New anticoagulants for the prevention and therapy of venous thromboembolism – a review

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Summary

Thrombin plays an essential role in haemostasis and thrombosis; therefore, anticoagulant strategies focus on direct or indirect inhibition of thrombin or factor Xa. Over the last 60 years, key players in antithrombotic treatment have been unfractionated heparin and vitamin K antagonists (VAKs), such as coumarin. New oral anticoagulants, with different mechanisms of action and administration, have the potential to promote dramatic changes in the management of patients with venous thromboembolic disease. This review provides an overview of the newer anticoagulants likely to be used in this indication.

Key words: new oral anticoagulations; venous thromboembolism; prophylaxis; therapy

Introduction

Acute venous thromboembolism (deep-vein thrombosis (DVT) or pulmonary embolism) is a common disorder with an annual incidence of approximately 1 or 2 cases per 1000 persons in the general population [1]. Short-term treatment is effective, with the risk of recurrent disease reduced from an estimated 25% to about 3% during the first 6 to 12 months of therapy [2].

Standard treatment for acute venous thromboembolism is limited by the need for parenteral heparin initially, with overlapping administration of a vitamin K antagonist.

Oral vitamin K antagonists (e.g., warfarin, acenocoumarol, phenoprocoumon, fluindione), which have been used for the past 60 years, have several limitations [3] (see accompanying editorial).

New oral anticoagulants, with different mechanisms of action, are poised to replace the vitamin K antagonists (VKA) and have the potential to promote dramatic changes in our management strategy for patients at risk for venous and arterial thromboembolic disease (fig. 1).

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New oral anticoagulants

These new drugs reach peak maximal effect within a few hours, possibly eliminating the need for a two-drug (i.e., heparins and VKAs) regimen to treat acute thromboembolism. The drugs have predictable dose responses, thus eliminating the need for routine monitoring, and they have few if any important food or drug interactions, thus simplifying management. However, they have different routes of metabolism and elimination. Renal and hepatic clearance plays a variable yet potentially important role with each drug [4].

Several new oral anticoagulants are currently under development. The three newest oral anticoagulants with the most advanced clinical trial programs are dabigatran etexilate, rivaroxaban and apixaban (table 1).

Dabigatran etexilate

Dabigatran is a univalent direct thrombin inhibitor that binds to the active site, thereby inactivating both fibrin-bound and unbound thrombin [5]. Indirect thrombin inhibitors, such as unfractionated heparin and low-molecular-weight heparin, cannot inhibit fibrin-bound thrombin. The ability to inhibit fibrin-bound thrombin is an important theoretical advantage of dabigatran over the heparins because bound thrombin can continue to trigger thrombus expansion [6]. By inhibiting thrombin, dabigatran prevents a number of events including the conversion of fibrinogen into fibrin, positive feedback amplification of coagulation activation, cross-linking of fibrin monomers, platelet activation and inhibition of fibrinolysis [7].

The absolute bioavailability of dabigatran etexilate after oral administration is only 6.5%, so relatively high doses must be given to ensure that adequate plasma concentrations are achieved. Dabigatran plasma concentration and anticoagulant effects are

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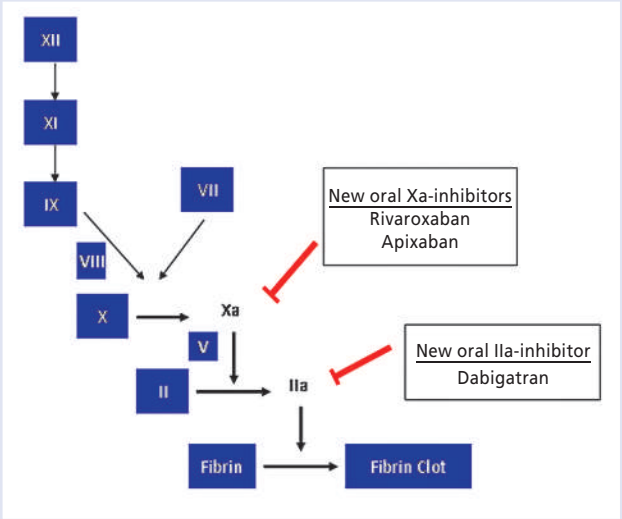

Figure 1
Sites of action of new oral anticoagulants in the coagulation cascade.

dose dependent and predictable, and peak within 0.5 to 2 hours (average, 1.5 hours) of oral administration [8].

In patients with mild hepatic impairment, the area under the curve (AUC) after a single oral dose of dabigatran etexilate was comparable to that of healthy control subjects, and the bioconversion of the prodrug was only slightly reduced. The mean terminal half-life of dabigatran after oral administration is approximately 8 hours after a single dose, and this ranges from 12 to 14 hours after multiple doses [8].

The half-life is increased to >24 hours in patients with a creatinine clearance of <30 ml/min [9], which might explain some of the side effects that recently lead to the implementation of box warning in Australia [10].

Renal excretion is the predominant elimination pathway. The consequence of reduced kidney function is elevated dabigatran plasma concentrations and a prolonged drug half-life [9]. For patients taking dabigatran who have or are at risk of developing renal impairment, regular monitoring of renal function is imperative during long-term therapy [7].

The RECOVER trial, a randomised, double-blind, noninferiority trial was conducted in 2539 patients with acute symptomatic venous thromboembolism or pulmonary embolism, who were randomised to six months of treatment with either dabigatran 150 mg twice daily or dose-adjusted warfarin therapy once daily, after initial parenteral anticoagulation [11].

A total of 30 of the 1274 patients randomly assigned to receive dabigatran (2.4%), as compared to 27 of the 1265 patients randomly assigned to warfarin (2.1%), had recurrent venous thromboembolism. The difference in risk was 0.4 percentage points (95% confidence interval [CI]: –0.8 to 1.5; p <0.001 for the prespecified noninferiority margin). The hazard ratio with dabigatran was 1.10 (95% CI: 0.65 to 1.84).

Major bleeding episodes occurred in 20 patients assigned to dabigatran (1.6%) and in 24 patients assigned to warfarin (1.9%) (Hazard ratio with dabiga-

Table 1
Characteristics of new oral anticoagulants.

Characteristics	Dabigatran etexilate	Rivaroxaban	Apixaban
Target	Thrombin	Factor Xa	Factor Xa
Prodrug	Yes	No	No
Biovailability (%)	Approximately 6.5	80–100	50–85
Time to peak drug level (hours)	0.5–2	2–4	3
HLF-life (hours)	11 h in healthy young subjects, 14–17 h in patients	5–9 h in healthy young subjects, 7–11 h in patients	9–14 h
Frequency of administration	Once or twice daily	Once daily	Twice daily
Renal excretion (%)	85	66	25
Specific antidote	No	No	No
Regulatory status	Approved in all EU and Canada for VTE prophylaxis after TKR and THR. Approved in all EU, US and Canada for the prevention of stroke and systemic embolism in patients with AF.	Approved in all EU, Canada and Switzerland for VTE prophylaxis aftr TKR and THR. In the US approved for the prevention of stroke and systemic embolism in patients with AF. Approved in all EU for DVT treatment, as well as secondary prophylaxis of DVT and PE.	Approved in EU and Switzerland for VTE prophylaxis after TKR and THR

European Union (EU), venous thromboembolism (VTE), total knee replacement (TKR), total hip replacement (THR), atrial fibrillation (AF), deep vein thrombosis (DVT), pulmonary embolism (PE).

tran: 0.82; 95% CI: 0.45 to 1.48), and episodes of any bleeding were observed in 205 patients assigned to dabigatran (16.1%) and 277 patients assigned to warfarin (21.9%; hazard ratio with dabigatran: 0.71; 95% CI: 0.59 to 0.85). The numbers of deaths, acute coronary syndromes, and abnormal liver-function tests were similar in the two groups. In the RECOVER trial, dyspepsia was more frequent in Dabigatran group, probably rather due to the formulation with Etexilate than to the dabigatran itself.

The RECOVER II trial [12] was designed to confirm and extend the original RECOVER study, which had a low rate of the primary outcome, a composite of recurrent VTE or fatal pulmonary embolism (PE). This study also included significantly more Asian patients than the original 2500-patient RECOVER trial. RECOVER II included 2568 patients with acute VTE who were treated with low molecular weight or unfractionated heparin for 5–11 days. Following heparin treatment, the patients were randomly assigned to receive dabigatran 150 mg twice daily (n = 1279) or warfarin dose-adjusted therapy (n = 1289). Both treatments were given for six months.

Regarding the primary outcome, recurrent VTE or PE occurred in 2.4% of patients treated with dabigatran and in 2.2% of patients treated with warfarin, a difference that met the prespecified noninferiority margin (p <0.0001). Subgroup analyses, including in the 537 Asian patients, all showed that dabigatran was non inferior to warfarin.

No significant differences in the number of major bleeding events between dabigatran and warfarin, at 15 versus 22 events, were observed. The number of overall bleeding events, however, was significantly lower with dabigatran than with warfarin, at 200 versus 285 events (hazard ratio: 0.67; 95% CI: 0.56–0.81). This corresponds to a 33% risk reduction for bleeding with dabigatran. No difference in mortality (n = 25 in both groups) and no difference in the rate of serious adverse events were observed between two groups.

These findings provide data to support dabigatran as a fixed dose oral treatment for acute deep-vein thrombosis and pulmonary embolism. However, experiences available so far suggest that clinical surveillance is needed with regard to renal function.

Specific information on regulatory issues, approvals and dose modifications specifically in renal impairment can be found in tables 1 and 2 [13–15].

Rivaroxaban

Factor Xa initiates the final common pathway of the coagulation cascade and results in the formation of thrombin, which catalyses additional coagulation-related reactions and promotes platelet activation. Rivaroxaban is a potent and direct inhibitor of factor Xa. It acts by inhibiting circulating factor Xa as well as factor Xa bound within the prothrombinase complex or the fibrin complex [16].

Rivaroxaban has a relatively high bioavailability (80–100%), is well tolerated and has a rapid onset of action with a predictable dose of proportional pharmacokinetics and pharmacodynamics. Its half-life is about 5–9 hours and it is predominantly excreted via the kidneys (2/3), while 1/3 is excreted via the liver [17]. Co-administration with food intake only slightly increases peak plasma concentration of rivaroxaban, and only low potential interactions with other drugs have been shown [18].

Rivaroxaban is efficient for thromboprophylaxis in orthopedic surgery and atrial fibrillation (see also tables 1 and 2) [19–23].

The EINSTEIN program consists of three randomised trials of rivaroxaban: one for the treatment of acute deep-vein thrombosis (the Acute DVT Study), one for the treatment of acute pulmonary embolism (the Acute PE Study), and one for continued treatment in patients who have received treatment for acute deep-vein thrombosis or pulmonary embolism (the Continued Treatment Study EINSTEIN-Extension). The Acute PE Study is onging [24].

Table 2
Recommendation for the use of the new oral anticoagulants in patients with renal impairment.

	Moderate renal impairment (creatinine clearance 30–50 ml/min)	Severe renal impairment (creatinine clearance <30 ml/min)
Dabigatran	EU: Treat with caution. Recommended starting dose of 75 mg, and continued at 150 mg daily, taken as two capsules of 75 mg each. US: 75 mg twice daily	Contraindicated
Rivaroxaban	EU: No dose adjustment specified. US: 15 mg daily	Contraindicated in Canada. Cautionated with creatinine clearance 15–29 ml/min, and contraindicated with creatinine clearance <15 ml/min in the European Union. US: 15 mg daily
Apixaban	No dose adjustment specified.	Cautionated with creatinine clearance 15–29 ml/min, and contraindicated with creatinine clearance <15 ml/min in the European Union

The study of rivaroxaban for treatment of acute DVT included 3449 patients without symptomatic pulmonary embolism and without initial parenteral anticoagulation: 1731 were given rivaroxaban (15 mg twice daily for the first 3 weeks, followed by 20 mg once daily for the intended 3, 6, or 12 months of treatment) and 1718 were given enoxaparin followed by vitamin K antagonist.

Results of the Phase III EINSTEIN-DVT study show that rivaroxaban is noninferior with regard to the primary outcome (36 events with rivaroxaban [2.1%], vs 51 events with enoxaparin – vitamin K antagonist [3.0%]; hazard ratio: 0.68; 95% CI]: 0.44 to 1.04; p <0.001) [24].

The EINSTEIN-Extension trial, a randomised, double-blind, placebo-controlled, superiority study, compared the efficacy and safety of rivaroxaban (20 mg once daily) and placebo in the secondary prevention of recurrent symptomatic venous thromboembolism for 6 or 12 months, and enrolled approximately 1200 patients.

The primary efficacy outcome was symptomatic recurrent VTE (i.e., the composite of recurrent DVT, nonfatal PE, and fatal PE). The principal safety outcome was major bleeding. The occurrence of clinically relevant non-major bleeding was recorded. The study was event-driven requiring a minimum of 30 confirmed recurrent events.

In the continued-treatment study, which included 602 patients in the rivaroxaban group and 594 in the placebo group, rivaroxaban had superior efficacy (8 events [1.3%], vs 42 with placebo [7.1%]; hazard ratio: 0.18; 95% CI: 0.09 to 0.39; p <0.001). Four patients in the rivaroxaban group had nonfatal major bleeding (0.7%), versus none in the placebo group (p = 0.11).

Major bleeding did not occur in placebo patients and was observed in 4 (0.7%) rivaroxaban recipients (p = 0.106). None of these bleeding events were fatal or in a critical site. Clinically relevant non-major bleeding was noted in 7 (1.2%) and 32 (5.4%) of the placebo and rivaroxaban recipients, respectively. Two (0.3%) patients in the placebo group died versus one (0.2%) in the rivaroxaban group [24].

The MAGELLAN trial compared extended prophylaxis with oral rivaroxaban and with enoxaparin in medically ill patients. At day 35, the rate of the primary efficacy outcome was significantly lower with extended rivaroxaban than with enoxaparin. However, an increase in treatment-related major and clinically relevant nonmajor bleeding with rivaroxaban was observed as compared with enoxaparin [25, 26]. Thus, the net clinical benefit was in favour of enoxaparin.

Apixaban

Apixaban is another new oral direct Factor Xa inhibitor. Apixaban has an oral bioavailability of more than 50%. Its plasma peak is achieved in about 3 hours and its half-life is about 12 hours [27]. The drug is absorbed in the gastrointestinal tract, metabolised in the liver by cytochrome-dependent and cytochrome independent mechanisms. It is excreted through the liver (approximately 2/3) and the kidney (approximately 1/3). Food does not interfere with its absorption, so the drug generates a predictable anticoagulation effect [28].

For specific information on regulatory issues and approval see tables 1 and 2 [29].

Apixaban is currently under review for stroke prevention in atrial fibrillation after positive results for stroke prevention, both in comparison to Aspirin® as well as coumadin in the AVEROSE [30] and ARISTOTLE [31] trials.

In medically ill patients the ADOPT study, a double-blind, double-dummy, placebo-controlled trial [32], tested an extended course of thromboprophylaxis with apixaban compared to a shorter course of enoxaparin. The ADOPT trial included more than 6000 patients who were hospitalised for congestive heart failure, acute respiratory failure and other medical disorders and at least one additional risk factor for venous thromboembolism and who were hospitalised for at least 3 days to receive twice-daily apixaban 2.5 mg for 30 days (n = 3255) or once-daily enoxaparin 40 mg for 6 to 14 days (n = 3273).

Among the patients who could be evaluated, 2211 in the apixaban group and 2284 in the enoxaparin group, 2.71% in the apixaban group (60 patients) and 3.06% in the enoxaparin group (70 patients) met the criteria for the primary efficacy outcome (relative risk with apixaban: 0.87; 95% CI: 0.62 to 1.23; p = 0.44). By day 30, major bleeding had occurred in 0.47% of the patients in the apixaban group (15 of 3184 patients) and in 0.19% of the patients in the enoxaparin group (6 of 3217 patients) (relative risk: 2.58; 95% CI: 1.02 to 7.24; p = 0.04).

The two major trials that investigate apixaban in the treatment of DVT and PE are presently still ongoing: The AMPLIFY trial is enrolling approximately 4800 patients with acute DVT or PE and will investigate the safety and efficacy of apixaban 10 mg twice daily for 1 week followed by 5 mg twice daily for 6 months compared to enoxaparin plus warfarin, the two drugs used as the current standard of care [33].

The AMPLIFY-EXT trial has initiated enrollment and will include approximately 2430 patients who will receive, for an extended 12-month period, apixaban 2.5 mg dose or 5 mg twice daily compared to patients taking placebo to determine the effects of apixaban on recurrent VTE [34]. Results are not expected before mid 2013.

Potential problems with the new oral anticoagulants

Bleeding events

The most worrisome complication of anticoagulant is bleeding.

By far greatest amount of new oral anticoagulants' safety data available to date were generated in orthopedic surgery trials. A recent study showed that rates of major and nonmajor clinically relevant bleeding (as the main measure of treatment safety) were similar in the rivaroxaban and warfarin groups. Bleeding that proved fatal or that involved a critical anatomical site occurred less frequently in the rivaroxaban group, mainly because of a lower rate of haemorrhagic stroke and other intracranial bleeding. In contrast, bleeding from gastrointestinal sites (e.g., upper, lower and rectal sites) occurred more frequently in the rivaroxaban group [35].

Another study showed that rivaroxaban at a dose of 10 mg per day was more effective than enoxaparin and was associated with significantly lower incidences of total venous thromboembolism and major venous thromboembolism, whereas the rates of major bleeding and clinically relevant nonmajor bleeding were similar or marginally higher [23].

Another study demonstrated that, in patients undergoing orthopedic surgery, the incidence of major bleeding and clinically relevant nonmajor bleeding was significantly lower with apixaban than with enoxaparin [36].

Studies of two dabigatran regimens (150 mg per day and 220 mg per day) in patients undergoing hip replacement showed statistically non-inferior efficacy rates and similar bleeding rates for dabigatran compared with enoxaparin [37, 38].

Drug-drug interactions with concomitant administration of certain medications may also increase the risk of bleeding. Bleeding events were higher in patients also receiving clopidrogel than in patients without clopidogrel treatment. However, these data were collected in non-surgical patients [39].

Renal impairment

The currently approved recommendations for the use of new oral anticoagulants in patients with renal insufficiency are shown in table 2 [36, 40–43].

Liver toxicity

Idiosyncratic drug reactions have been found to be the presumptive cause of more than one in ten of all cases of acute liver failure. Furthermore, drug-induced hepatic toxicity is the most common reason cited for the withdrawal of an approved drug on the market. The exact mechanisms responsible for the liver toxicity observed with an earlier introduced factor IIa inhibitor (Ximelagatran) have not been fully identified; therefore, prediction of whether newer oral direct thrombin or factor Xa inhibitors could cause similar toxicity is difficult [44]. However, the studies and market experience so far do not suggest increased liver toxicity for the new oral anticoagulants.

Cardiac toxicity

The newer anticoagulants may cause a rebound effect after treatment cessation. This may lead to increased arterial thromboembolic events. However, accurate assessment of the true potential impact of new oral anticoagulants on the rebound phenomenon may be limited in clinical trials, because the pre-specified endpoints in clinical trials are commonly short-term [45].

An increased risk of arterial adverse events, including myocardial infarction, was reported in patients following termination of ximelagatran (direct thrombin inhibitor) treatment [46]. However, the data were insufficient for a clear conclusion on the pathophysiology involved [45]. A pro-arryhthmic effect is another potential clinical concern with the newer anticoagulants but no such evidence was found for dabigatran and rivaroxaban [47, 48].

In the RECORD studies, the overall rate of cardiovascular events was similar between rivaroxaban (0.50%) and enoxaparin (0.63%) study groups [49]. Adjudicated ischaemic stroke was reported in 0.19% of patients receiving rivaroxaban and in 0.11% of the enoxaparin group. However, more ischaemic stroke events occurred after drug discontinuation in the rivaroxaban group (0.10%) than in the enoxaparin group (0.02%).

In a phase II study of VTE prophylaxis following TKR, 0.33% of patients in the apixaban group had a myocardial infarction and 0.55% had a stroke. No such events were reported in the enoxaparin patient group [50]. In the ADVANCE-1 study the incidence of cardiovascular events was low in both the apixaban and enoxaparin groups (0.1% vs 0.3%, respectively) [36].

Similar rates of myocardial infarction were reported in the recent ADVANCE-2 and ADVANCE-3 studies (<1% in both the apixaban and enoxaparin groups) [29, 51]. In the ADVANCE-2 study, stroke occurred in two patients in the apixaban group (<1%) vs none in enoxaparin group (0%) [35]. Rates of stroke were similar in the ADVANCE-3 study, at <0.1%, in the apixaban group and 0.2% in the enoxaparin group [51].

Drug and food interactions

Dabigatran is not metabolised by CYP450; however, it is a substrate for the efflux transporter P-glycoprotein, which has an impact on drug-drug interactions. Potent inducers (e.g., quinidine and rifampicin) or inhibitors (e.g., veraparamil, clarithromycin and amiodarone) of P-glycoprotein may impact dabigatran metabolism and affect its clinical efficacy and safety. Dose reduction of dabigatran to 150 mg once daily is recommended for patients on amiodarone. In the case of P-glycoprotein

inducers, caution is advised for their use because of possible reduction of dabigatran bioavailability. Concomitant use of dabigatran and anti-inflammatory drugs, such as aspirin, is not recommended [52–54].

Rivaroxaban does not inhibit or induce any major CYP450 enzymes. Rivaroxaban is also a substrate for P-glycoprotein transporters. Thus, the use of rivaroxaban is not recommended in patients taking inhibitors of P-glycoprotein and CYP3A4, such as ketoconazole, itraconazole, voriconazole, posaconazole or ritonavir. These drugs may increase rivaroxaban plasma concentrations and thereby increase bleeding risk. The use of rivaroxaban with non-steroidal anti-inflammatory drugs, opioids or statins is cautioned because of increased bleeding risk [55].

The elimination of apixaban involves multiple pathways, including intestinal and renal excretion. The primary metabolite of apixaban, the O-demethylated product, is formed mainly by CYP3A4.

Currently, no data are available on food interactions with apixaban [56].

The effect of food on the pharmacokinetics of dabigatran and rivaroxaban was investigated in healthy volunteers. Consumption of a high-fat, high-caloric breakfast delayed the absorption of dabigatran (150 mg); however, the extent of absorption was not different when compared with the fasting state [57].

The experience with new oral anticoagulants in elderly patients is limited. The manufacturer of dabigatran recommends reducing the dose to 150 mg p.o. in patients older than 75 years, as well as keeping close clinical surveillance due to potential increased bleeding risk [41]. Elderly patients receiving rivaroxaban have approximately 1.5-fold higher mean plasma AUC values compared to younger patients, probably because of reduced renal clearance in the elderly. At present, no recommendation of dose adjustment is available for rivaroxaban use in the elderly [35].

No dose adjustments in elderly patients (>65 years) are indicated. However, there is limited clinical experience in co-administered apixaban with acetylsalicylic acid. Therefore, this combination should be used cautiously because of a potentially higher bleeding risk [43].

Conclusion

Current standard treatment for acute venous thromboembolism is limited by the need for parenteral heparin therapy, with overlapping administration of VKAs. However, new antithrombotic agents have many potential advantages over the VKAs, including their rapid onset of action, predictable therapeutic effects and limited drug-drug interactions.

The lack of a requirement for monitoring may reduce the exposition of the patient to his physician and might thus reduce the opportunity for patient education and earlier detection of problems. Also, it makes it difficult to determine if the specific therapy has failed. If a patient develops a thromboembolic event on VKAs (e.g., warfarin), the INR is measured to determine if the event is truly a failure of therapy or whether the patient was subtherapeutic. Dosing can be adjusted to increase the INR, and patient education can be provided if deemed necessary [58]. For the new oral anticoagulants, respective drug quantitation procedures need to be validated first.

Other potential facts to be considered include dosing adjustment for renal and/or hepatic dysfunction. The absence of a direct antidote may be problematic for patients who are at a high risk of bleeding or for those who present with a bleed early after ingestion of one of new oral anticoagulants. The use of Prothrombin Complex Concentrate might be a potential alternative in such situations.

Finally, warfarin is available as a generic medication and is relatively inexpensive. New agents will be significantly more expensive [4]. Patients with a condition requiring lifelong therapy with minimal to no symptoms will likely seek out such agents to improve their quality of life by eliminating the need for frequent monitoring and reducing dietary and drug-drug interaction concerns. However, warfarin will remain the mainstay of treatment for patients with mechanical heart valves for now, because studies in this population have not been initiated. Warfarin may also hold favour with patients who are considered noncompliant with therapy and as an option for those patients who "fail" or who develop an event while on one of the new agents [4].

At present, new oral anticoagulants are approved for the prevention of stroke in AF and for thromboprophylaxis after elective hip and knee replacement.

But results on patients with deep vein thrombosis and/or pulmonary embolism suggest that the new oral anticoagulants are effective and safe in this particular setting.

For dabigatran, the phase III acute treatment study included patients with pulmonary embolism while this was not the case for rivaroxaban. However, the dabigatran study tested treatment after parenteral anticoagulation while patients in the rivaroxaban study immediately started on the trial drug.

In conclusion, currently available data show that the new oral anticoagulants will likely change the way antithrombotic therapy is done. Specifically, postoperative thromboprophylaxis with the new oral anticoagulants has already started to change perioperative managment of patients undergoing orthopaedic surgery. Treatment and secondary prophylaxis of venous thromboembolism is likely to see the rise of the new oral anticoagulants as initially additional, later standard therapy; the same holds true for stroke prevention in atrial fibrillation.

More data are still needed in patients with heart

valves, cancer patients, and patients undergoing non-orthopaedic surgery before final conclusions on the value of the new oral anticoagulants in these settings can be drawn. Also, new indications might arise in non-surgical patients if new studies with different dosing schedules were performed.

Thus, it seems reasonable to believe that the new oral anticoagulants harbour the potential to change current daily practice and therefore current guidelines.

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