declines or is uncooperative with injections or an IPCD, use apixaban or dabigatran (if both are unavailable then rivaroxaban or VKA), all (Grade 1B)

Table 2.4 Prevention of venous thromboembolism in patients undergoing major orthopedic surgery. These recommendations are from the American College of Chest Physicians evidence-based clinical practice guidelines. IPCD, intermittent pneumatic compression device; LDUH, low-dose unfractionated heparin; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist. Data from Guyatt et al [21].

In the MATISSE-DVT (Mondial Assessment of Thromboembolism treatment Initiated by Synthetic pentasaccharide with Symptomatic Endpoints – Deep Vein Thrombosis) trial [29], once-daily subcutaneous administration of fondaparinux was found to be noninferior to twice-daily injection of the LMWH enoxaparin, with no differences in the recurrence of DVT, major hemorrhage or death at 3 months.

A disadvantage of LMWHs is that they require daily subcutaneous injections, often by trained personnel. Consequently, oral anticoagulation is considered an attractive option. Available data indicate that warfarin is non-inferior to LMWH in patients with VTE (without cancers), with a similar rate of VTE recurrence or hemorrhage [30]. Of interest, these positive results with warfarin were noted despite patients spending a relatively low proportion of time within the therapeutic international normalized ratio (INR) range, thus mirroring real life primary care practice. However, in patients with coexistent malignancies, treatment with LMWH appears to be more efficacious compared with warfarin [31].

Decisions with regard to the duration of warfarin anticoagulation in patients with VTE should be guided by whether or not the etiology is idiopathic. In many trials the VTE patient cohorts have been highly heterogeneous; nevertheless, it is clear from the pooled analyses that, compared with early termination of treatment, prolonged anticoagulation with warfarin (INR 2–3) is associated with a significant reduction in the recurrence of VTE [32–34], albeit with a nonsignificant increase in the risk of hemorrhage. Conventional intensity warfarin therapy (INR 2–3) has also been found to be more effective than low-intensity (INR 1.5–2) warfarin anticoagulation [35,36], without any increased risk of hemorrhage in patients with symptomatic VTE.

The indirect factor Xa inhibitor idraparinux (injected subcutaneously once weekly) was found in a randomized trial [37] to be as effective and safe as warfarin in patients with VTE, with no differences in DVT recurrence. However, idraparinux was comparatively less effective in patients with PE, and long-term therapy carried higher hemorrhage risks than did warfarin.

As an alternative to oral and parenteral anticoagulation for VTE management, catheter-directed thrombolysis [38–40] and thrombus removal [41] can be used and have been shown to improve the venous patency and outcomes in patients with acute DVT. By contrast, the available evidence for the utility of inferior vena cava filters [42,43] for treatment of VTE is conflicting, and therefore their routine use is not recommended. If they are used, patients should also receive conventional anticoagulation treatment. With regard to thrombolysis in acute PE, a meta-analysis of trials comparing thrombolysis with heparin showed a nonsignificant reduction in PE recurrence (OR 0.67, 95% CI 0.4–1.12) and all-cause mortality (OR 0.70, 95% CI 0.37–1.30) with thrombolysis, but this was achieved at the expense of a significant increase in nonmajor hemorrhage (OR 2.63, 95% CI 1.53–4.54) and intracranial hemorrhages [44].

Guidelines for treatment of venous thromboembolism

Current guidelines recommend long-term oral anticoagulation at a conventional intensity (INR 2–3 for vitamin K antagonist [VKA]) for patients with VTE (Table 2.5) [21,45]. The duration of the treatment should be 3–6 months in those with precipitating risk factors and 12 months for 'idiopathic' VTE; however, in the event of further recurrences, the therapy should be further extended (for 12 months or more). Thrombolysis in patients with PE is reserved for those with hemodynamic instability or with other poor prognostic features, such as hypoxia, dilated and hypokinetic right ventricle, or elevated cardiac markers. Importantly, precipitating factors, such as occult malignancies (4–10% of VTE cases) [46], should be carefully considered in VTE patients, particularly in those with 'idiopathic' VTE.

In patients with acute VTE warfarin should be immediately initiated together with parenteral anticoagulation. Parenteral anticoagulation (LMWH of fondaparinux) should be used for at least 5 days and should not be discontinued until the INR reaches 2.0 for at least 24 hours. First episodes of VTE should be managed with an INR target of 2.5 (2.0–2.5), while more advanced anticoagulation should be employed with a target of INR 3.5 (3.0–4.0) in patients with recurrent VTE [21].

Current guidelines for the treatment of venous thromboembolism

Condition	Anticoagulation
Acute DVT	
Initial treatment	Parenteral anticoagulants (LMWH, fondaparinux, or UFH) (Grade 1B)
Long-term treatment	Adjusted VKA (INR 2–3) (Grade 1B)
DVT provoked by surgery or by a nonsurgical transient risk factor	3 months (Grade 1B)
First unprovoked proximal DVT (low or moderate bleeding risk)	Extended (Grade 2B)*
First unprovoked proximal DVT (high bleeding risk)	3 months (Grade 1B)†
First unprovoked isolated distal DVT	3 months (Grade 2B if a low or moderate bleeding, Grade 1B a high bleeding risk)†
Second unprovoked VTE (low or moderate bleeding risk)	Extended (Grade 1B if low bleeding risk, Grade 2B if a moderate bleeding risk)*
Second unprovoked VTE (high bleeding risk)	3 months (Grade 2B)†
Any DVT and active cancer	Extended (Grade 1B if non high bleeding risk, Grade 2B if a high bleeding risk)*
Acute PE	
Initial treatment	Parenteral anticoagulants and VKA (Grade 1B). Parenteral anticoagulation for a minimum of 5 days and until the INR is 2.0 or above for at least 24 hours (Grade 1B)
If hypotension or high risk of hypotension and no high bleeding risk	Systemic thrombolysis (Grade 2C)
Long-term treatment	Adjusted VKA (INR 2–3) (Grade 1B)
PE provoked by surgery or by a nonsurgical transient risk factor	3 months (Grade 1B)
First unprovoked PE (low or moderate bleeding risk)	Extended (Grade 2B)*
First unprovoked PE of the leg (high bleeding risk)	3 months (Grade 1B)†
Second unprovoked VTE (low or moderate bleeding risk)	Extended (Grade 1B if low bleeding risk, Grade 2B if a moderate bleeding risk)*
Second unprovoked VTE (high bleeding risk)	3 months (Grade 2B)†
Any PE and active cancer	Extended (Grade 1B if low or moderate bleeding risk, Grade 2B if high bleeding risk)*

Table 2.5 Current guidelines for the treatment of venous thromboembolism. DVT, deep vein thrombosis; INR, international normalized ratio; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; VKA, vitamin K antagonist; UFH, unfractionated heparin. *The continuing use of treatment should be reassessed at periodic intervals (eg, annually). †The risk–benefit ratio of extended therapy should be reassessed after 3 months. Data from Guyatt et al [21] and Keeling [45].

Atrial fibrillation

Epidemiology and thromboembolic risks with atrial fibrillation

The overall prevalence of atrial fibrillation (AF) was 6% in the Framingham and Rotterdam studies [47,48]. Both of these studies found a one in four lifetime risk of developing AF, for both men and women aged 40 years and above. The population-based Renfrew–Paisley study in west Scotland found the prevalence of AF among patients aged 45–64 years to be 6.5% [49]; the prevalence of AF increases with age and is higher in males. The incidence of AF has risen by 13% over the past two decades, and it is predicted that 15.9 million people in the USA will have AF by 2050 [50].

The clinical significance of AF is largely associated with its increased risk for thromboembolic complications. The risk of ischemic stroke or thromboembolism is four- to five-fold higher across all age groups in patients with AF, and is similar in patients with either paroxysmal or permanent AF [51].

Acute atrial fibrillation

At present no clinical trial data are available that assesses the role of anticoagulation in acute AF with hemodynamic instability. Consensus statements made by the UK National Institute for Health and Clinical Excellence (NICE) and the European Society of Cardiology (ESC) guidelines (2010) [54] advocate the use of heparin prior to cardioversion in acute AF, irrespective of the method used. In a randomized clinical trial of 155 patients with AF duration between 2 and 19 days and who were undergoing transesophageal echocardiograph-guided cardioversion, no significant differences between UFH and LMWH were observed in rates of stroke, systemic embolism, thrombus formation, or hemorrhage [55]. The use of LMWH simplifies the treatment regimen and allows early discharge from hospital [56]; however, for patients with planned cardioversion (whether electrical or pharmacological), oral anticoagulation has to be initiated and therapeutic levels maintained for at least 3 weeks before and 4 weeks after the procedure.

Long-term oral anticoagulation should be considered in patients with stroke risk factors or if there is a high risk of AF recurrence. If successful

cardioversion has not been achieved, the need for long-term thromboprophylaxis should be assessed according to the patient's individual stroke risk.

Long-term thromboprophylaxis

The long-term risk of stroke is not homogeneous among AF patients. Each patient with AF should be assessed for thromboembolic risk, contraindications, and comorbidities prior to commencement of antithrombotic therapy [55]. The state-of-the-art approach for anticoagulation in AF has been presented in the updated guidelines of the ESC on management of this disorder [52]. These recommendations include the introduction of a more advanced system of stroke-risk stratification.

The guidelines recommend to perform an initial rapid risk assessment using the simplest risk assessment scheme called the CHADS2 score (Cardiac failure, Hypertension, Age ≥75 years, Diabetes, Stroke [2 points]) based on a point system in which 2 points are assigned for a history of stroke or transitory ischemic attack and 1 point each for other risk factors. Life-long oral anticoagulation therapy should be initiated in patients with a CHADS2 score ≥2 (INR target of 2.5 [range, 2.0–3.0]), unless contraindicated.

A more detailed stroke risk-assessment schema is recommended in subjects with CHADS2 scores 0–1, which considers both 'major' and 'clinically relevant nonmajor' stroke risk factors. This new schema is abbreviated as CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 [doubled], Diabetes, Stroke [doubled], Vascular disease, Age 65–74, and Sex category [female]) (Table 2.6) [56]. Patients with 1 'major' or >2 'clinically relevant nonmajor' risk factors are considered high-risk and should receive oral anticoagulant therapy. In patients with one 'clinically relevant nonmajor' risk factor antithrombotic therapy is recommended either as oral anticoagulant therapy (INR 2.0–3.0) or aspirin 75–325 mg daily. Patients with no risk factors, such as those aged <65 years with lone AF, should receive aspirin 75–325 mg daily or no antithrombotic therapy at all.

It is important to point out that the same approach towards anticoagulation should be applied to subjects with paroxysmal, persistent, or

Stroke and bleeding risk assessment: the CHA_2DS_2-VASc schema for stroke risk assessment

	Clinical characteristics	Clinical characteristics
C	Congestive heart failure/LV dysfunction	1
H	Hypertension	1
A_2	Age ≥75 years	2
D	Diabetes mellitus	1
S_2	Stroke/TIA/TE	2
V	Vascular disease	1
A	Age 65–74 years	1
Sc	Sex category (ie, female gender)	1
		Maximum 9 points

Table 2.6 Stroke and bleeding risk assessment: the CHA_2DS_2-VASc schema for stroke risk assessment. In patients with thyrotoxicosis, antithrombotic therapy should be chosen based on the presence of other stroke risk factors, as listed in this figure. 'Vascular disease' refers to myocardial infarction, complex aortic plaque, and PAD, including prior revascularization, amputation due to PAD or angiographic evidence of PAD. LV, left ventricular; PAD, peripheral artery disease; TE, thromboembolic event; TIA, transient ischemic attack. Data from Lip et al [56].

permanent AF and those with atrial flutter. Subjects with AF who have mechanical heart valves should receive chronic oral anticoagulation based on the type and position of the prosthesis, with INR of at least 2.5 in the mitral position and at least 2.0 for an aortic valve.

While warfarin is still the most commonly used oral anticoagulant, novel non-VKA anticoagulants have been recently introduced and will be discussed in detail in Chapter 5. Additionally the risk of bleeding associated with chronic oral anticoagulation in AF should not be neglected. Approaches for individual assessment of risk of bleeding have been validated and introduced into clinical practice recently and are discussed in Chapter 4.

Warfarin versus placebo

The clinical trials that have compared warfarin with either control or placebo are summarized in Table 2.7 [55,57–61]. The results of these trials and a meta-analysis of adjusted-dose warfarin in AF patients showed a two-thirds reduction, compared with placebo, in the relative risk of ischemic stroke or systemic embolism in high-risk patients [62,63].

Thromboprophylaxis in atrial fibrillation: clinical trials comparing warfarin with control

Study	Number of patients (warfarin)	Target INR	Thromboembolic event/patients, warfarin vs placebo	RRR (%); comments
AFASAK [55]	671 (335)	2.8–4.2	5/335 vs 21/336	54
BAATAF [57]	420(212)	1.5–2.7	3/212 vs 13/208	78
CAFA [58]	378 (187)	2.0–3.0	6/187 vs 9/191	33
EAFT [59] (secondary prevention study)	439 (225)	2.5–4.0	20/225 vs 50/214	68; mean follow-up 2.3 years; annual rate of outcome event was 8% vs 17%
SPAF-I [60]	421 (210)	2.0–4.5	8/210 vs 19/211	60
SPINAF [61]	571 (281)	1.4–2.8	7/281 vs 23/290	70; mean follow up 1.8 years; annual event rate among patients over 70 years of age: 4.8% in placebo group, 0.9% in warfarin group (risk reduction 0.79)

Table 2.7 Thromboprophylaxis in atrial fibrillation: clinical trials comparing warfarin with control. AFASAK, Atrial Fibrillation, Aspirin, Anticoagulation trial; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation trial; EAFT, European Atrial Fibrillation Trial; INR, international normalized ratio; RRR, relative risk reduction; SPAF, Stroke Prevention in Atrial Fibrillation trial; SPINAF, Stroke Prevention in Non-rheumatic Atrial Fibrillation trial. Data from [55,57–61].

Aspirin versus placebo

The clinical trials that have compared antiplatelet therapy with either placebo or control are summarized in Table 2.8 [55,59,60,64–67]. Various aspirin doses between 50 and 1200 mg daily have been employed in these trials and evaluated during follow-up periods ranging from 1.2 years to 4.0 years. Recent meta-analyses have reported that antiplatelet drugs, when compared with controls, reduced overall stroke risk by 19–22% [62,68]. However, this magnitude of stroke reduction is similar to that seen with the use of antiplatelet therapy in high-risk vascular disorders and, given that AF commonly coexists with vascular disease, the effect of aspirin may simply reflect the effect on vascular disease.

Warfarin versus antiplatelet therapy

A meta-analysis of 12 large randomized trials involving 12,721 participants found a 39% RR reduction in all strokes when INR-adjusted-dose warfarin

Thromboprophylaxis in atrial fibrillation: clinical trials comparing aspirin with control

Study	Number of patients (aspirin)	Doses (mg/day)	Thromboembolic event/ patients	RRR (%); comments
AFASAK [55]	672 (336)	75	16/336 vs 19/336	17
EAFT [59]	782 (404)	300	88/404 vs 90/378	11
ESPS [64]	211 (104)	50	17/104 vs 23/107	At mean follow-up of 2 years. Stroke risk was reduced by 18% with aspirin compared with placebo
SPAF-I [60]	1120 (552)	325	25/552 vs 44/568	44
UK-TIA [65]	(a) 28 (13) (b) 36 (21)	300 1200	3/13 vs 4/15 5/21 vs 4/15	17 14
JAST [66]	871 (426)	150	20/426 vs 19/445	10
LASAF [67]	(a) 195 (104) (b) 181 (90)	125 125 mg/ alt day	4/104 vs 3/91 1/90 vs 3/91	17 67

Table 2.8 Thromboprophylaxis in atrial fibrillation: clinical trials comparing aspirin with control. AFASAK, Atrial Fibrillation, Aspirin, Anticoagulation trial; alt, alternate; EAFT, European Atrial Fibrillation Trial; ESPS, European Stroke Prevention Study; JAST, Japan Atrial Fibrillation Stroke Trial; LASAF, Low-dose Aspirin, Stroke, Atrial Fibrillation; RRR, relative risk reduction; SPAF, Stroke Prevention in Atrial Fibrillation trial; UK-TIA, United Kingdom Transient Ischaemic Attack. Data from [55,59,60,64–67].

was compared with aspirin [62]. Clopidogrel plus aspirin versus oral anticoagulation for AF in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W) [69], the largest of these trials, was stopped early because of the clear evidence of superiority of adjusted-dose warfarin.

In the randomized Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study [70], warfarin (INR 2–3) was compared with aspirin 75 mg daily in 973 patients with AF aged 75 years or older in a primary care setting. The study demonstrated that during the average 2.7-year follow-up warfarin was significantly more effective than aspirin in preventing stroke (by over 50%, with nearly 2% annual absolute risk reduction), without any difference between warfarin and aspirin in the risk of major hemorrhage.

At present, adjusted-dose warfarin remains the most efficacious prophylaxis for AF patients who have at least moderate risk of stroke.

Anticoagulation in other medical conditions

Valve disease and endocarditis

In patients with prosthetic mechanical heart valves, oral anticoagulation offers superior and consistent protection against systemic thromboembolism compared with antiplatelet agents and is therefore recommended in all such patients [71]. VKA are medications of choice in patients with mechanical cardiac prosthetic valves. Novel oral anticoagulants should not be used in patients with a mechanical prosthesis, due to lack of evidence of their effectiveness and safety in these settings [72].

Target INR is established based on the presence of risk factors and the thrombogenicity of the prosthesis. Carbomedics, Medtronic Hall, St Jude Medical and ON-X prostheses have low thrombogenicity; other bileaflet valves have medium thrombogenicity, whilst Lillehei-Kaster, Omniscience, Starr-Edwards, Bjork-Shiley and other tilting-disc valves pose high risk of thrombogenicity. The target median INR should be 2.5, 3.0, and 3.5 for prostheses with low, medium, and high thrombogenicity, respectively. The target INR values should be increased by 0.5 in a patient who has one or more of the following patient-related risk factors: mitral or tricuspid valve replacement; previous thromboembolism; atrial fibrillation; mitral stenosis of any degree; left ventricular ejection fraction 35%. The target INR recommendations may need to be reduced if recurrent bleeding occurs, or increased in cases of embolism that has developed despite an acceptable INR level. Low-dose aspirin rather than anticoagulants is now considered as a preferable option in patients after aortic bioprostheses [72].

Both infective and nonbacterial thrombotic endocarditis carry a higher risk of embolic stroke. Persistent vegetation of >10 mm despite treatment, or one or more embolic events in the first 2 weeks of treatment, are indications for acute surgical treatment of the affected valves [73]. Nevertheless, data on the benefits of anticoagulant drugs in these clinical settings are lacking.

Acute myocardial infarction, left ventricular thrombus, and aneurysm

The risk of stroke associated with acute myocardial infarction (MI) accompanied by left ventricular (LV) mural thrombus can be as high as

15% [74]. Nearly half of all patients with LV aneurysm have LV thrombus, and in such patients the extent of MI, severity of LV dysfunction, and age are independent predictors of stroke [75]. Anticoagulation has been associated with a 68% risk reduction in stroke in post-MI patients with LV thrombus and is now recommended for 3 months where LV thrombus formation post-MI occurs [76].

Trials evaluating the effectiveness of oral anticoagulation in post-MI patients have shown conflicting and inconclusive results. In a subgroup of patients with AF post-MI in the Efficacy and Safety of the oral direct Thrombin inhibitor ximElagatran in patients with rEcent Myocardial damage (ESTEEM) trial, 6.9% of patients treated with the combination of ximelagatran and aspirin had death, nonfatal MI, or stroke during a 6-month follow-up, compared with 20.6% of patients who received aspirin alone 0.30 (95% CI 0.12–0.74) [77]. The Coumadin Aspirin Reinfarction study (CARS) compared fixed low-dose warfarin (INR 1.3–1.8) with low-dose aspirin (80 mg daily) and found no difference in nonfatal reinfarction, nonfatal stroke or cardiovascular death (8.6% with aspirin versus 8.4% with warfarin) at a median of 14 months of follow-up [78]. Similar results were obtained in the Combination Haemotherapy and Mortality Prevention (CHAMP) trial [79]; this compared aspirin monotherapy with warfarin (mean INR 1.8) plus aspirin after acute MI, and found no differences in stroke (3.5% with aspirin and 3.1% with combination therapy) at a median 2.7-year follow-up.

By contrast, the Warfarin, Aspirin, Reinfarction (WARIS) II study [80] showed that anticoagulation with warfarin plus aspirin or with warfarin alone (within 4 weeks of MI) reduced a composite of mortality, nonfatal reinfarction, or stroke compared with aspirin alone (15% versus 16.7% versus 20%, respectively). There was an overall risk reduction of 29% with combination therapy and 19% with warfarin compared with aspirin alone at a median follow-up of 2.7 years, but at the expense of more hemorrhagic events in the warfarin groups (0.62% [warfarin groups] versus 0.17% [aspirin alone] per treatment year). The Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) study showed similar benefits of oral anticoagulation compared with antiplatelet therapy; there was a

reduction in mortality, MI, and strokes (9% aspirin versus 5% warfarin versus 5% warfarin plus aspirin), but with a trend towards a higher hemorrhage rate with warfarin [81].

Nonetheless, there is still no clear consensus as to whether anticoagulant treatment of the whole cohort of patients with acute MI in sinus rhythm is more effective compared with conventional treatment with antiplatelets in reducing adverse cardiac events and, if it is, how long the treatment should continue.

A proportion (6–8%) of subjects presenting with ACS have pre-existing indications for long-term oral anticoagulation, for example, due to AF, mechanical heart valves, or VTE. Oral anticoagulation in ACS settings potentially poses several problems, which need to be considered. For example, triple therapy (two antiplatelet agents plus warfarin) tend to be associated with a higher risk of bleeding complications. Interruption of VKA therapy may expose the patient to an increased risk of thromboembolic episodes.

Accordingly, several precautions should be considered. Bare metal stents should be used, while usage of drug-eluting stents should be restricted to clinical and/or anatomical conditions, where their benefits are clearly established (eg, long lesions, small vessels, diabetes). Radial access should be the preferred choice in order to reduce the risk of periprocedural bleeding, particularly when repeated interventions are needed. Percutaneous coronary interventions without interruption of warfarin are generally preferred to avoid bridging therapy, which may increase the risk of bleeding or ischemic events.

Nevertheless, triple therapy (warfarin, aspirin, and clopidogrel) seems to have an acceptable risk–benefit ratio and should be used in the initial 3–6 months (or for longer in some patients at low-bleeding risk) [51]. ST segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI) patients with a high-risk of cardiovascular thrombotic complications should be followed with a prolonged (up to 12 months) therapy of warfarin plus clopidogrel 75 mg daily (or, alternatively, aspirin 75–100 mg daily, plus gastric protection) [52,82].

Heart failure

Heart failure is an increasingly common condition and is associated with increased thromboembolic risk; however, the utility of chronic anticoagulant therapy in patients with heart failure is still controversial. The authors of a Cochrane systematic review of antithrombotic drugs in patients with heart failure found no robust evidence for additional benefits of anticoagulation over administration of aspirin in reducing mortality and thromboembolism [83,84]. Of note, hospitalizations were more common in aspirin users than in those managed with warfarin.

Possible benefits of long-term oral anticoagulation have been addressed in several trials (Table 2.9) [85,86]. For example, the Warfarin/Aspirin Study in Heart failure (WASH) trial was a small pilot study that compared aspirin, warfarin, and no treatment in heart failure patients [85]. It found no statistical differences in the primary endpoint of death, nonfatal MI, or nonfatal stroke (26 [no treatment], 32 [aspirin], and 26% [warfarin]), after a mean follow up of 27 months. Nonetheless, the rate of hospitalization for worsening heart failure was significantly higher in the aspirin arm compared with the warfarin arm and the no-treatment arm (P=0.044 for warfarin versus aspirin).

Heart failure: summary of randomized clinical trials comparing warfarin and aspirin

Trials	Follow-up (months)	Head-to-head comparison	Results
WASH [85]	27	Warfarin (n=89) vs aspirin (n=91) vs no treatment (n=99)	No differences observed in primary outcomes (death or nonfatal MI or stroke) between treatment groups. More patients in aspirin group than warfarin group had CV-related hospitalizations or death (HR 1.39, 95% CI 0.95–2.00) during first 12 months of follow-up
WATCH [86]	18	Warfarin (n=540) vs aspirin (n=523) or clopidogrel (n=524)	No significant differences noted in primary outcomes (death or nonfatal MI or nonfatal strokes) between treatment groups. However, patients on aspirin had more heart failure related hospitalizations than those on warfarin (P=0.019)

Table 2.9 Heart failure: summary of randomized clinical trials comparing warfarin and aspirin. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; WASH, Warfarin/Aspirin Study in Heart failure; WATCH, Warfarin and Antiplatelet Therapy in Chronic Heart failure. Data from Cleland et al [85] and Massie et al [86].

Similar results were seen in the Warfarin and Antiplatelet Therapy in Chronic Heart failure (WATCH) trial in which patients with ejection fraction <35% were randomized to blinded antiplatelet therapy (aspirin or clopidogrel) or warfarin to prevent thromboembolic events [86]. In this study no difference was observed in the composite primary endpoint of stroke, MI, or death (20.7% [aspirin] versus 21.6% [clopidogrel] versus 19.6% [warfarin]) at 18 months, follow-up. However, because of poor recruitment of patients, the study was terminated earlier than expected and therefore was underpowered.

The ongoing multicenter, double-blind, randomized Warfarin versus Aspirin with ReduCed Ejection Fraction (WARCEF) trial [87] is studying the benefits of warfarin or aspirin in heart failure patients and may provide evidence for the benefits of appropriate antithrombotic therapy in these patients.

Conclusions

Compelling evidence favors the use of appropriate antithrombotic therapies for the prevention of VTE as well as treatment of patients with VTE, AF, and implantation of prosthetic valves, and the range of indications for anticoagulant therapy may expand further. However, despite this, each patient who might require anticoagulation should be individually assessed in terms of the potential benefits and risks of the therapy. Furthermore, the approach towards treatment needs to be holistic, and success is largely based on appropriate patient education to facilitate safer and effective use of anticoagulant therapies.

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