

Role of new anticoagulants for the prevention of venous thromboembolism after major orthopaedic surgery and in hospitalised acutely ill medical patients

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Summary

Anticoagulation therapy for the prevention of venous thromboembolic events (VTE) is indicated in patients after major orthopaedic surgery and in hospitalised acutely ill medical patients who have a high or moderate risk of VTE, respectively. Clinical trials have clearly demonstrated that short-term anticoagulation reduces the risk of VTE in these patient groups and that longer-term anticoagulation is beneficial for some indications. Evidence-based guidelines for thromboprophylaxis have been developed based on these studies. However, despite these guidelines, thromboprophylaxis is still underused, or used suboptimally, in many patients. This is, in part, because of the limitations of traditional anticoagulants such as unfractionated heparin, low-molecular-weight heparin, synthetic pentasaccharides, and vitamin K antagonists. Newer oral anticoagulants, such as rivaroxaban, apixaban, and dabigatran etexilate, have certain advantages over traditional agents. They can be

administered orally at a fixed dose without routine coagulation monitoring and have minimal food and drug interactions. These characteristics may result in better adherence to guidelines and improved patient outcomes. This review provides an overview of phase III clinical trial data for these newer anticoagulants in major orthopaedic surgery and in hospitalised acutely ill medical patients, and discusses their potential for extended use in the post-hospital discharge setting. All three newer oral anticoagulants are approved in many countries for the prevention of VTE after hip replacement or knee replacement surgery in adult patients, and it is likely that these drugs will contribute considerably towards reducing the substantial healthcare burden associated with VTE.

Keywords

Apixaban, dabigatran etexilate, medically ill, orthopaedics, rivaroxaban

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Introduction

Venous thromboembolism (VTE), which comprises deep-vein thrombosis (DVT) and pulmonary embolism (PE), causes considerable morbidity and mortality and places a substantial burden on healthcare resources (1, 2). Patients who undergo major orthopaedic surgery, which includes total knee replacement (TKR), total hip replacement (THR), and hip fracture surgery (HFS), are at a high risk of VTE. In this patient group, the rate of asymptomatic, objectively confirmed DVT is 40–60% without thromboprophylaxis. In comparison, patients admitted for an acute medical illness (such as infection, respiratory failure, cardiovascular disease, or neurological disease) are at a moderate risk of VTE; the rate of DVT is 10–20% (3). Oncology patients have an increased risk of new or recurrent VTE when compared with patients who do not have cancer. The risk of VTE in patients with cancer is increased by three- to five-fold for those who undergo surgery and by 6.5-fold

for those receiving chemotherapy (4, 5).

The benefits of thromboprophylaxis after major orthopaedic surgery are well established (3), and clinical trials have shown that the use of anticoagulants reduces the risk of VTE in hospitalised acutely ill medical patients (6–10). Identification of patients at risk of VTE will facilitate the administration of appropriate thromboprophylaxis and reduce the incidence of VTE and its complications. VTE risk factors can be patient related (e.g. age, obesity, hormonal therapy, cancer, previous VTE, molecular thrombophilia, chronic venous insufficiency, and prolonged immobility or bed rest >3 days) or treatment related (e.g. type and length of surgery, and type of anaesthesia) (11–13). VTE risk factors are generally cumulative (14), and as many as 80% of patients hospitalised for DVT have three or more predisposing factors (15). Risk assessment models have been recently validated in clinical trials to predict the risk of VTE for hospitalised acutely ill medical patients (16, 17) or cancer patients (18); however, these are not yet routinely used.

Several evidence-based guidelines for VTE prevention exist. For patients undergoing THR, TKR, or HFS, the American College of Chest Physicians (ACCP) guidelines recommend low-molecular-weight heparin (LMWH), fondaparinux, or a vitamin K antagonist (VKA); unfractionated heparin (UFH) is also recommended for HFS. Thromboprophylaxis is recommended for up to 35 days after THR and HFS and for at least 10 days after TKR, and there is some evidence that continuing prophylaxis for up to 35 days after TKR is beneficial (3). The current American Academy of Orthopaedic Surgeons (AAOS) guidelines differ from those of the ACCP in that they do not recognise DVT as a critical outcome (19). The AAOS guidelines do not recommend specific anticoagulants for VTE prophylaxis in patients undergoing TKR or THR; the choice of prophylaxis and duration of treatment depends on the perceived bleeding risk of each individual patient (19). For VTE prophylaxis in hospitalised acutely ill medical patients with risk factors for VTE, the ACCP guidelines recommend low-dose UFH, LMWH, or fondaparinux. However, there are no recommendations for the optimal duration of thromboprophylaxis for acutely ill medical patients (20). Mechanical methods (graduated compression stockings and intermittent pneumatic compression) are recommended primarily for surgical and non-surgical patients with contraindications to anticoagulant thromboprophylaxis (3).

In patients with cancer who are immobilised and have an acute medical illness, low-dose UFH, LMWH, or fondaparinux are recommended by several organisations, including the ACCP, International Union of Angiology, and American Society of Clinical Oncology (ASCO) (3, 21, 22). There is little guidance on the optimal duration of thromboprophylaxis in patients with cancer, although the ASCO guidelines recommend continuing thromboprophylaxis for the duration of hospital stay or until the patient is ambulatory. Outpatient VTE prophylaxis is recommended only for patients receiving highly thrombogenic thalidomide- or lenalidomide-based combination chemotherapy regimens.

Traditional anticoagulants have limitations: UFH, LMWH, and fondaparinux are administered parenterally; VKAs require routine coagulation monitoring for prophylaxis and have numerous food and drug interactions (23). Newer oral anticoagulants, such as the direct factor Xa inhibitors rivaroxaban and apixaban, and the thrombin inhibitor dabigatran etexilate, are being developed and have the potential to address some of these limitations. This review will provide an overview of the phase III clinical trial data for these newer anticoagulants in major orthopaedic surgery and in hospitalised acutely ill medical patients, and discuss their potential for extended use in the post-hospital discharge setting. The pharmacology of these agents and VTE prevention studies in patients undergoing THR or TKR have been reviewed previously by Ufer (24).

New oral anticoagulants

The pharmacological profiles of the newer oral anticoagulants rivaroxaban, apixaban, and dabigatran etexilate are summarised in

► Table 1 (25–27). These three agents have been studied in phase III trials for VTE prevention after THR and TKR surgery (► Table 2) (28–40). Rivaroxaban 10 mg once daily (od) (25, 41) and dabigatran etexilate 220 mg od (27, 41) are widely approved for the primary prevention of VTE in adults after elective hip or knee replacement surgery. Apixaban 2.5 mg twice daily (bid) has been approved recently for VTE prevention in this patient group in the EU (26). For VTE prevention in acutely ill medical patients, rivaroxaban and apixaban have recently completed phase III trials (42, 43). There are currently no phase III trials for dabigatran etexilate in this population.

VTE prevention after major orthopaedic surgery

Anticoagulation therapy is indicated for all patients undergoing TKR or THR, with the aim to achieve an optimal balance between VTE prevention and the risk of bleeding (44). For both types of procedure, post-surgery hospital stays are typically 3–10 days (45). There is a continued risk of VTE after hospital discharge; therefore, post-discharge administration of effective, well-tolerated, and convenient anticoagulants would be beneficial for patients.

Rivaroxaban was evaluated in four phase III studies: RECORD1 and RECORD2 (THR studies), and RECORD3 and RECORD4 (TKR studies) (28–31). RECORD1 compared rivaroxaban 10 mg od with the LMWH enoxaparin 40 mg od for 31–39 days (28). RECORD2 compared rivaroxaban 10 mg od for 31–39 days with enoxaparin 40 mg od for 10–14 days followed by placebo (29). RECORD3 and RECORD4 compared rivaroxaban 10 mg od with enoxaparin 40 mg od or 30 mg bid, respectively, for 10–14 days (30, 31). In all four trials rivaroxaban was superior to the enoxaparin regimens in terms of the primary efficacy outcome (composite of any DVT, non-fatal PE, and all-cause mortality), without significant differences in the rates of major bleeding (28–31). A pooled analysis of the four RECORD studies indicated that rivaroxaban regimens reduced symptomatic VTE plus all-cause mortality compared with enoxaparin regimens; this finding was consistent across patient subgroups, irrespective of age, gender, body mass index, and renal function (32).

Apixaban was evaluated in three phase III clinical trials. In the ADVANCE-1 study in TKR, apixaban (2.5 mg bid) for 10–14 days did not meet the prespecified statistical criteria for non-inferiority versus enoxaparin (30 mg bid) in terms of efficacy (composite of any DVT, non-fatal PE, and all-cause mortality) (33). However, in both ADVANCE-2 (TKR; 10–14 days) and ADVANCE-3 (THR; 35 days), apixaban 2.5 mg bid showed superior efficacy to enoxaparin 40 mg od (34, 35). In all three studies, there were no significant differences in the rates of major bleeding between apixaban and enoxaparin (33–35). A meta-analysis of ADVANCE-1, ADVANCE-2, and a phase II study of apixaban in patients undergoing TKR surgery showed that apixaban was more effective than enoxaparin in reducing the risk of proximal DVT but no more effective in reducing the risk of PE or all-cause mortality (46).

Table 1: Summary of pharmacological profiles of apixaban, rivaroxaban and dabigatran etexilate.

	Rivaroxaban (25)	Apixaban (26)	Dabigatran etexilate (27)
Target	Factor Xa	Factor Xa	Thrombin
Prodrug	No	No	Yes
Bioavailability (%)	~80	~50	6
Half-life, hours	5–13	~13	12–17
Time to peak, T _{max} , hours	3	3–4	0.5–2.0
Renal elimination (%)	33 as unchanged drug; 33 as inactive metabolites	~27	~85
Drug interactions*	Potent inhibitors of both CYP3A4 and P-gp, CYP3A4 inducers, anticoagulants, NSAIDs, platelet aggregation inhibitors	Potent inhibitors of CYP3A4	Potent inhibitors or inducers of P-gp, anticoagulants, NSAIDs, platelet aggregation inhibitors
Antidote	None	None	None
Coagulation monitoring	No	No	No
Dosing	Once daily [†]	Twice daily [†]	Once daily [§]

*Clinically significant drug interactions. [†]Dosing approved in many countries (including the USA) for thromboprophylaxis after elective hip or knee replacement surgery, and used in a study assessing rivaroxaban for thromboprophylaxis in medically ill patients (MAGELLAN). [‡]Dosing used in THR and TKR studies (ADVANCE-2 and ADVANCE-3) that met statistical non-inferiority criteria for apixaban versus enoxaparin, and used in a study assessing apixaban for thromboprophylaxis in medically patients (ADOPT). [§]Dosing approved in several countries (not including the USA) for thromboprophylaxis after elective hip or knee replacement surgery. CYP3A4, cytochrome P450 3A4; NSAID, non-steroidal anti-inflammatory drug; P-gp, P-glycoprotein; THR, total hip replacement; TKR, total knee replacement.

Dabigatran etexilate was evaluated in four phase III studies. Dabigatran etexilate (150 mg or 220 mg od) failed to show non-inferiority versus an enoxaparin regimen of 30 mg bid in terms of efficacy (composite of any DVT, symptomatic PE, and all-cause mortality) in the RE-MOBILIZE study in TKR with a treatment duration of 12–15 days (39). However, non-inferiority was demonstrated versus an enoxaparin regimen of 40 mg od in RE-MODEL (TKR; 6–10 days), RE-NOVATE, and RE-NOVATE II (THR; 28–35 days), and there were no significant differences in the rates of major bleeding (36–38). A meta-analysis of RE-MODEL, RE-NOVATE and RE-MOBILIZE was performed by Wolowacz et al., and the results of this were consistent with those of the individual studies.(47)

There was considerable variation in efficacy and safety outcomes for rivaroxaban, apixaban, dabigatran etexilate and enoxaparin across the studies described, reflecting differences in patient populations, treatment regimens, and safety outcome definitions (► Table 2). Definitions of efficacy endpoints were similar for all studies, and incidences of VTE were generally higher for patients undergoing TKR rather than THR surgery (► Table 2). Studies of dabigatran etexilate generally showed higher incidences of VTE than studies of rivaroxaban or apixaban for comparable indications.

Definitions of major bleeding varied across studies of rivaroxaban, apixaban, and dabigatran etexilate, confounding a direct comparison of major bleeding rates between the three agents. Nonetheless, incidences of major bleeding were generally low across all studies, with no clear separation between studies in patients undergoing THR or TKR surgery (► Table 2).

VTE prevention in hospitalised acutely ill medical patients

Evidence suggests that VTE prophylaxis in hospitalised acutely ill medical patients is under-used or used inappropriately (48–50). The ENDORSE study found that only 6,119 (39.5%) of 15,487 enrolled acutely ill medical patients considered to be at risk of VTE received appropriate thromboprophylaxis (51). In the IMPROVE registry, approximately 60% of 15,156 patients classified as likely to benefit from pharmacological prophylaxis received appropriate prophylaxis (52). Other studies support these findings: the DVT FREE study found that only 42% of the 2,726 hospitalised acutely ill medical patients received thromboprophylaxis within the 30 days before DVT diagnosis (53); and in the CURVE study, although 90% of the 1,702 hospitalised medically ill medical patients had indications for thromboprophylaxis, only 16% received appropriate medication (54).

The lack of consensus on the most appropriate duration of thromboprophylaxis in acutely ill medical patients poses a challenge to clinicians. Several studies have assessed the benefits of 6–14 days (considered as the standard duration) of thromboprophylaxis in acutely ill medical patients (6–8, 55, 56). MEDENOX (prophylaxis in medical patients with enoxaparin) was a double-blind, randomised, placebo-controlled study with 1,102 hospitalised patients who were >40 years of age and received enoxaparin or placebo subcutaneously od for 6–14 days (7). ARTEMIS (fondaparinux for the prevention of VTE in older acutely ill medical patients) was a double-blind, randomised, placebo-controlled trial that included 849 hospitalised medical patients aged ≥60 years who were expected to remain in bed for at least four days and received 2.5 mg fondaparinux or placebo subcutaneously od for 6–14 days

Table 2: Comparison of phase III studies of apixaban, rivaroxaban, and dabigatran etexilate for VTE prevention after total hip or knee replacement surgery.

Study	Comparison	Primary efficacy outcome	Main safety outcome
Rivaroxaban			
RECORD1	Rivaroxaban 10 mg od vs. enoxaparin 40 mg od (THR)	1.1% vs. 3.7%, respectively; p<0.001 for superiority	0.3% vs. 0.1%, respectively; p=0.18
RECORD2	Rivaroxaban 10 mg od vs. enoxaparin 40 mg od (THR)	2.0% vs. 9.3%, respectively; p<0.0001 for superiority	<0.1% vs. <0.1%, respectively
RECORD3	Rivaroxaban 10 mg od vs. enoxaparin 40 mg od (TKR)	9.6% vs. 18.9%, respectively; p<0.001 for superiority	0.6% vs. 0.5%, respectively; p=0.77
RECORD4	Rivaroxaban 10 mg od vs. enoxaparin 30 mg bid (TKR)	6.9% vs. 10.1%, respectively; p=0.0118 for superiority	0.7% vs. 0.3%, respectively; p=0.11*
RECORD1–4 pooled†	Rivaroxaban regimens vs. enoxaparin regimens (THR and TKR)	Day 12 ± 2 active treatment period: 0.5% vs. 1.0%, respectively; p=0.001 Total treatment period:‡ 0.6% vs. 1.3%, respectively	Day 12 ± 2 active treatment period: 0.3% vs. 0.2%, respectively; p=0.23 Total treatment period:‡ 0.4% vs. 0.2%, respectively
Apixaban			
ADVANCE-1	Apixaban 2.5 mg bid vs. enoxaparin 30 mg bid (TKR)	Apixaban failed non-inferiority to enoxaparin: 9.0% vs. 8.8%, respectively; p=0.06 for non-inferiority	0.7% vs. 1.4%, respectively; p=0.05
ADVANCE-2	Apixaban 2.5 mg bid vs. enoxaparin 40 mg od (TKR)	15.1% vs. 24.4%, respectively; p<0.0001 for non-inferiority and superiority	0.6% vs. 0.9%, respectively; p=0.30*
ADVANCE-3	Apixaban 2.5 mg bid vs. enoxaparin 40 mg od (THR)	1.4% vs. 3.9%, respectively; p<0.001 for non-inferiority and superiority	0.8% vs. 0.7%, respectively; p=0.54
ADVANCE-1, ADVANCE-2, and phase II study pooled	Apixaban regimens vs. enoxaparin regimens (TKR)	Proximal DVT: 0.6% vs. 1.2%, respectively; p=0.007 PE: 0.6% vs. 0.3%; p=0.055	0.6% vs. 1.2%, respectively; p=0.034
Dabigatran etexilate			
RE-MODEL	Dabigatran etexilate 150 mg od or 220 mg od vs. enoxaparin 40 mg od (TKR)	Both doses non-inferior to enoxaparin: 40.5% (150 mg) and 36.4% (220 mg) vs. 37.7%, respectively; p=0.82 (150 mg), p=0.38 (220 mg)	1.3% (150 mg) and 1.5% (220 mg) vs. 1.3%, respectively; p=1.0 (150 mg), p=0.82 (220 mg)
RE-NOVATE	Dabigatran etexilate 150 mg od or 220 mg od vs. enoxaparin 40 mg od (THR)	Both doses non-inferior to enoxaparin: 8.6% (150 mg) and 6.0% (220 mg) vs. 6.7%, respectively; p<0.0001 (150 mg), p<0.0001 (220 mg) (both for non-inferiority)	1.3% (150 mg) and 2.0% (220 mg) vs. 1.6%, respectively; p=0.60 (150 mg), p=0.44 (220 mg)
RE-NOVATE II	Dabigatran etexilate 220 mg od vs. enoxaparin 40 mg od (THR)	Dabigatran non-inferior to enoxaparin: 7.7% vs. 8.8%, respectively; p<0.0001 for non-inferiority	1.4% vs. 0.9%, respectively; p=0.40
RE-MOBILIZE	Dabigatran etexilate 150 mg od or 220 mg od vs. enoxaparin 30 mg bid (TKR)	Both doses failed non-inferiority to enoxaparin: 33.7% (150 mg) and 31.1% (220 mg) vs. 25.3%, respectively; p=0.0009 (150 mg), p=0.0234 (220 mg)	0.6% (150 mg) and 0.6% (220 mg) vs. 1.4%, respectively
Dabigatran pooled†	Dabigatran etexilate regimens vs. enoxaparin (THR and TKR)	3.8% (150 mg) and 3.0% (220 mg) vs. 3.3%, respectively; p=0.91 (150 mg), p=0.20 (220 mg)	1.1% (150 mg) and 1.4% (220 mg) vs. 1.4%, respectively; p=0.54 (150 mg), p=0.19 (220 mg)
*p-value rounded up to two decimal points. †Both primary outcomes excluded asymptomatic events. ‡Planned treatment period for double-blind study medication for each RECORD study, including the placebo phase in RECORD2. bid, twice daily; DVT, deep-vein thrombosis; THR, total hip replacement; TKR, total knee replacement; od, once daily; PE, pulmonary embolism.			

(6). PREVENT (prospective evaluation of dalteparin efficacy for prevention of VTE in immobilised patients) was an international, multicentre, randomised, double-blind, placebo-controlled trial that included 3,706 patients receiving subcutaneous dalteparin

5,000 IU daily or placebo for 14 days (8). These studies showed significant reductions in VTE without a significant increase in the risk of bleeding. However, this duration of thromboprophylaxis may not provide adequate protection against VTE after hospital dis-

charge in at-risk acutely ill medical patients (20). In one study, 36.8% of patients developed VTE in the outpatient setting within three months of hospitalisation (57). A recent study in 3,039 patients admitted to post-acute care facilities after medical disease or surgery showed that 2.4% developed VTE within a median of 13 days, although 75.1% received thromboprophylaxis. Multivariate Cox regression analysis identified previous VTE (hazard ratio [HR] 5.67, 95% confidence interval [CI] 3.30–9.77; $p < 0.001$) and cancer (HR 2.26, 95% CI 1.36–3.75; $p < 0.01$) as conditions that were significantly associated with the occurrence of VTE (58).

The EXCLAIM study (extended prophylaxis for VTE in acutely ill medical patients with prolonged immobilisation) aimed to determine whether there was a benefit for extended-duration (28 ± 4 days) compared with standard-duration (10 ± 4 days) thromboprophylaxis with enoxaparin 40 mg od. In this study, all patients had previously received open-label enoxaparin for two weeks. After randomisation to placebo for standard-duration therapy or enoxaparin for extended-duration therapy, events were analysed between day 10 and day 38. The inclusion criteria were hospitalisation for a medical illness, age ≥ 40 years, life expectancy of at least six months, and reduced mobility level 1 (defined as total bed rest or sedentary) or level 2 (defined as level 1 with bathroom privileges; after interim analyses of efficacy and safety outcomes, the definition of level 2 immobility was revised to include ≥ 1 risk factor for VTE, including age > 75 years, previous VTE, and active or previous cancer) (9). Analysis of the total patient population found that extended-duration enoxaparin reduced the risk of VTE when compared with placebo (2.5% vs. 4.0%, respectively; absolute risk difference -1.53% [95% CI -2.54 to -0.52]). However, the rate of major bleeding events was significantly higher in the extended-duration enoxaparin group versus the placebo group (0.8% vs. 0.3%, respectively; absolute risk difference 0.51% [95% CI 0.12–0.89]). Subgroup analyses found that the benefit of extended-duration enoxaparin was restricted to women, patients > 75 years of age, and those with mobility level 1.

Rivaroxaban has been evaluated in the MAGELLAN study: a multicentre, randomised, parallel-group efficacy and safety study for the prevention of VTE in hospitalised acutely ill medical patients that compared rivaroxaban with enoxaparin (10, 42). A total of 8,101 patients were randomised to receive either subcutaneous enoxaparin 40 mg od for 10 ± 4 days followed by placebo, or oral rivaroxaban 10 mg od for 35 ± 4 days. Patients were eligible if they were hospitalised for an acute medical illness, aged ≥ 40 years, at risk of VTE, and had a life expectancy of at least six months. Those with acute infectious, inflammatory, or rheumatic diseases and those with acute respiratory insufficiency were required to have at least one additional risk factor for VTE (e.g. history of VTE or cancer). The primary efficacy outcomes of this study were the composite of asymptomatic proximal DVT, symptomatic DVT (proximal or distal), symptomatic non-fatal PE, and VTE-related death at day 10 + 5 (test for non-inferiority) or at day 35 + 6 (test for superiority). Rivaroxaban was non-inferior in reducing risk of VTE when compared with enoxaparin at day 10 (2.7% vs. 2.7%, $p = 0.0025$), but was superior at day 35 when compared with enoxaparin followed by placebo (4.4% and 5.7% respectively;

$p = 0.0211$). Clinically relevant bleeding, the composite of major bleeding and non-major clinically relevant bleeding, was assessed as the principal safety outcome. Overall rates of clinically relevant bleeding were low, but were significantly higher in patients receiving rivaroxaban than in patients receiving enoxaparin (4.1% vs. 1.7% respectively, $p < 0.0001$ for events between day 1 and day 35). There were no significant differences in rates of other adverse events including liver and cardiovascular events, and all-cause mortality (10).

The double-blind, multicentre ADOPT study compared extended-duration (30 days) apixaban 2.5 mg bid with standard-duration (6–14 days) enoxaparin 40 mg od (43). Patients were eligible if they were ≥ 40 years of age and were hospitalised (expected stay of at least three days) with congestive heart failure, respiratory failure, or other medical disorders, and had at least one additional risk factor for VTE. A total of 6,528 patients were randomised, 4,495 of whom were evaluated for the primary efficacy outcome, defined as the 30-day composite of VTE-related death, PE, symptomatic DVT (proximal or distal), or asymptomatic proximal-leg DVT as detected by systematic bilateral compression ultrasonography. The primary efficacy outcome occurred in 60 of 2,211 patients (2.71%) of patients in the apixaban group and in 70 of 2,284 patients (3.06%) in the enoxaparin group (relative risk [RR] with apixaban 0.87; 95% CI 0.62–1.23; $p = 0.44$). The primary safety outcome was major bleeding; during the 30-day treatment period, this outcome occurred in 0.47% of patients receiving apixaban and in 0.19% of patients receiving enoxaparin (RR 2.58; 95% CI 1.02–7.24; $p = 0.04$). Major plus non-major clinically relevant bleeding occurred in 2.67% versus 2.08% of patients, respectively (RR 1.28; 95% CI 0.93–1.76).

The study designs of MAGELLAN and ADOPT were broadly similar (10, 42, 43). The two studies both enrolled acutely ill medical patients at risk of VTE, had a comparator arm in common – enoxaparin 40 mg od for 10 ± 4 days (MAGELLAN) or 6–14 days (ADOPT) – and evaluated extended-duration thromboprophylaxis. The primary efficacy outcome was also similarly defined for the two studies. However, the outcomes of the studies differed; in the MAGELLAN study, extended-duration rivaroxaban was shown to be significantly more effective than standard-duration enoxaparin for VTE prevention (10), whereas in ADOPT, extended-duration apixaban was shown to be not superior to enoxaparin (43). In both studies the risk of bleeding was increased with extended-duration regimens.

Most evidence for VTE prophylaxis in patients with cancer comes from subgroup analyses of general surgery studies. There is a need for studies of VTE prophylaxis in patients with cancer alone that will differentiate between ambulatory and hospitalised cancer patients. In one of the few investigations of ambulatory patients with advanced cancer, the PROTECHT (PROphylaxis of ThromboEmbolic events during CHEmoTherapy) study showed that the LMWH nadroparin given for the duration of chemotherapy up to four months significantly reduced the incidence of thromboembolic events compared with placebo (2.0% vs. 3.9%, respectively; $p = 0.02$), with no significant difference in the rates of major bleeding events (59). Trials of the newer oral anticoagulants rivaroxaban

(MAGELLAN study) and apixaban (ADOPT study) include patients with cancer, and subgroup analyses of these data will help to increase our understanding of the potential role of new oral anticoagulants in VTE prevention in patients with cancer.

Discussion

The benefits of both short (after TKR) and extended (after THR and HFS) pharmacological thromboprophylaxis after major orthopaedic surgery are well established and this is reflected in VTE prevention guidelines (3). In hospitalised acutely ill medical patients at risk of VTE, clinical trials have shown that short-term (6–14 days) thromboprophylaxis reduces the risk of VTE, although the optimal duration of thromboprophylaxis in these patients is not known.

The average length of hospital stay for critical care, medical, and surgical patients at risk of VTE is only 5.3 days (60), meaning that patients who discontinue thromboprophylaxis when discharged from hospital are at continued risk of VTE. Therefore, there is a clinical need for anticoagulants that are effective and convenient to use, particularly in the outpatient setting. In addition, from an economic perspective, a reduction in VTE rates that is achieved by using extended-duration prophylaxis compared with standard-duration therapy in at-risk medical and surgical patients could be more cost-effective (20, 61).

Despite the availability of effective anticoagulant therapies and guideline recommendations, many patients (both surgical and non-surgical) do not receive appropriate VTE prophylaxis in both the inpatient and post-discharge settings (3, 60, 62, 63). One study found that an estimated 36.8% of all at-risk patients did not receive any thromboprophylaxis in hospital (60). Another study indicated that 24.9% of patients after medical disease or surgery who were at risk of VTE did not receive thromboprophylaxis in post-acute care facilities, and in an additional study only 54.4% of orthopaedic surgery patients had filled a prescription for thromboprophylaxis 30 days after discharge (58, 64). A reason for suboptimal thromboprophylaxis in these patient groups may be the limitations of traditional anticoagulants, such as the need for daily subcutaneous injections of UFH, LMWH, or fondaparinux – posing a particular problem with compliance in the outpatient setting – or the requirement for routine coagulation monitoring, or the presence of food and drug interactions (65).

The newer oral anticoagulants – rivaroxaban, apixaban, and dabigatran etexilate – may have an advantage over parenteral agents, particularly for patients who require prolonged thromboprophylaxis, because they can be administered orally as a fixed dose without routine coagulation monitoring. These agents have demonstrated superior efficacy for VTE prevention after THR or TKR surgery without increasing the risk of bleeding (28–31, 34–37, 39). In addition, both extended-duration rivaroxaban and apixaban have been evaluated compared with standard-duration enoxaparin for VTE prevention in hospitalised acutely ill medical patients; rivaroxaban showed superior efficacy and apixaban showed simi-

lar efficacy to enoxaparin (10, 42, 43). Rivaroxaban, but not apixaban, recorded a significant increase in the risk of clinically relevant bleeding, compared with enoxaparin.

Most clinical data for the newer oral anticoagulants have demonstrated equal or superior efficacy compared with LMWHs (66). However, the risk of bleeding complications persists, reinforcing the importance of evaluating the full benefit–risk profile of an antithrombotic agent when considering its role in real-life clinical practice (66).

The increased risk of bleeding observed in acutely ill medical patients receiving extended thromboprophylaxis compared with major orthopaedic surgery patients is likely a result of the differing patient populations. Data from the IMPROVE registry identified factors associated with increased bleeding risk in acutely ill patients; these factors include active gastroduodenal ulcer, prior bleeding, and low platelet count. Risk factors for bleeding also included increased age, hepatic or renal failure, intensive care unit stay, central venous catheter, rheumatic disease, cancer, and male gender (67). In comparison with hospitalised acutely ill medical patients, patients undergoing elective major orthopaedic surgery procedures are likely to be younger and fitter and therefore at reduced risk of bleeding events.

The characteristics of the newer oral anticoagulants may increase adherence to thromboprophylaxis guidelines, thereby reducing rates of VTE and consequently morbidity and mortality (3). The evidence provided by the large randomised trials of these newer oral anticoagulants is likely to contribute to updated guidelines and recommendations for VTE prevention in the future. However, further research is still necessary in acutely ill medical patients to determine if there are patient subgroups that might benefit from extended thromboprophylaxis.

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Conflicts of interest

Dr Ageno has received honoraria from Bayer HealthCare, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, and sanofi-aventis. Dr Spyropoulos has received honoraria as a consultant for Bayer HealthCare, Eisai, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and sanofi-aventis. Dr Spyropoulos is also on the Drug Safety Monitoring Board for Astellas and on the Steering Committee for Bayer HealthCare. Dr Turpie has been a consultant to Bayer HealthCare, Johnson & Johnson, Astellas, Portola, and Takeda.

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