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REVIEW

New anticoagulants for the prevention of venous thromboembolism

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Cecilia Becattini
Alessandra Lignani
Giancarlo Agnelli

Internal and Cardiovascular Medicine and Stroke Unit, University of Perugia, Italy

Abstract: Anticoagulant drugs have an essential role in the prevention and treatment of thromboembolic diseases. Currently available anticoagulants substantially reduce the incidence of thromboembolic events in a number of clinical conditions. However, these agents have limitations that strengthen the case for the development of new anticoagulants. An ideal anticoagulant should be at least as effective as those currently in use, as well as safe, simple to use, and widely applicable.

The majority of new anticoagulants currently under investigation are small molecules with a selective and direct anti-Xa or antithrombin action, allowing oral administration in fixed doses. These new agents are in different phases of clinical development. The anti-Xa agent rivaroxaban and the antithrombin agent dabigatran are already available for the prophylaxis of venous thromboembolism in some countries. Apixaban is in an advanced phase of clinical development and several anti-Xa agents are currently approaching phase III clinical trials. Promising results in terms of efficacy and safety profiles have been obtained with these agents in different clinical conditions. Differences in pharmacokinetics and pharmacodynamics could offer the potential for individualized anticoagulant therapies in the near future.

Keywords: anticoagulant therapy, antithrombotic therapy, anticoagulants, direct thrombin inhibitors, factor Xa inhibitors

Introduction

Antithrombotic prophylaxis is essential in order to reduce morbidity (symptomatic and asymptomatic venous thromboembolism) and mortality (overall mortality and fatal pulmonary embolism) in patients at risk for venous thromboembolism (VTE).[1] The risk of bleeding complications is the trade-off for antithrombotic efficacy with all anticoagulant agents.

Heparin, either unfractionated (UFH) or low molecular weight (LMWH), fondaparinux and warfarin have been shown to be very effective for the prophylaxis of VTE. However, the parenteral route of administration can be a limitation to the use of heparin or fondaparinux, while the need for laboratory monitoring and ongoing dose adjustment is the main limitation to the use of warfarin.

Newer anticoagulant agents with the potential for oral administration in fixed doses without the need for regular laboratory monitoring and dose adjustments, or significant food and drug interactions, should improve the use of antithrombotic prophylaxis. Indeed, nearly half of the patients undergoing major surgery or hospitalized for medical illnesses do not receive appropriate antithrombotic prophylaxis.[2]

Correspondence: Cecilia Becattini
Internal and Cardiovascular Medicine and Stroke Unit, University of Perugia, Italy
Tel +39 075 578 6424
Fax +39 075 578 2436
Email cecila.becattini@unipg.it

Several new anticoagulant agents are currently in various phases of clinical development for the prophylaxis of VTE. This paper reviews the evidence for the efficacy and safety of the new anticoagulants for VTE prophylaxis in different clinical settings.

Risk stratification

Risk stratification is essential to identify candidates for antithrombotic prophylaxis (Table 1). VTE complications occur in 10% to 40% of patients admitted with a medical illness or undergoing general surgery, and in 40% to 60% of patients undergoing orthopedic surgery.[1] The risk of VTE varies according to both patient-related and surgery-related risk factors. Patient-related risk factors include age, obesity, hormonal therapy, cancer, previous VTE, molecular thrombophilia, and chronic venous insufficiency. Surgery-related risk factors include type of surgery (eg, general, orthopedic, minor, major), length of surgery, and type of anesthesia. An individual's risk of VTE increases in the presence of multiple risk factors. The duration of postoperative immobilization and the occurrence of perioperative complications are additional risk factors for VTE in patients undergoing surgery.[3]

Major orthopedic surgery, eg, elective total knee replacement (TKR), hip replacement (THR) and hip fracture repair put patients at highest risk of VTE complications. Pulmonary embolism (PE) is the main cause of death in these patients, and is the most common cause of readmission to the hospital following THR.[4] However, fatal PE is uncommon after major orthopedic surgery if antithrombotic prophylaxis is used.[5,6] Minor arthroscopic procedures are associated with a lower risk of VTE than conventional orthopedic surgery.[7]

Patients hospitalized for a medical illness have an approximately eight-fold risk of VTE compared with the general population.[8,9] VTE, proximal DVT, and fatal VTE occur in 10% to 20%, 4% to 5%, and 1% of all patients hospitalized for medical illnesses, respectively.[7,10–11] Previous VTE, stroke, heart failure, chronic obstructive.pulmonary disease, sepsis, and bed rest are risk factors for VTE in medical patients.[10] The incidence of VTE in patients with cancer varies from 4% to 20%, and is a leading cause of death in these patients.[12,13] The risk of VTE in cancer patients is higher while in hospital for medical illnesses, during chemotherapy, and/or surgery.[14–16]

New anticoagulants

New anticoagulant agents under clinical development have been developed using advanced molecular technology that enables their effect to be targeted to a selected step or enzyme in the coagulation cascade.[17–19] The large majority of new anticoagulants under clinical development are oral anti-Xa or anti-thrombin agents. Pharmacodynamic features of the newer anticoagulants are shown in Table 2.

Table 1 Risk stratification for the incidence of VTE

Risk level	Distal DVT	Prox DVT	Fatal PE	DVT total	Patients	Antithrombotic prophylaxis
Low	<10%	<1%	<0.1%	<10%	Minor surgery in mobile patients (eg, arthroscopic surgery)	Prophylaxis recommended only for patients with additional risk factors
				<10%	Medical patients who are fully mobile	No prophylaxis recommended
Moderate	10%–40%	1%–10%	0.1%–1%	10%–40%	General, gynecologic, urologic surgery	LMWH, UFH or fondaparinux
				10%–40%	Medical patients, bed rest, sick	LMWH, UFH or fondaparinux recommended for acutely ill hospitalized medical patients with additional risk factors*
High	40%–80%	10%–30%	>1%	40%–80%	Hip or knee arthroplasty	LMWH, fondaparinux or adjusted-dose vitamin K antagonists
				40%–80%	Hip fracture surgery	
				40%–80%	Major trauma, spinal cord injury	LMWH or UFH

*Congestive heart failure, severe respiratory disease or who are confined to bed.
Abbreviations: DVT, deep vein thrombosis; LMWH, low molecular weight heparin; prox, proximal; PE, pulmonary embolism; UFH, unfractionated heparin.

Table 2 Main features of new anticoagulants

Drug	Class	Pro-drug	Route of administration	Bioavailability	Liver metabolism	Excretion	Drug or food interaction	Half life	Laboratory monitoring	Direct	Selective	Reversible	Competitive
Rivaroxaban[19–21]	anti-Xa	no	oral	80%	CYP3A4	kidney 2/3 biliary 1/3	low	9 h in young 12–16 inelderly	no	yes	yes	yes	yes
Razaxaban[29]	anti-Xa	no	oral	NR	NR	kidney	NR	30 m–6 h	no	yes	yes	yes	NR
Apixaban[22–24]	anti-Xa	no	oral	50%–80%	CYP3A4	biliary 75% kidney 25%	low	12 h	no	yes	yes	yes	NR
LY517717[28]	anti-Xa	no	oral	43%–88%	no	mainly GI	NR	25 h	no	yes	yes	NR	yes
Edoxaban[26]	anti-Xa	NR	oral	45%	NR	NR	NR	9–11 h	no	yes	yes	NR	yes
Betrixaban[25]	anti-Xa	no	oral	47%	no	biliary 85% kidney 5%	minimal	20 h	no	yes	yes	yes	yes
YM150[27]	anti-Xa	no	oral	25%–82%	NR	NR	low	NR	no	yes	yes	NR	NR
Eribaxaban[30]	anti-Xa	NR	oral	NR	NR	NR	NR	NR	no	yes	yes	yes	yes
TAK442[33]	anti-Xa	NR	oral	NR	NR	NR	NR	NR	no	yes	NR	NR	NR
GW813893	anti-Xa	NR	oral	NR	NR	NR	NR	NR	no	NR	NR	NR	NR
Dabigatran[31]	anti-II	yes	oral	6.5%	3.5%–5%	kidney 80%	amiodarone, chinidine	single dose: 7–9 h multiple doses: 15 h	no	yes	yes	yes	NR
AZD0837/ AVE5026[32]	anti-Xa anti-II	yes	sc	NR	NR	NR	NR	16–20 h	no	NR	NR	yes	yes

Abbreviations: GI, gastrointestinal; h, hours; m, minutes; NR, not reported; Plt, piastrine; sc, subcutaneous.

Orthopedic surgery: Clinical trials with new anti-Xa agents

A number of new anti-Xa and anti-thrombin agents are currently under evaluation for the prophylaxis of VTE in patients undergoing orthopedic surgery.

Rivaroxaban

Three Phase II, randomized, dose-ranging studies have been performed with rivaroxaban (initiated 6–8 hours post-surgery) in comparison with enoxaparin (using European or North American dosing regimens) in patients undergoing major orthopedic surgery (see Table 3). Two studies included patients undergoing THR and one study included patients undergoing TKR.[34–36] The primary efficacy endpoint used in these studies was the composite of any DVT (proximal and/or distal), confirmed nonfatal PE, and all-cause mortality. In all studies treatment was continued until mandatory bilateral venography 5–9 days after surgery. Based on the results of these studies, the 10 mg once daily regimen of rivaroxaban was selected for investigation in Phase III studies.

The Phase III development program for rivaroxaban comprised four Phase III clinical trials, known as the REgulation of Coagulation in major Orthopedic surgery reducing the Risk of DVT and PE (RECORD) studies, assessing the efficacy and safety of rivaroxaban 10 mg once daily compared with enoxaparin given at US or European doses. The primary composite efficacy endpoint of the RECORD studies was any DVT, nonfatal PE, or death from any cause. The RECORD 1 and RECORD 3 studies showed that rivaroxaban started postoperatively was significantly more effective than enoxaparin started preoperatively in patients undergoing THR and TKR.[37–38] The absolute risk reduction of the primary endpoint was 2.6% at 36 days in RECORD 1 and 9.2% at two weeks in RECORD 3, with similar safety profiles. In RECORD 2, extended (five-week) prophylaxis with rivaroxaban was compared with short-term (10–14 days) prophylaxis with enoxaparin in patients undergoing THR.[39] As expected, the study showed that extended prophylaxis with rivaroxaban is superior to short-term prophylaxis with enoxaparin in patients undergoing THR, without safety concerns. In RECORD 4, rivaroxaban was compared with enoxaparin, both started postoperatively and continued for 10–14 days in patients undergoing TKR.[40] Rivaroxaban was significantly more effective than enoxaparin (incidence of primary efficacy outcome at day 17 after surgery 6.9% and 10.1% in patients randomized to rivaroxaban or enoxaparin, respectively) in patients undergoing TKR. Major bleeding occurred in 0.7% patients randomized to rivaroxaban and in 0.3% patients randomized to enoxaparin.

A pooled analysis of the four RECORD studies has been performed to assess the clinical benefit of rivaroxaban compared with enoxaparin in terms of hard clinical endpoints. The analysis showed that rivaroxaban is more effective than enoxaparin for the prevention of symptomatic VTE and all-cause death in patients undergoing major orthopedic surgery, irrespective of age, weight, gender, or renal function.[41] Rivaroxaban reduced the composite endpoint of symptomatic VTE, cardiovascular events, all-cause mortality, and major bleeding significantly more than enoxaparin ($P = 0.004$). A similar effect was observed in the incidence of symptomatic VTE and/or death at 10–14 days (0.47% versus 0.97%; $P = 0.001$) and for the total study duration (0.81% versus 1.63%; $P < 0.001$). However, rivaroxaban was associated with a higher incidence of major bleeding than enoxaparin at 10–14 days (0.34% versus 0.21%) and for the total study duration (0.44% versus 0.27%).[42] Further studies should address the issue of the cardiovascular rebound phenomenon to establish the safety of rivaroxaban.[43] Based on the results of the RECORD studies, rivaroxaban has been recently licensed for the prevention of VTE after elective hip and knee replacement in Europe and Canada. A Phase IV clinical trial is ongoing to assess additional information on the risk-benefit profile of rivaroxaban (NCT00831714 www.clinicaltrial.gov).

Apixaban

Apixaban was compared with enoxaparin (30 mg twice daily) and warfarin (INR 1.8–3.0) in a dose-finding study in 1238 patients undergoing TKR.[44] All apixaban groups had lower primary efficacy event rates (composite of VTE [assessed by mandatory venography] and all-cause mortality during treatment) than either comparator. Based on these results, apixaban 2.5 mg twice daily was selected for Phase III development.

Three Phase III trials have been designed to explore the efficacy and safety of apixaban for the prevention of thromboembolism after major orthopedic surgery (ADVANCE program). The primary efficacy outcome of these studies was the composite of DVT (by venography or diagnosed on symptoms), PE, and death from any cause during the treatment period. In the ADVANCE 1 trial apixaban did not meet the criteria for noninferiority compared with enoxaparin for prevention of VTE in patients undergoing TKR.[45] The primary efficacy outcome occurred in 9% of patients in the apixaban group and in 8.8% in the enoxaparin group.

Table 3 Efficacy and safety results with new Xa inhibitors in different clinical indications

Trial/drug	Phase	Drug	Comparator	Indication	Primary efficacy outcome	Major bleeding definition	Results
OdiXa-knee[34]	II	Rivaroxaban 2.5, 5, 10, 20, 30 bid	Enoxaparin 30 mg bid	TKR	Any DVT, nonfatal PE, all cause Mortality	Standard + bleeding warranting treatment cessation or leading to reoperation	All doses showed potential efficacy; dose effect for bleeding complications
OdiXa-hip[35]	II	Rivaroxaban 2.5, 5, 10, 20, 30 bid	Enoxaparin 40 mg od	THR			No significant dose-response relationship for efficacy significant dose-response relationship for safety
Rivaroxaban[36]	II	Rivaroxaban 5,10, 20, 30, 40 mg od	Enoxaparin 40 mg od	THR			
RECORD1[37]	III	Rivaroxaban 10 mg, 5 weeks	Enoxaparin 40 mg od 5 weeks	THR	Any VTE, all cause mortality	Fatal, involved a critical organ, or required re-operation; or clinically extra-surgical site bleeding associated with a decrease in the hemoglobin level of ≥2 g/dL or requiring infusion ≥2 units of blood	Superior efficacy of rivaroxaban similar safety
RECORD2[33]	III	Rivaroxaban 10 mg, 5 weeks	Enoxaparin 40 mg od 10–14 days	THR			
RECORD3[38]	III	Rivaroxaban 10 mg, 10–14 days	Enoxaparin 40 mg od 10–14 days	TKR			
RECORD4[40]	III	Rivaroxaban 10 mg, 10–14 days	Enoxaparin. 30 mg bid, 10–14 days	TKR			
Meta-analysis RECORD[41,42]		Rivaroxaban 10 mg	Enoxaparin 40 mg od enoxaparin 30 mg bid	THR, TKR	Symptomatic VTE, cardiovascular events, all-cause mortality and major bleeding		Superior efficacy of rivaroxaban similar safety
Razaxaban[29]	II	Razaxaban 25–50–75–100 mg	Enoxaparin 30 mg bid	TKR	DVT and symptomatic VTE	Major bleeding	Effective at any dosage; highest doses ... 5 associated with more bleedings
Apixaban[44]	II	Apixaban 5, 10, 20 mg od or bid divided dose	Enoxaparin 30 mg bid warfarin (INR 1.8–3)	TKR	Any VTE, all cause mortality	Standard + need to discontinue study medication	Effective dose effect in efficacy and safety
ADVANCE 1[45]	III	Apixaban 2.5 mg bid 10–14 days	Enoxaparin 30 mg bid, 10–14 days	TKR	Any VTE all cause mortality	Standard + bleeding into operated joint, requiring re-operation; intramuscular bleeding with compartment syndrome	Apixaban inferior to enoxaparin improved safety
ADVANCE 2[46]	III	Apixaban 2.5 mg bid	Enoxaparin 40 mg	TKR		Standard + bleeding into operated joint requiring re-operation, need to discontinue study medication; pericardial	Superior efficacy of apixaban

(*Continued*)

Table 3 (*Continued*)

Trial/drug	Phase	Drug	Comparator	Indication	Primary efficacy outcome	Major bleeding definition	Results
EXPERT[47]	II	Betrixaban 15/40 mg bid, 10–14 days	Enoxaparin 30 mg bid, 10–14 days	TKR	Any VTE	Fatal; involving vital organs; requiring additional surgery or a new therapeutic procedure; BI ≥ 2 and clinically significant nonmajor bleeding	Good safety and efficacy profile
Edoxaban[48]	II	Edoxaban 5, 15, 30, 60 mg	Placebo	TKR	Any VTE	Major and clinical relevant bleeding	Dose effect for safety and efficacy
STARTS II[49]	II	Edoxaban 15, 30, 60,90 mg	Dalteparin	THR		Major and clinically relevant bleeding	Dose effect for safety bleedings only with edoxaban
ONYX 1[27]	II	YM 150 3, 10, 30 and 60 mg	Enoxaparin 40 mg	THR	Any VTE	Standard + attributable BI ≥ 2.0 or CRNM	Safe and effective
ONIX II[50]	II	YM150 5, 10, 30, 60, 120 mg	Enoxaparin 40 mg	THR	DVT, symptomatic VTE, PE, death	Standard + attributable BI ≥ 2.0 or CRNM	Dose effect for efficay
LY517717[28]	II	LY517717 25, 50, 75, 100, 125, 150 mg	Enoxaparin 40 mg	THR TKR	Any VTE	Standard + associated with a BI ≥ 2 or required surgical intervention	Noninferiority similar safety
Eribaxaban [30]	II	Eribaxaban 0.1,0.3, 0.5, 1.0, 2.5, 4.0,10 mg	Enoxaparin 30 mg bid	TKR	Any VTE	Total bleeding	Nonsignificant increase of total bleeding
TREK[32]	II	AVE5026 5, 10, 20, 40, 60 mg qd	Enoxaparin 40 mg	TKR	Any VTE	Standard + surgical or nonsurgical site bleeding leading to intervention; nonsurgical site overt bleeding with a BI ≥ 2	Dose effect of AVE5026 for efficacy and safety

Notes: Standard: clinically overt bleeding associated with a fall in hemoglobin >2 g/dL within 24 hours, leading to transfusion of ≥2 units of blood; fatal bleeding; bleeding into a critical organ (including retroperitoneal, intracranial, intraocular, or intraspinal bleeding).

Abbreviations: BI, bleeding index (number of blood units transfused + pre-bleeding minus post-bleeding hemoglobin (g/dL); bid, twice daily; CRNM, clinically relevant nonmajor bleeding; DVT, deep vein thrombosis; qd, four times daily; THR, total hip replacement; TKR, total knee replacement.

Major or clinically relevant nonmajor bleeding occurred in 2.9% of patients in the apixaban group and in 4.3% in the enoxaparin group ($P = 0.03$). Major bleeding occurred in 0.7% of patients in the apixaban group and in 1.4% in the enoxaparin group ($P = 0.053$).

In the ADVANCE 2 trial apixaban was compared with enoxaparin in patients undergoing TKR.[46] The incidence of the primary efficacy outcome was 15.1% in the apixaban group and 24.4% in the enoxaparin group (relative risk 0.62, 95% CI 0.51–0.74). Proximal DVT, symptomatic nonfatal PE, and VTE-related death occurred in 1.1% of patients given apixaban and in 2.2% of patients given enoxaparin (relative risk 0.50, 95% CI 0.26–0.97). Clinically relevant bleeding (major or clinically relevant nonmajor) occurred in 3.5% and 4.8% of the patients given apixaban and enoxaparin, respectively ($P = 0.09$). A Phase III randomized, double-blind study has been recently completed aimed at assessing the relative efficacy and safety of apixaban and enoxaparin for 35 days in patients undergoing elective THR surgery (www.clinicaltrial.gov NCT00423319).

New anti-Xa in Phase II trials

The oral anti-Xa betrixaban has been compared with enoxaparin, both started postoperatively in patients undergoing TKR.[47] DVT on mandatory unilateral venography or symptomatic proximal, or PE was reported through to day 14 in 20%, 15%, and 10% of patients receiving increasing doses of betrixaban or enoxaparin, respectively. No bleeding complications were reported in the betrixaban 15 mg group. Major bleeding occurred in 2.3% of patients in the enoxaparin group.

Two Phase II studies have explored the efficacy and safety of edoxaban for the prevention of VTE in major orthopedic surgery. Edoxaban reduced the incidence of VTE in a dose-dependent fashion in comparison with placebo, without a significant increase in bleeding complications in patients undergoing TKR.[48] Edoxaban was compared with dalteparin in patients undergoing THR.[49] VTE occurred in 43.3% of patients in the dalteparin group and in 28.2%, 21.2%, 15.2%, and 10.6% of patients receiving edoxaban, respectively. No bleeding was reported in the dalteparin group. The incidence of major or clinically significant nonmajor bleeding in the edoxaban groups ranged from 1.6% with lower doses to 2.3% for higher doses.

The efficacy and safety of YM150 for the prevention of VTE in patients undergoing THR was investigated in a Phase II study.[27] Patients were randomized to once-daily YM150 starting 6–10 hours after hip replacement or to receive subcutaneous enoxaparin for 7–10 days. A significant dose-related trend in the incidence of VTE (confirmed symptomatic events and/or positive bilateral venography on the last treatment day) was observed with YM150. Three clinically relevant nonmajor bleedings were observed, one in the 3 mg and two in the 10 mg YM150 dose groups. The Phase II ONYX-2 study confirmed a significant decrease in the incidence of DVT, symptomatic VTE, PE, and death with increasing doses of YM150 in patients undergoing THR surgery.[50] A number of Phase II and Phase III studies have been designed testing this agent, of which some are completed and some are currently ongoing. The aim of these studies is to evaluate the efficacy and safety of various doses of YM150 for the prevention of VTE in patients undergoing major orthopedic surgery in comparison with enoxaparin or warfarin (NCT00902928, NCT00913120, NCT00937911, NCT00408239, NCT00917254, NCT00595426 www.clinicaltrials.gov).

The oral anti-Xa razaxaban has been compared with twice daily 30 mg enoxaparin in patients undergoing elective knee surgery.[29] Razaxaban was effective at any evaluated dosage, but highest doses were associated with more bleedings than enoxaparin. No further study has been conducted with razaxaban.

In patients undergoing THR or TKR, prophylaxis with LY517717 resulted in a dose-dependent decrease in the incidence of VTE. The incidences of overall, symptomatic, or asymptomatic VTE was 19%, 19%, and 16% with increasing doses of LY517717, respectively, compared with 21% for enoxaparin. All the doses of LY517717 met the predefined criteria for noninferiority compared with enoxaparin for the prevention of VTE after TKR or THR, with similar rates of bleeding complications.[28] No studies are currently ongoing with this agent in patients undergoing orthopedic surgery.

In a dose-finding study, the efficacy of different doses of eribaxaban has been compared with that of enoxaparin in patients undergoing TKR.[30] VTE occurred in 37%, 37%, 29%, 19%, 14%, 1.4%, and 11% of patients receiving increasing doses of eribaxaban, respectively, compared with 18% of patients receiving enoxaparin. This study showed a nonsignificant dose-related increase in the incidence of total bleeding, mainly accounted for by minor bleeding.

A dose-finding study is currently underway to assess the efficacy and safety of TAK-442 in comparison with enoxaparin for the prevention of VTE after TKR (NCT00641732 www.clinicaltrial.gov). A Phase II study has also been designed to assess the efficacy and safety of GW813893 in

the prophylaxis of VTE following TKR. (NCT00541320 www.clinicaltrial.gov).

In a Phase II study, 690 patients undergoing TKR surgery were randomized to AVE5026 or enoxaparin.[32] A significant dose-response effect was observed with AVE5026, the incidence of total VTE ranging from 44.1% to 5.3%. VTE occurred in 35.8% of patients receiving enoxaparin. The three highest doses of AVE5026 were significantly more effective than enoxaparin in reducing VTE. Also, a significant dose-response for AVE5026 was seen for major bleeding. The 20 mg dose of AVE5026 was selected for future investigation in Phase III studies of the prevention of VTE in patients undergoing THR surgery and hip fracture surgery (NCT00697099, NCT00721760 www.clinicaltrial.gov). The results of a multicenter, randomized, double-blind study comparing the efficacy and safety of AVE5026 with that of enoxaparin for the prevention of VTE in patients undergoing elective knee replacement surgery will be available in the near future (NCT00718224 www.clinicaltrial.gov).

Clinical trials with the new antithrombin agent dabigatran

The clinical development program for dabigatran in orthopedic surgery is almost completed (Table 4). The Phase II program comprises the dose-finding BISTRO I and II studies.[51,52] A significant dose-dependent decrease in VTE and an increase in major bleeding were observed with increasing doses of dabigatran in patients undergoing THR or TKR. The 150 mg and 220 mg once daily doses were selected for clinical development in the Phase III program.

In the RE-NOVATE study, dabigatran (starting 1–4 hours after surgery with half the dose) was compared with enoxaparin (starting the evening before surgery) both given for 28–35 days in 3494 patients undergoing THR.[53] The composite of total VTE (symptomatic and asymptomatic) and death from all causes occurred in 6.7% patients in the enoxaparin group versus 6.0% and 8.6% of the patients in the dabigatran 220 mg and 150 mg groups, respectively. Both dabigatran doses met the criteria for noninferiority in comparison with enoxaparin, with no significant difference in major bleeding. In the RE-MODEL study 2076 patients undergoing TKR were randomized to receive dabigatran (starting 1–4 hours after surgery with half the dose) or subcutaneous enoxaparin.[54] In this study, total VTE (symptomatic and asymptomatic) and death during treatment occurred in 37.7% of the patients in the enoxaparin group, compared with 36.4% and 40.5% of the patients in the dabigatran 220 mg or 150 mg groups, respectively. Both doses were found to be noninferior in comparison with enoxaparin. The incidence of major bleeding was similar across the three groups.

In the RE-MOBILIZE study, dabigatran (starting after surgery with half the dose) was compared with enoxaparin for 12 to 15 days after TKR.[55] Total VTE and all-cause mortality occurred in 31% and 34% of the patients in the dabigatran 220 mg and in the 150 mg groups, respectively, compared with 25% of patients receiving enoxaparin. In this study dabigatran did not achieve the criteria for noninferiority. The safety profile was similar in all three groups (0.6% in dabigatran groups and 1.4% in enoxaparin groups).

The results of the RE-MODEL, RE-NOVATE and RE-MOBILIZE studies were recently pooled in a meta-analysis that confirmed the noninferiority of dabigatran in comparison with enoxaparin 40 mg once daily in patients undergoing major orthopedic surgery, with a similar safety profile.[56] No significant differences in the incidence of liver enzyme elevation or coronary events between the treatment groups were observed in the Phase III development program. A trend toward increased gastrointestinal bleeding has been suggested with dabigatran in long-term indications.

The clinical development of dabigatran in orthopedic surgery is continuing with a Phase III study on the efficacy and safety of dabigatran (110 mg on the day of surgery followed by 220 mg once daily), compared with enoxaparin 40 mg for 28–35 days, in patients undergoing elective THR (NCT00657150 www.clinicaltrials.gov). In another study, patients undergoing TKR will receive in-hospital prophylaxis with nadroparin and dabigatran (110 mg twice daily) for 10 days after discharge from hospital (NCT00868179 www.clinicaltrials.gov).

Observational Phase IV studies of the safety and efficacy of dabigatran in predefined subpopulations of patients at increased risk of bleeding or VTE or with moderate renal impairment (creatinine clearance 30–50 mL/min) in a Mexican population are also about to start (NCT00847301, NCT00846807, NCT00967447 www.clinicaltrials.gov). Dabigatran has recently been licensed in Europe and in Canada for thromboprophylaxis in patients undergoing hip and knee replacement.

Prevention of VTE in general surgical patients

Two studies are currently ongoing aimed at assessing the efficacy and safety of new anticoagulant agents in the prevention of VTE in patients undergoing major abdominal

Table 4 Efficacy and safety results with new II inhibitors in different clinical indications

Trial/drug	Phase	Drug	Comparator	Indication	Primary efficacy outcome	Major bleeding definition	Results
BISTRO I[51]	II	Dabigatran 12.5, 25, 50,100,150, 200, 300 mg bid or 150, 300 mg od	No comparator	THR	Any DVT	Standard	Effective with no dose effect no major bleedings
BISTRO II[52]	II	Dabigatran 50,150, 225 mg bid or 300 mg od	Enoxaparin 40 mg od	THR TKR	Any VTE	Standard + surgical or nonsurgical site bleeding warranting treatment cessation or re-operation	Dose-dependent efficacy and safety VTE lower in 150, 225 mg bid and 300 mg od
RE-MODEL[54]	III	Dabigatran 150 or 220 mg 28–35 days	Enoxaparin 40 mg 6–10 days	TKR	Any VTE and death from all causes		Noninferiority of dabigatran similar safety
RE-MOBILIZE[55]	III	Dabigatran 150–220 mg 28–35 days	Enoxaparin 30 mg bid 12–15 days	TKR			Inferiority of dabigatran similar safety
RE-NOVATE[53]	III	Dabigatran 150–220 mg 28–35 days	Enoxaparin 40 mg 28–35 days	THR			Noninferiority of dabigatran similar safety
Dabigatran metanalysis[56]		Dabigatran 220 mg, 150 mg	Enoxaparin 40 mg Enoxaparin 30 mg	TKR THR	Any VTE and death from all causes		Noninferior to enoxaparin 40 mg Similar safety

Notes: Standard: clinically overt bleeding associated with a fall in hemoglobin >2 g/dL within 24 hours, leading to transfusion of ≥2 units of blood; fatal bleeding; bleeding into a critical organ (including retroperitoneal, intracranial, intraocular, or intraspinal bleeding).
Abbreviations: THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.

surgery. One is a Phase III, randomized, double-blind study comparing the efficacy and safety of AVE5026 (given once daily by subcutaneous injection) with enoxaparin (40 mg once daily) (NCT00679588 www.clinicaltrials.gov, see Table 5).

The other is a Phase III open-label study aimed at evaluating the efficacy and safety of the oral anti-Xa YM150 for prevention of VTE and all-cause death in patients undergoing major abdominal surgery in comparison with mechanical prophylaxis (NCT00942435 www.clinicaltrials.gov).

Prevention of VTE in medical patients

Several studies are currently ongoing or are about to start with new anticoagulant agents for the prevention of VTE in patients hospitalized for acute medical illnesses.

A Phase III study has been recently completed and the results will be available in the near future for AVE5026 in comparison with enoxaparin for the prevention of VTE in patients hospitalized for acute medical illnesses (NCT00714597 www.clinicaltrial.gov).

A randomized, double-blind trial is currently ongoing aimed at comparing the efficacy and safety of rivaroxaban (10 mg once daily) given for 31–39 days with that of enoxaparin (40 mg once daily) given for 6–14 days (NCT00571649 www.clinicaltrial.gov). The incidence of any VTE is diagnosed by compression ultrasonography is evaluated at the end of the treatment period.

A Phase III double blind study is evaluating apixaban (2.5 mg twice daily) given for 30 days plus subcutaneous placebo for 6–14 days, with respect to enoxaparin (40 mg once daily) given for 6–14 days plus oral placebo for 30 days, in patients hospitalized for medical illnesses (NCT00457002 www.clinicaltrial.gov).

Cancer patients

Several clinical trials have compared different agents for the prophylaxis of VTE in patients undergoing surgery for cancer or evaluated the need for extended out-of-hospital prophylaxis in these patients.[57–60]

A Phase II study is currently underway to assess whether apixaban (5 mg once daily for 12 weeks) administered to

Table 5 Ongoing phase II and III studies

Drug	Dose	Comparator	Duration of therapy	Phase	Indication
Apixaban	2.5 mg bid	Enoxaparin 40 mg	35 days	III	THR
YM 150	NR	Enoxaparin	NR	II III	THR (ONIX3)
YM 150	NR	Enoxaparin	NR	II	TKR (PEARL1)
YM 150	NR	Enoxaparin	NR	II III	TKR
YM 150	NR	Warfarin	NR	II	TKR (PEARL)
YM 150	NR	NR	NR	II III	THR
YM 150	NR	NR	NR	III	Hip fracture, lower extremities surgery
TAK442	10–20–40–80 mg bid or 40–80 mg od	Enoxaparin	NR	II	TKR
GW813893	NR	NR	NR		TKR
AVE5026	20 mg	Enoxaparin	7 to 10 days	III	TKR (SAVE KNEE)
AVE5026	NR	Enoxaparin	7 to 10 days	III	THR (SAVE-HIP 1)
AVE5026	NR	Enoxaparin 40 mg	7 to 10 days	III	Hip fracture surgery (SAVE-HIP 2)
Dabigatran	110 mg followed by 220 mg od	Enoxaparin 40 mg	28–35 days	III	THR (RE-NOVATE II)
AVE5026	NR	Enoxaparin 40 mg	NR	III	Major abdominal surgery
YM 150	NR	Mechanical prophylaxis	NR	III	Major abdominal surgery
Apixaban	5 mg od	Placebo	12 week	II	Metastatic cancer
AVE5026	NR	Placebo	NR	III	Cancer and chemotherapy (SAVE ONCO)
Rivaroxaban	10 mg	Enoxaparin 40 mg	31–39 days enoxaparin 6–14 days	III	Medical ill patients (MAGELLAN)
Apixaban	2.5 mg bid	Enoxaparin 40 mg	Apixaban 30 days vs enoxaparin 14 days	II	Medical ill patients (ADOPT)
AVE5026	NR	Enoxaparin	NR	III	Medical ill patients with restricted mobility

Abbreviations: bid, twice daily; NR, not reported (the studies have been described according to data reported on the web, www.clinicaltrials.gov); od, once daily.

patients with advanced or metastatic cancer for the prevention of VTE will be well tolerated compared with placebo (NCT00320255 www.clinicaltrial.gov).

A Phase III study comparing the efficacy and safety of AVE5026 (once daily subcutaneous injections) with placebo for the prevention of VTE in high-risk cancer patients undergoing chemotherapy is currently ongoing (NCT00694382 www.clinicaltrial.gov).

Conclusions

Several new anticoagulant drugs are currently in clinical development for the prophylaxis of VTE. New agents have the potential to make anticoagulant treatment and prophylaxis easier as they are mostly available for oral administration in fixed doses, have short half-lives, and rapid onset of action. Given their different mechanisms of action and pharmacokinetic properties, the new anticoagulants also offer the potential for anticoagulation to be tailored for individual patients. Whether different mechanisms of action (eg, anti-Xa or anti-IIa effect) can influence the efficacy and safety profiles of new anticoagulants is currently only speculative.

The real advantage of new anticoagulants is expected for chronic indications more than for time-limited ones. It is conceivable that the use of new anticoagulants for the prophylaxis of VTE will increase after their approval for long-term indications.

If these new agents complete clinical development and become available for clinical use, clinicians will have the potential to choose the optimal anticoagulant regimen on an individual patient basis, taking into account not only safety, efficacy, and the clinical setting, but also patient characteristics, including age, renal failure, and liver disease.

Disclosures

The authors report no conflicts of interest in this work.

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