New drugs

Novel oral anticoagulants: focus on stroke prevention and treatment of venous thrombo-embolism

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Anticoagulation for the long-term treatment and prevention of thrombo-embolic diseases as well as for stroke prevention in atrial fibrillation (AF) has been accomplished by vitamin K antagonists for the last half century. Although effective under optimal conditions, the imminent risk of a recurrent event vs. the risk of bleeding due to the narrow therapeutic window, numerous food- and drug interactions, and the need for regular monitoring complicate the long-term use of these drugs and render treatment with these agents complicated. As a result, novel anticoagulants which selectively block key factors in the coagulation cascade are being developed. The efficacy and safety of the direct thrombin inhibitor dabigatran etexilate, as well as of the selective factor Xa inhibitors rivaroxaban and apixaban, have been demonstrated in Phase III trials for stroke prevention in AF and the treatment and secondary prophylaxis of venous thrombo-embolism. This review summarizes the results from recently published pivotal clinical trials and discusses the opportunities as well as uncertainties in the clinical applications of these novel agents.

Keywords
Apixaban • Atrial fibrillation • Dabigatran etexilate • Edoxaban • Novel anticoagulants • Rivaroxaban • RE-LY AVERROES • ROCKET AF • ENGAGE-TIMI 48

Introduction

Activation of the plasma coagulation cascade is central to thrombus formation in the ‘low pressure’ segment of the circulation, including the venous system and left atrium (Figure 1).1,2 Anticoagulation for the long-term treatment and prophylaxis of thrombo-embolic diseases as well as for stroke prevention in atrial fibrillation (AF) is accomplished by vitamin K antagonists (VKAs). The latter are very effective under optimal conditions, in which a stable level of anticoagulation can be obtained.3,4 The difficulty, however, of achieving such optimal conditions is not infrequently problematic since various foods, especially vegetables, may significantly alter both the pharmaceutokinetics and pharmacodynamics of VKAs.5 Furthermore, numerous drugs, in particular inducers and inhibitors of hepatic P450 isoenzymes that metabolize VKAs, are notorious for unpredictably increasing or decreasing the anticoagulant effects of these drugs.6–7 As such, the long-term use of VKAs is frequently problematic due to their narrow therapeutic window, requiring tedious life-long coagulation monitoring, and careful drug dosing.8 Indeed, the risk of bleeding (in the case of excessive anticoagulation) as well as the risk of a recurrent thrombotic event (in the case of insufficient anticoagulation) are pertinent and constant threats in the management of these patients.9

As a result of these limitations, several novel agents have been developed to replace VKAs.10 In contrast to the latter, which block the synthesis of the inactive forms of vitamin K-dependent coagulation factors II, VII, IX, and X, these novel agents inhibit selectively the active form of a single factor of the coagulation cascade (Figure 1). Out of the numerous classes of new drugs, factor Xa (FXa) blockers and direct thrombin inhibitors have been most successfully studied in various indications. This review focuses on the most recent trials investigating these substances for stroke prevention in AF and for the treatment of venous thrombo-embolic (VTE) disorders (Table 1).
Table 1  Overview over the most important Phase III randomized controlled trials involving the substances discussed in the text

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<td>Long-term secondary prevention</td>
<td>EINSTEIN-Ext (42)</td>
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Green, met pre-defined endpoint; red, did not meet pre-defined endpoint or was terminated early due to safety concerns (APPRAISE-2); black, ongoing. See text for details.
Direct thrombin inhibitors

Direct thrombin (factor IIa) inhibitors selectively block the activity of thrombin both in solution as well as in its fibrin-bound state, thus preventing both the amplifying auto-feedback activation of the coagulation cascade as well as the conversion of fibrinogen to fibrin (Figure 1).

Dabigatran etexilate

Dabigatran etexilate (Pradaxa®) is absorbed as a prodrug with a bioavailability of ~6%. It is subsequently converted into its active form by circulating esterases.11,12 Elimination is 80% renal, which has to be taken into account when the drug is given to patients with impaired renal function. Its half-life is 14–17 h, and it is given twice daily.11

Atrial fibrillation

In the landmark Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) trial, 18 113 patients with AF and at least one additional risk factor for stroke were randomized in a partial PROBE design (Prospective Randomized Open Trial with Blinded Adjudication of Events) to receive dabigatran 110 mg bid, dabigatran 150 mg bid, or an adjusted dose of warfarin to an INR of 2.0–3.0.13,14 After a mean follow-up of 2 years, both doses of dabigatran proved non-inferior to warfarin; the primary endpoint, stroke or systemic embolism, occurred at 1.69%/year with warfarin as compared to 1.53%/year with dabigatran 110 mg bid [relative risk (RR) 0.91; 95% confidence interval (CI) 0.74–1.11] and 1.11%/year with dabigatran 150 mg bid (RR 0.66; 0.53–0.82; Figure 2). Major bleeding rates were similar among patients on warfarin (3.36%/year) and those on dabigatran 150 mg bid (3.11%/year, P = 0.31), while bleeding was less frequent in patients on the low dose of dabigatran (2.71%/year, P = 0.003 for dabigatran 110 mg bid vs. warfarin). Haemorrhagic strokes were less frequent with both dabigatran doses compared with warfarin, occurring at 0.38%/year in warfarin-treated patients as compared to 0.12%/year (P < 0.001) and 0.10%/year (P < 0.001) in patients on 110 and 150 mg bid dabigatran, respectively. In contrast, gastrointestinal bleeding was more frequent with dabigatran 150 mg bid (1.51%/year) when compared with warfarin (1.02%/year, P = 0.001), whereas it was not statistically different between warfarin and dabigatran 110 mg bid. Finally, dabigatran 150 mg bid fell just short of reducing the most important endpoint, all-cause mortality (3.6 vs. 4.1%/year with warfarin, P = 0.051), further substantiating the beneficial overall effect of this agent.

In the original analysis of the data, an increase in the risk of myocardial infarction was observed with both doses of dabigatran.13 A recent comprehensive analysis of patients’ ECGs, however, identified 28 silent myocardial infarctions, which were not included in the original analysis. When these additional events were included in the data, no statistically significant increase in myocardial infarction was observed with the 110 mg [hazard ratio (HR) 1.29; 95% CI 0.96–1.75; P = 0.09] and the 150 mg doses of dabigatran (HR 1.27; 95% CI 0.94–1.71; P = 0.12) when compared with warfarin.14

In the RE-LY trial, dyspepsia was more common with dabigatran 110 mg bis (11.8%) and 150 mg bis (11.3%) when compared with warfarin (5.8%), which most likely contributed to a more frequent rate of study drug discontinuation after 2 years (21, 21, and 17% for dabigatran 110 mg, dabigatran 150 mg, and warfarin, respectively). Importantly, and in contrast to the experience with ximelagatran,15 no elevation in liver enzymes was observed with either of the dabigatran doses in RE-LY (2.1 vs. 1.9 vs. 2.2% in patients on dabigatran 110 mg, dabigatran 150 mg, and warfarin, respectively).13 Results from subgroup analyses from RE-LY were similar.
to those of the total population, confirming its findings in the subgroup of patients with a prior stroke, in patients with different CHADS2 scores, as well as in patients undergoing cardioversion.

When comparing dabigatran with different average levels of INR control in the warfarin population, patients in centres with the poorest INR control appeared to profit most in terms of stroke prevention (although no statistically significant interaction was observed). Similarly, no difference in time to major bleeding or intracranial bleeding was seen across different INR strata, indicating a favourable efficacy and safety profile of the drug across all strata of INR control.

As a result of these robust data, the FDA has approved dabigatran 150 mg bid for stroke prevention in atrial fibrillation. Furthermore, the American College of Cardiology Foundation, American Heart Association and Heart Rhythm Society has very recently given a Class I / level of evidence B recommendation for anticoagulant treatment of these patients with dabigatran. In contrast, the 110 mg bid dose did not gain approval. Although reduced bleeding rates were observed with the 110 mg dose, the similar stroke rate when compared with warfarin as well as post hoc analyses showing superiority of dabigatran 150 mg bid over 110 mg bid led the FDA to deny approval of the latter regimen. In contrast, to the surprise of many, a reduced dosing regimen (dabigatran 75 mg bid) was approved for patients with renal insufficiency (as defined by a creatinine clearance of 15–30 ml/min). This dose was not studied in the RE-LY trial and was approved based on pharmacokinetic data from other dabigatran trials to enable the treatment of patients with severe renal insufficiency.

Venous thrombo-embolism
Dabigatran etexilate has been approved by the EMEA for the prevention of VTE events in patients undergoing elective total hip or knee replacement, based mainly on the results from the RE-NOVATE and RE–MODEL trials.

In the Phase III RE-COVER trial, dabigatran etexilate 150 mg bid was compared with INR-adjusted warfarin for 6 months in the treatment of an acute VTE. Recurrent VTE occurred in 2.4% of the patients on dabigatran as compared to 2.1% on warfarin (P < 0.001 for non-inferiority), with an HR of 1.10 for dabigatran (0.65–1.84). Overall bleeding was more frequent in warfarin-treated patients [21.9 vs. 16.1%, HR with dabigatran 0.71 (0.59–0.85); P < 0.001], whereas major bleeding was similar in the two study groups (1.6 and 1.9% for dabigatran and warfarin, respectively). As in RE-LY, dyspepsia was more frequent with dabigatran. These results indicate that fixed-dose dabigatran etexilate is as effective and safe as INR-adjusted warfarin for the treatment of acute VTEs.

A second VTE treatment study (RE-COVER II, NCT00680186) is currently ongoing. Furthermore, two trials are underway for the secondary prevention of VTE following successful treatment with warfarin for 3–6 months (RE–MEDY, NCT00329238) or 6–18 months (NCT00558259) after an acute symptomatic VTE event.

Acute coronary syndromes
For secondary prevention after an acute coronary syndrome (ACS), the placebo-controlled Phase II RE-DEEM trial revealed a dose-dependent increase in bleeding events, but showed an overall acceptable safety profile of dabigatran on top of dual antiplatelet therapy with major and clinically relevant minor bleeding rates <2%. A Phase III study for this indication, however, has not yet been initiated, most likely due to the inherent threat of excess major haemorrhage with ‘triple anticoagulation’ (as it has been observed in the APPRAISE-2 trial with apixaban).

Factor Xa inhibitors
Factor Xa inhibitors exert an anticoagulant effect by blocking the generation of thrombin from prothrombin. They are divided into ‘direct’ and ‘indirect’ inhibitors, the latter blocking FXa via its physiologic inhibitor antithrombin. Oral direct Xa inhibitors such as rivaroxaban, apixaban and edoxaban are furthest advanced in the development for stroke prevention in AF and treatment of VTE.

Rivaroxaban
Rivaroxaban (Xarelto®) is an oral FXa inhibitor that blocks FXa both in its free and prothrombin-bound states. It has a half-life of 7–11 h requiring once- or twice-daily dosing, and a dual mode of elimination, with two-thirds of the drug being metabolized by the liver and one-third eliminated unchanged by the kidneys. As a result, rivaroxaban is contraindicated in patients with a clinically relevant bleeding risk as well as in patients with liver disease associated with coagulopathy, and care should be taken when using it in patients with impaired renal function.

Atrial fibrillation
In the Phase III, double-blind, double-dummy ‘Rivaroxaban Once-daily oral direct FXa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation’ (ROCKET AF) study, rivaroxaban 20 mg once daily (15 mg daily for patients with creatinine clearance 30–45 ml/min) was compared with INR-adjusted warfarin for stroke prevention in 14 264 patients with AF. In contrast to the RE-LY trial with dabigatran which was not blinded (see above), ROCKET AF was double blinded. The results, presented at the American Heart Association Meeting 2010 demonstrated non-inferiority of rivaroxaban when compared with warfarin (HR 0.79; 95% CI 0.66–0.96; P < 0.001) with event rates of 1.71 and 2.16%/year, respectively. Furthermore, rivaroxaban was superior to warfarin in the ‘on treatment’ analysis (P = 0.013). However, in the intention-to-treat analysis, statistical superiority was not observed with event rates of 2.12 and 2.42%/year with rivaroxaban and warfarin, respectively (HR 0.88; 95% CI 0.74–1.03; P = 0.117). Most likely, the long period during which events were included of the analysis after drug discontinuation in the intention-to-treat analysis resulted in a significant degree of regression to the mean of the results, leading to non-superiority of rivaroxaban in this analysis.

No difference between rivaroxaban and INR-adjusted warfarin was observed in the rate of major and non-major clinically relevant bleeding (HR 1.03; 95% CI 0.96–1.11; P = 0.442). Although epitaxis as well as bleeding requiring transfusion were more common with rivaroxaban (HR 1.25, 95% CI 1.01–1.55), the most serious forms of haemorrhage, i.e. fatal bleeding (HR 0.50;
95% CI 0.31–0.79; \( P = 0.003 \) and intracranial haemorrhage (HR 0.67; 95% CI 0.47–0.94; \( P = 0.019 \)), were less common than with warfarin. Also, haemorrhagic stroke was less frequently observed with rivaroxaban (HR 0.59; 95% CI 0.37–0.93). Finally, a trend towards a reduction in all-cause mortality (HR 0.85; 95% CI 0.70–1.02) was observed with rivaroxaban in the on-treatment analysis.

There was no difference in other side effects, including serious adverse events, acute myocardial infarction, and liver enzyme elevations. The main results of ROCKET AF were consistent across pre-specified subgroups including patients with renal insufficiency, different CHADS\(_2\) scores, prior warfarin use, centre time in therapeutic range, and prior stroke.\(^{36}\) Publication of the final results is anticipated for Spring 2011.

**Venous thrombo-embolism**

In the European Union and several other countries worldwide (although not in the USA), rivaroxaban has been approved for the prevention of VTE in adult patients undergoing elective hip or knee replacement due to the convincing results of the ‘REgulation of Coagulation in major Orthopaedic surgery reducing the Risk of Deep vein thrombosis and pulmonary embolism’ (RECORD) study programme.\(^{37–41}\) A Phase III study for the prevention of VTE in medically ill patients including \( \sim 8000 \) subjects is currently ongoing (MAGELLAN, NCT00571649).

In the Phase III EINSTEIN-DVT study, 3449 patients received either rivaroxaban or a VKA for the treatment of deep vein thrombosis.\(^{42}\) Initial treatment for 3 weeks with a high dose of rivaroxaban (15 mg bid) followed by 20 mg once daily was compared with initial treatment with subcutaneous enoxaparin or fondaparinux followed by a VKA for 3, 6, or 12 months (individual treatment duration was according to the treating physician’s discretion). The primary endpoint, first symptomatic VTE, occurred in 36 patients (2.1%) on rivaroxaban as compared to 51 patients (3.0%) in the conventional treatment arm [HR 0.68 (95% CI 0.44–1.04), \( P < 0.0001 \) for non-inferiority and \( P = 0.076 \) for superiority of rivaroxaban; Figure 3A]. Bleeding was similar in both groups with 139 (8.1%) and 138 (8.1%) of the patients on rivaroxaban and on the conventional regimen, respectively, experiencing first major bleeding or clinically relevant non-major bleeding (HR 0.97; 0.76–1.22; \( P = 0.77 \)).

Both efficacy and safety outcomes were consistent across all subgroups. Fifty-one patients (2.9%) in the rivaroxaban group and 73 (4.2%) in the conventional treatment group reached the net clinical benefit endpoint defined as the primary efficacy outcome + major bleeding, indicating the superiority of rivaroxaban over enoxaparin followed by a VKA for this secondary...
endpoint (HR 0.67; 95% CI 0.47–0.95; \( P = 0.03 \)). Total mortality occurred in 38 (2.2%) and 49 (2.9%) of the patients on rivaroxaban and on the conventional regimen, respectively (HR 0.67; 95% CI 0.44–1.02; \( P = 0.06 \)), clearly indicating non-inferiority but failing just short of superiority of rivaroxaban.

Taken together, these results demonstrate that rivaroxaban is at least as effective as enoxaparin/fondaparinux followed by a VKA for the treatment of DVT with a similar risk of bleeding. EINSTEIN-DVT’s sister study, EINSTEIN-PE (NCT00439777), investigating rivaroxaban for the treatment of pulmonary embolism in a very similar study design is expected to be completed by the middle of 2011.

The EINSTEIN-Extension study, performed in parallel to EINSTEIN DVT and included in the same publication,\(^7\) was designed to assess the efficacy and safety of rivaroxaban for prevention of secondary VTE. According to the current guidelines, the initial treatment duration for acute VTE depends on the presumed aetiology of the event; however, the optimal duration of treatment is still debated.\(^8\) Therefore, EINSTEIN-Extension included patients, who according to their treating physician’s decision, had completed their designated duration of anticoagulation (6–12 months) for an acute episode of VTE. Importantly, patients with an indication for longer anticoagulation (e.g. cancer-related VTE) were excluded from the trial. A total of 1197 patients were recruited both from the EINSTEIN-DVT and EINSTEIN-PE cohorts as well as from patients independently treated with a VKA for symptomatic VTE. After a mean treatment duration of 190 days, symptomatic recurrent VTE events were reduced by 82% with rivaroxaban as compared to placebo (HR 0.18; \( P < 0.0001 \); Figure 3B) with similar bleedings rates.\(^9\) These impressive results not only demonstrated efficacy and safety of rivaroxaban in the secondary prevention of VTE, but also challenge the current guidelines with respect to the optimal treatment duration in these patients.

**Acute coronary syndrome**

In the Phase II randomized, double-blind, placebo-controlled, dose-finding ATLAS-1 TIMI 46 trial of patients with a recent ACS,\(^3\) rivaroxaban increased the risk of clinically significant bleeding in a dose-dependent manner when compared with placebo (\( P < 0.0001 \)), while leading to a (non-significant) relative reduction in the primary composite efficacy endpoint of death, MI, stroke, or severe recurrent ischaemia requiring revascularization (5.6 vs. 7.0%, \( P = 0.10 \)). As a result, a Phase III randomized, double-blind, placebo-controlled trial (ATLAS ACS TIMI 51, NCT00809965) is comparing two doses of rivaroxaban (2.5 and 5 mg bid) with placebo in patients with ACS who are receiving standard antiplatelet therapy with aspirin and clopidogrel or aspirin alone. Enrolment has been completed, and it is expected that the results will be available in late 2011.\(^4\)

**Apixaban**

The oral direct FXa inhibitor apixaban inhibits both free and prothrombin-bound FXa.\(^5,6\) It is partly metabolized via the CYP3A4 pathway and eliminated largely via the faecal route (\(~70%)\),\(^7\) which may prove to reduce its risk in patients with impaired renal function.

**Atrial fibrillation**

Preliminary results of the Phase III, double-blind, randomized, AVERROES trial (NCT00496769) were recently published. Patients with AF and at least one additional risk factor, who had either used and discontinued a VKA (40%) or who were expected to be unsuitable for treatment with a VKA (60%), were randomized to receive either aspirin (81–324 mg/day) or apixaban (5 mg bid or, in selected patients, 2.5 mg bid). The average patient age was 70 years, and the mean CHADS\(_2\) risk score was 2.1 in both groups. At the first planned interim analysis of efficacy, the data monitoring committee recommended early study termination for compelling evidence of efficacy. After a median follow-up of 1 year, the incidence of stroke or systemic embolism occurred in 52 patients (1.6%/year) and 113 patients (3.7%/year) in the apixaban and aspirin groups, respectively (HR 0.45; 95% CI 0.32–0.62; \( P < 0.001 \)). This was not entirely unexpected since it is well established that VKA is superior to aspirin in protecting patients with AF from the development of a thrombo-embolic stroke. Although major bleeding (1.4 vs. 1.2%/year for apixaban and aspirin, respectively, \( P = 0.57 \)), intracranial bleeding (0.4 vs. 0.4%, \( P = 0.69 \)), and fatal bleeding (0.1% in both groups, \( P = 0.53 \)) were similar between the two study arms, minor bleeding was more common with apixaban (6.3 vs. 5.0%, \( P = 0.05 \)). Furthermore, a trend towards a reduction in the secondary endpoint of overall mortality was observed with apixaban (110 patients, 3.5%/year) vs. aspirin (139 patients, 4.4%/year; HR 0.79 (0.62–1.02), \( P = 0.07 \)). These results indicate a favourable profile for apixaban when compared with aspirin in patients with AF unsuitable for VKA treatment. As a consequence, aspirin use is likely to be replaced in many of such patients with a novel anticoagulant.

However, in order to have an impact on the current guidelines and allow for a change in daily clinical practice, ‘unsuitability’ for VKA treatment needs to be clearly defined. Results of the ARISTOTLE Phase III trial, in which \(~18\,000\) patients with AF have been randomized to receive either apixaban 5 mg bid or a VKA, are eagerly awaited;\(^8\) study completion is anticipated for the Spring of 2011, with presentation at the ESC meeting in 2011.

**Venous thromboembolism**

Apixaban has been studied extensively for the prevention of VTE in patients undergoing orthopaedic surgery in the ‘Apixaban Dosed Orally Versus Anticoagulation with Injectable Enoxaparin to Prevent Venous Thromboembolism’ (ADVANCE) study programme, although with partly conflicting results.\(^4,5\)

A Phase II trial for the treatment of symptomatic DVT reported a favourable efficacy and safety profile for all doses of apixaban when compared with low-molecular-weight heparin followed by warfarin.\(^53\) In the ongoing Phase III AMPLIFY trial, initial treatment with apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily is being compared with initial treatment with enoxaparin followed by a VKA for 6 months for the treatment of acute DVT and pulmonary embolism (NCT00643201). The Phase III double-blind AMPLIFY-EXTENSION trial (NCT00633893) is comparing apixaban (2.5 or 5 mg twice daily) and placebo in the secondary prevention in patients with VTE who have completed 6- to 12-month treatment with apixaban or VKA.
The Phase III double-blind double-dummy ADOPT trial comparing extended treatment with apixaban 2.5 mg twice daily for 30 days with enoxaparin 40 mg once daily for at least 7 days followed by placebo for the prevention of VTE in medically ill patients is ongoing (NCT00457002).

Acute coronary syndrome
Apixaban was studied for secondary prevention after ACS [non-ST elevation myocardial infarction (STEMI) or STEMI] in the Phase II double-blind, placebo-controlled, dose-ranging APPRAISE trial. A dose-dependent increase in the risk of major or clinically relevant non-major bleeding was observed. A reduction in ischaemic events was also seen, but the trial was not powered to assess efficacy endpoints with confidence. The follow-up Phase III APPRAISE-2 trial (NCT00831441), comparing 5 mg bid apixaban vs. placebo in post-ACS patients who were receiving aspirin and clopidogrel (or aspirin only in a subgroup of patients), has recently been stopped on the recommendation of the data safety monitoring committee because of excessive bleeding and lack of efficacy.

Edoxaban
The free base of DU-176b, edoxaban, is a reversible direct inhibitor of FXa, which is rapidly absorbed with good bioavailability, a half-life of 8–10 h, and elimination largely via the kidneys. A Phase III study comparing edoxaban with warfarin (after initial treatment with heparin in both arms) (NCT00986154) for the treatment of VTE disease is currently underway.

Atrial fibrillation
In the Phase II study for stroke prevention in AF (NCT00504556), once-daily dosing of either 30 or 60 mg of edoxaban was associated with less bleeding than the respective twice-daily dosing regimens. A large randomized, double-blind, double-dummy Phase III trial (ENGAGE AF TIMI 48, NCT00781391) is being conducted comparing two doses of edoxaban (30 and 60 mg once daily) with INR-adjusted warfarin. The trial design allows for a dose reduction in edoxaban-treated patients deemed to be at an increased risk of bleeding based on anticipated drug exposure levels and risk factors. Thus, this Phase III trial is the first to study three doses of a Factor X inhibitor (60, 30, and 15 mg, the latter in patients assigned to 30 mg and adjusted downwards). Enrolment has been completed with 21 107 patients, and trial completion is scheduled for mid-2012.

Implications and conclusions
Several novel, orally active anticoagulants have now been successfully tested against standard therapy with VKAs in the treatment and prevention of VTE as well as for stroke prevention in patients with AF. Studies with the direct thrombin inhibitor dabigatran etexilate as well as the FXa inhibitors rivaroxaban and apixaban are furthest advanced; indeed, rivaroxaban is approved for VTE prevention in orthopaedic patients in many countries (albeit not in the USA), whereas dabigatran has recently been approved for stroke prevention in AF in the USA. When compared with VKAs, these drugs possess a number of the desired properties of an ‘ideal’ anticoagulant (Table 2), including enhanced safety and efficacy profiles, oral bioavailability, and no requirement for routine coagulation monitoring—all of which are particularly attractive in the long-term use in stroke or VTE prevention. As a result, broad-based application of these agents may substantially increase the number of patients on adequate anticoagulation, many of whom are not receiving such therapy due to the inconvenience and drawbacks of VKA treatment. Furthermore, the favourable risk–benefit profile of these agents may have a substantial impact on current guidelines, resulting in a significant increase in the number of patients with a treatment indication as well as in a prolongation of treatment duration (in the case of VTE). A third potential application is to add the novel anticoagulant to the antiplatelet regimen in the secondary prevention of patients with ACS. Vitamin K antagonists are usually not administered to such patients, unless a clear indication such as AF or VTE is present.

In spite of the enthusiasm associated with the chance of replacing warfarin for its present indications, some uncertainties remain.

Lack of coagulation monitoring: friend or foe?
One of the greatest advantages of these novel agents in long-term treatment is the lack of need for routine monitoring of coagulation. Pharmacokinetic and Phase II studies with dabigatran and the three anti-Xa agents discussed above (rivaroxaban, apixaban, and edoxaban) have demonstrated drug levels and treatment effects independent of most concomitant medication and food intake. Furthermore, data from several Phase III trials have indicated that this approach appears to be safe and effective for the studied indications. Indeed, it may be possible that for each drug, one (or two) doses will be suitable for a large majority of patients. However, without appropriate means of controlling treatment intensity, safety and efficacy of application of these novel agents for long-term care of patients with multiple co-morbidities, intercurrent illnesses and receiving multiple medications, will require large observational studies. Since both overtreatment and undertreatment may lead to serious sequelae, some monitoring of the intensity of anticoagulation may be desirable both from an efficacy and safety standpoint. The latter is especially true in view of the fact that none of the novel anticoagulants has a specific antidote, which may complicate treatment, especially in patients at an

### Table 2 The ‘ideal’ anticoagulant

<table>
<thead>
<tr>
<th>Property</th>
<th>Edoxaban</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Dabigatran</th>
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<tbody>
<tr>
<td>Proven efficacy</td>
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<tr>
<td>Low bleeding risk</td>
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<tr>
<td>Fixed dosing</td>
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<tr>
<td>Good oral bioavailability</td>
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<tr>
<td>No routine monitoring</td>
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<tr>
<td>Reversibility</td>
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<tr>
<td>Rapid onset of action</td>
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<tr>
<td>Little interaction with drugs or food</td>
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<td></td>
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<tr>
<td>Antidote available</td>
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</table>
increased bleeding risk. Some recent efforts, however, have reported on the development of an antidote for anti-Xa drugs.59,60

Several studies have recently been initiated with the goal of establishing the parameter (activated partial thromboplastin time, anti-FXa activity, INR, drug level) and target range for monitoring of these agents.45,61–66 However, these investigations are relatively small and lack correlation of the anticoagulant markers with hard clinical endpoints, an important prerequisite to assess their widespread adoption. Hence, both the question of the desirability for monitoring and the appropriate variables to be monitored remain unclear at present.

**Which patient needs to be switched from vitamin K antagonists?**

Several lines of evidence indicate that a large proportion of patients will likely benefit from being switched from VKAs to one of the novel anticoagulants. Most data supporting this approach currently stem from the RE-LY trial, in which a consistent signal for efficacy without an increase in bleeding was reported for the 150 mg dose across all subgroups, including older patients, patients with different CHADS2 scores, prior warfarin use, or prior stroke.13,16,17,19 In relative terms, patients least likely to derive an incremental benefit from being switched from a VKA to dabigatran are those who are well controlled on warfarin with INR values consistently in the target range. However, even these patients would benefit from a reduced probability for intracranial bleeding, which seems to occur less when compared with VKAs. Conversely, patients with poor medication adherence are notoriously difficult to treat with VKAs. However, it is unlikely that their management will be greatly improved with novel anticoagulants with short half-lives requiring twice-daily dosing.

Since VKAs are usually administered for a limited duration in the treatment and prevention of DVT, switching to a novel anticoagulant during the ongoing course of therapy does not appear warranted for the majority of these patients. However, results from the EINSTEIN-Extension trial indicate that switching to rivaroxaban and prolonging the duration of treatment may be indicated in patients for the secondary prevention of DVT.42 This benefit is likely to be seen with the other novel anticoagulants as well.

**Which drug for which patient?**

With several novel agents becoming available for stroke prevention in AF in the near future, it will be of great interest to assess which group of patients will profit most with these new agents. The recent results of the ROCKET AF trial36 have sparked considerable debate as to whether rivaroxaban may be as effective as dabigatran, given that superiority was only reached in the on-treatment, but not in the intention-to-treat analysis of the former. Valid cross-trial comparisons, however, are impossible to perform in view of the different study designs and the different patient populations studied. Indeed, although superiority was shown for the higher dose of dabigatran in the intention-to-treat analysis of RE-LY, the double-blind double-dummy design in ROCKET AF is clearly superior to the PROBE design in RE-LY. Furthermore, patients in the ROCKET AF trial were significantly sicker as indicated by a higher prevalence of congestive heart failure and hypertension as well as substantially higher CHADS2 scores, rendering valid cross-trial comparison of the two studies virtually impossible. Since both trials compared the novel anticoagulant to warfarin, it would be interesting to examine the comparison in matched subsets of patients from each trial. The data required for such a comparison, however, are not yet available. At this time, given the robust data from RE-LY and ROCKET AF, both rivaroxaban and dabigatran appear to be valid alternatives to warfarin.

Factors to consider when choosing an anticoagulant include appreciation of the patient’s individual stroke and bleeding risks, co-morbidities, compliance (once-daily dosing for rivaroxaban compared to twice-daily dosing for dabigatran). It will be interesting to compare the results when the other two trials of new orally active FXa inhibitors which have completed enrolment (apixaban in ARISTOTLE and edoxaban in ENGAGE-TIMI 48) become available.

The low rate of bleeding events in patients on 110 mg bid dabigatran etexilate in RE-LY imply that this dose could prove particularly beneficial in patients judged to be at an increased risk for bleeding, such as the elderly. With the denial of FDA approval of this dosing regimen, however, the latter will not be an option, at least in the USA, and it is currently unclear whether the European Medicines Agency (EMEA) will follow the FDA’s course.

In patients ‘unsuitable’ for VKA treatment, apixaban has clearly shown superiority when compared with the current practice of aspirin treatment.67 However, as indicated above, ‘unsuitability’ for VKA treatment needs to be clearly defined, and the fraction of patients unsuitable for a VKA, but suitable for the novel anticoagulants, needs to be addressed. It is very likely that the other three novel anticoagulants, although they have not yet been tested in this patient population, will, like apixaban, be superior to aspirin.

Both rivaroxaban and dabigatran may be considered as alternatives to warfarin for the treatment and prophylaxis of DVT and, probably, VTE in general, given the robust results from EINSTEIN-DVT42 and RECOVER.25 Furthermore, the impressive reduction in events seen in the EINSTEIN-Extension trial42 may result not only in the replacement of warfarin for the treatment of VTE, but more importantly in a prolongation of the recommended duration of therapy.

**Cost effectiveness**

The use of novel anticoagulants for stroke prevention in AF or prophylaxis and treatment of VTE will be substantially more expensive than VKAs. Dabigatran, for example, is available in the USA at ~20 times the cost of warfarin. However, these differences are reduced by the lack of need for laboratory monitoring as well as the improvement in clinical benefit for the novel anticoagulant. One study has recently indicated the cost-effectiveness of dabigatran when compared with warfarin for stroke prevention in AF.68 Also, since it is likely that the three other novel anticoagulants (rivaroxaban, apixaban, and edoxaban) will ultimately be approved to prevent stroke and/or systemic embolism in AF, there may be downward price pressure on the manufacturers of all four drugs. Ultimately, carefully conducted analyses will be necessary to define the patients in which these novel anticoagulants are cost-effective.
Conclusions
Data from recent large-scale Phase III trials add to the growing evidence that VKAs will most likely be replaced by several novel anticoagulants which will improve substantially the management of stroke prevention in AF, VTE prophylaxis and treatment, and possibly ACS. Awareness of the potential limitations of these drugs as well as continuing research is indispensable for identifying the characteristics of patients who should receive these agents, and the relative advantages and disadvantages of each. It is likely that the pages of this (and other) Heart journals will be filled with articles and guidelines statements on the subject of this review.

Conflict of interest: J.S. has received consulting and/or speakers’ fees from AstraZeneca, Bayer HealthCare, Boehringer Ingelheim, Bristol–Myers Squibb, and Sanofi-aventis. E.B. chairs the ATLAS-2-TIMI 51 trial of rivaroxaban in ACS that is sponsored by Johnson and Johnson as well as by Bayer Health Care; he chairs the ENGAGE-TIMI 48 trial of edoxaban in AF that is sponsored by Daiichi-Sankyo; is Founding Chairman of the TIMI Study Group at the Brigham and Women’s Hospital—The Brigham and Women’s Hospital—The Brigham and Women’s Hospital (or has received within the past 24 months) grant support for the TIMI Study Group from the following pharmaceutical companies: AstraZeneca Pharmaceuticals LP, Johnson & Johnson, Beckman Coulter, Inc., Eli Lilly, Genentech, Integrated Therapeutics Group, Merck & Co., Inc., Roche Diagnostics Corp., sanofi aventis, Daiichi Sankyo, Glaxo Smith Kline, and Bristol Myers Squibb. He has also received honoraria and has participated in advisory board meetings and acted as a consultant for Daiichi Sankyo, Eli Lilly, Merck & Co., and Genzyme.

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