New developments in anticoagulants: Past, present and future

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Summary
Thrombosis is a leading cause of death and disability worldwide, and anticoagulants are the mainstay of its prevention and treatment. Starting with unfractionated heparin (UFH) and vitamin K antagonists (VKAs) such as warfarin, the choices of anticoagulants have exploded in the past 20 years. With over 90% subcutaneous bioavailability, no need for coagulation monitoring and dose adjustment, and a lower risk of heparin-induced thrombocytopenia, low-molecular-weight heparin and fondaparinux have replaced UFH for prevention and initial treatment of venous thromboembolism and for secondary prevention in cancer patients. In patients undergoing percutaneous interventions, bivalirudin is often used instead of UFH. Oral anticoagulation therapy has advanced with the introduction of the non-vitamin K antagonist oral anticoagulants (NOACs), which include dabigatran, rivaroxaban, apixaban and edoxaban. With efficacy at least equal to that of VKAs but with greater safety and convenience, the NOACs are now replacing VKAs for many indications. This paper a) highlights these advances, b) outlines how specific reversal agents for the NOACs will enhance their safety, c) reviews some of the ongoing trials with the NOACs, and d) describes the inhibitors of factor XII and XI that are under investigation as anticoagulants.

Keywords
Thrombosis, anticoagulant, heparin, low-molecular-weight heparin, warfarin, non-vitamin K antagonist oral anticoagulant

Introduction

Thrombosis is the underlying cause of venous thromboembolism (VTE), and most heart attacks and strokes. Collectively, thrombosis is responsible for one in four deaths worldwide (1). Therefore, given the burden of disease, development of anticoagulants for prevention and treatment of thrombosis remains a priority.

Rapidly acting parenteral anticoagulants are used for prevention and initial treatment of thrombosis and during revascularisation procedures (2), whereas oral agents are used for long-term therapy (3). Advances have been made in both parenteral and oral anticoagulants. On the parenteral side, unfractionated heparin (UFH) has largely been replaced with low-molecular-weight heparin (LMWH) and in some cases, with synthetic agents, such as fondaparinux and bivalirudin. For oral anticoagulation, vitamin K antagonists (VKAs), such as warfarin, are being replaced with non-vitamin K antagonist oral anticoagulants (NOACs), such as dabigatran, rivaroxaban, apixaban and edoxaban. Therefore, from past to present, we now have many effective, safe and easy to use parenteral and oral anticoagulants.

Building on this momentum, anticoagulation therapy is advancing on several fronts. Thus, specific reversal agents for the NOACs have been developed to streamline management of patients with life-threatening bleeding or requiring urgent surgery; the NOACs are under investigation for new indications, and factor (F)XII and FXI have emerged as targets for potentially safer anticoagulants (4). Focusing on these developments, this paper a) outlines how LMWH, fondaparinux, bivalirudin and the NOACs overcome the limitations of UFH and VKAs, b) describes the current status of reversal agents for the NOACs, c) reviews potential new indications for the NOACs, and d) identifies the strategies for inhibition of FXII and FXI.

The past: Overcoming the limitations of heparin and VKAs

Anticoagulation therapy started early in the 20th century with the introduction of UFH and VKAs such as warfarin (Figure 1). Little changed until the introduction of LMWH, fondaparinux and bivalirudin in the 1980s and early 1990s. Although effective, UFH is cumbersome to administer because it requires intravenous infusion and coagulation monitoring to ensure that a therapeutic response is obtained (2). Monitoring is important because the therapeutic dose of heparin varies among patients and because failure to obtain a therapeutic response compromises its efficacy. LMWH and fondaparinux have advantages over UFH because they can be given subcutaneously in fixed or weight-adjusted doses without coagulation monitoring, thereby enabling outpatient therapy. Furthermore, the risk of heparin-induced thrombocytopenia (HIT) is lower with LMWH than with UFH, and almost nonexistent with fondaparinux (2). Therefore, LMWH and fondaparinux simplify parenteral anticoagulation therapy and are safer than UFH.
Bivalirudin is an effective and safe alternative to UFH in patients undergoing percutaneous coronary intervention (PCI) or cardiopulmonary bypass, even those with HIT (5). UFH and bivalirudin are preferred over LMWH for short-term anticoagulation in these situations because their doses can be titrated based on results of point-of-care coagulation tests (2).

Oral anticoagulants are preferable to parenteral agents for long-term treatment (3). Although effective, VKAs have numerous limitations. These include a slow onset and offset of action and variable dose requirements reflecting, at least in part, common genetic polymorphisms that influence their metabolism, differences in dietary intake of vitamin K, and drug–drug interactions. Consequently, frequent coagulation monitoring is necessary to maintain the international normalised ratio (INR) in the therapeutic range (3). Such monitoring is inconvenient for patients and physicians and costly for the healthcare system. The many limitations of VKAs prompted the development of the NOACs. Progress stumbled initially when ximelagatran, the first of the NOACs, was briefly licensed in Europe but was withdrawn because of potential hepatic toxicity (6). However, this situation soon changed with the introduction of dabigatran, rivaroxaban, apixaban and edoxaban, which are now overtaking VKAs for many indications.

The present: Era of the NOACs

The NOACs are more convenient to administer than VKAs because they can be given in fixed doses without routine coagulation monitoring (7). When compared with VKAs for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) and for treatment of VTE, the NOACs were at least as effective, but were associated with less serious bleeding, particularly less intracranial haemorrhage (8, 9). The advantages of the NOACs over VKAs have been confirmed in the community. Thus, results of observational studies in patients with atrial fibrillation suggest that compared with warfarin, the NOACs produce reductions in the risk of stroke, major bleeding and intracranial bleeding in the community similar to those observed in the randomised trials (10). With this wealth of evidence, guidelines give preference to the NOACs over VKAs for stroke prevention in most patients with NVAF and for VTE treatment in patients without active cancer (11, 12).

Despite their ease of use and enhanced safety compared with VKAs, there are issues with the NOACs that still need to be addressed. First, there is systemic overuse of the lower dose NOAC regimens in patients with NVAF, likely reflecting fear of bleeding (13). Use of lower doses is problematic because it places patients at higher risk of stroke. Second, registries and quality improvement programs reveal that even with the introduction of the NOACs, at least one-third of eligible NVAF patients are either not receiving any antithrombotic therapy or are only on aspirin (14, 15). Therefore, education is needed to enhance use of the NOACs at the appropriate doses.

Although the risk of bleeding is lower with the NOACs than that with VKAs, annual rates of major bleeding with the NOACs range from 2% to 3% in elderly NVAF patients (8). In addition, patients taking NOACs may require urgent intervention or surgery. Consequently, there is a need for specific reversal agents. Idarucizumab is licensed for reversal of dabigatran and andexanet alfa and ciraparantag are under development for reversal of the others (Table 1). Therefore, widespread availability of reversal agents for the NOACs will streamline management of patients with life-threatening bleeding or who require urgent surgery.

Idarucizumab is a monoclonal antibody fragment against dabigatran that binds the drug with high affinity to form a stoichiometric complex that is cleared by the kidneys (16). When given as a 5 g intravenous bolus, idarucizumab rapidly and completely reverses the anticoagulant effects of dabigatran (17). Idarucizumab is licensed for dabigatran reversal in patients with serious bleeding or requiring urgent surgery based on preliminary evidence that it safely and effectively reverses dabigatran in such patients (18). Consequently, dabigatran is the first NOAC with a specific reversal agent.

Andexanet alfa is a recombinant FXa variant that lacks enzymatic activity and the capacity to incorporate into prothrombinase. By competing with FXa for binding rivaroxaban, apixaban or edoxaban, andexanet sequesters the drugs until they can be eliminated (19). When given as an intravenous bolus followed by a 2 hour (h) infusion, andexanet reversed the anti-FXa activity of rivaroxaban and apixaban in volunteers (20) and in patients taking

Figure 1: Timeline for development of anticoagulants and antidotes.
these drugs who presented with serious bleeding (21). Andexanet also reverses UFH, LMWH, and fondaparinux by competing with FXa for binding to the antithrombin-heparin complex. Therefore, andexanet has the potential to reverse both direct and indirect FXa inhibitors.

Ciraparantag is a synthetic cationic small molecule reported to bind UFH, LMWH, fondaparinux and all of the NOACs. Studies in patients are lacking but an intravenous bolus of ciraparantag restored the whole blood clotting time to baseline levels in volunteers given a single dose of edoxaban or enoxaparin (22, 23). Additional studies are needed to determine the efficacy and safety of ciraparantag.

The future: New indications for the NOACs

The greater convenience and better safety profile of the NOACs compared with VKAs has enabled investigations of the NOACs for new indications. On the arterial side these include embolic stroke of unknown source (ESUS), coronary and peripheral artery disease, and heart failure, and on the venous side their comparison with LMWH for treatment of cancer-associated thrombosis and with aspirin for secondary VTE prevention (Table 2).

### Embolic stroke of unknown source

Previously known as cryptogenic stroke, ESUS represents about 25 % of all ischaemic strokes (24). Most of these strokes are embolic in origin and thrombi in such patients may originate from the left atrial appendage, deep veins of the leg via paradoxical embolism through right-to-left cardiac shunts, and disrupted atherosclerotic plaques in the aortic arch or carotid or cerebral arteries. The optimal management of patients with ESUS is uncertain and most patients now receive aspirin. The RE-SPECT ESUS and NAVIGATE ESUS trials are comparing aspirin with dabigatran or rivaroxaban, respectively, for reducing the risk of recurrent stroke.

### Coronary and peripheral artery disease

Patients with coronary or peripheral artery disease are at risk of cardiovascular events. Aspirin, the current standard of care, reduces the risk of thrombotic events by about 25 %. Therefore, there is an unmet need for more effective therapy. Rivaroxaban is the only NOAC to successfully undergo phase III evaluation in patients with acute coronary syndrome. The addition of rivaroxaban (2.5 mg twice daily) to dual antiplatelet therapy in such patients reduced the risk of cardiovascular death, myocardial infarction and stroke (25). Capitalising on these findings, the three-arm COM-PASS trial has randomised 27,400 patients with coronary or peripheral artery disease to aspirin, rivaroxaban at a dose of 5 mg twice daily, or the combination of aspirin plus rivaroxaban at a dose of 2.5 mg twice daily.

Focusing on patients undergoing lower limb revascularisation for symptomatic peripheral artery disease, the VOYAGER study is investigating whether compared with placebo on top of usual care, which includes aspirin, rivaroxaban at a dose of 2.5 mg twice daily reduces the risk of cardiovascular death, myocardial infarction, stroke, acute limb ischaemia, and amputation. Therefore, these studies will investigate the utility of rivaroxaban in peripheral artery disease patients undergoing a revascularisation procedure or with stable disease.

### Heart failure

Patients with heart failure are prone to both venous thromboembolism and systemic embolic events. When compared with placebo in patients with acute coronary syndrome and concomitant heart failure, rivaroxaban at a dose of 2.5 mg twice daily reduced the primary efficacy outcome of cardiovascular death, myocardial infarction or stroke from 16.8 % to 10.1 % and was associated with a similar rate of major bleeding (26). To validate this finding, the COMMANDER HF trial is comparing the efficacy and safety of low-dose rivaroxaban and placebo in heart failure pa-

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Table 1: Reversal agents for NOACs.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Idarucizumab</th>
<th>Andexanet</th>
<th>Ciraparantag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Monoclonal antibody fragment</td>
<td>Truncated inactive recombinant factor Xa variant</td>
<td>Di-arginyl synthetic molecule</td>
</tr>
<tr>
<td>Mass</td>
<td>47,776</td>
<td>39,000</td>
<td>512</td>
</tr>
<tr>
<td>Target</td>
<td>Dabigatran only</td>
<td>Rivaroxaban, apixaban, edoxaban and heparins</td>
<td>Dabigatran, rivaroxaban, apixaban, edoxaban and heparins</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Binds dabigatran with high affinity and specificity</td>
<td>Competes with factor Xa for binding rivaroxaban, apixaban, edoxaban, and antithrombin-heparin complex</td>
<td>Binds drugs via charge-dependent hydrogen bonding</td>
</tr>
<tr>
<td>Administration</td>
<td>Intravenous bolus</td>
<td>Intravenous bolus followed by a 2-hour infusion</td>
<td>Intravenous bolus</td>
</tr>
<tr>
<td>Laboratory monitoring of reversal</td>
<td>Activated partial thromboplastin time, diluted thrombin time or ecarin clot time</td>
<td>Calibrated anti-factor Xa assays</td>
<td>Whole blood clotting time</td>
</tr>
<tr>
<td>Stage of development</td>
<td>Approved</td>
<td>Phase III</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

Cryptogenic stroke, cardiovascular death, myocardial infarction and stroke, acute limb ischaemia, and amputation. Therefore, these studies will investigate the utility of rivaroxaban in peripheral artery disease patients undergoing a revascularisation procedure or with stable disease.
Table 2: Ongoing studies of NOACs.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Trial (NCT number)</th>
<th>Intervention</th>
<th>Control</th>
<th>Duration</th>
<th>Sample Size</th>
<th>Efficacy Outcome</th>
<th>Safety Outcome</th>
<th>Expected Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial Thrombosis</td>
<td></td>
<td></td>
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<tr>
<td>Embolic stroke of unknown source</td>
<td>RE-SPECT ESUS</td>
<td>Dabigatran 150 or 110 mg BID</td>
<td>Aspirin</td>
<td>3 years</td>
<td>6,000</td>
<td>Recurrent stroke</td>
<td>Major bleeding</td>
<td>2018</td>
</tr>
<tr>
<td></td>
<td>(02239120)</td>
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<td></td>
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<tr>
<td></td>
<td>NAVIGATE ESUS</td>
<td>Rivaroxaban 15 mg OD</td>
<td>Aspirin</td>
<td>3 years</td>
<td>7,000</td>
<td>Recurrent stroke or systemic embolism</td>
<td>Major bleeding</td>
<td>2018</td>
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<tr>
<td></td>
<td>(02313909)</td>
<td></td>
<td></td>
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<tr>
<td>Coronary or peripheral artery disease</td>
<td>COMPASS</td>
<td>Rivaroxaban 5 mg BID or rivaroxaban 2.5 mg BID plus aspirin</td>
<td>Aspirin</td>
<td>5 years</td>
<td>27,000</td>
<td>Major adverse cardiac events</td>
<td>Major bleeding</td>
<td>2018</td>
</tr>
<tr>
<td></td>
<td>(01776424)</td>
<td></td>
<td></td>
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<tr>
<td>VOYAGER</td>
<td></td>
<td>Rivaroxaban 2.5 mg BID on top of aspirin</td>
<td>Placebo on</td>
<td>2 years</td>
<td>6,500</td>
<td>Cardiovascular death, myocardial infarction, stroke, acute limb ischaemia, and amputation</td>
<td>Major bleeding</td>
<td>2019</td>
</tr>
<tr>
<td></td>
<td>(02504216)</td>
<td></td>
<td>top of aspirin</td>
<td></td>
<td></td>
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<tr>
<td>Heart failure</td>
<td>COMMANDER HF</td>
<td>Rivaroxaban 2.5 mg BID</td>
<td>Placebo</td>
<td>7–31 months</td>
<td>5,000</td>
<td>Death, MI or stroke</td>
<td>Fatal or critical site bleeding</td>
<td>2018</td>
</tr>
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<td></td>
<td>(08177915)</td>
<td></td>
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<tr>
<td>Venous Thrombosis</td>
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<tr>
<td>Extended treatment</td>
<td>EINSTEIN Choice</td>
<td>Rivaroxaban 10 mg OD or rivaroxaban 20 mg OD</td>
<td>Aspirin</td>
<td>1 year</td>
<td>3,399</td>
<td>Recurrent VTE</td>
<td>Major bleeding</td>
<td>2017</td>
</tr>
<tr>
<td></td>
<td>(02064439)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cancer-associated thrombosis</td>
<td>HOKUSAI VTE-Cancer</td>
<td>Edoxaban 60 mg OD</td>
<td>Dalteparin</td>
<td>1 year</td>
<td>1,050</td>
<td>Recurrent VTE</td>
<td>Clinically relevant bleeding</td>
<td>2018</td>
</tr>
<tr>
<td></td>
<td>(02073682)</td>
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BID, twice daily; MI, myocardial infarction; OD, once daily; VTE, venous thromboembolism.

Patients with significant coronary artery disease who are admitted for exacerbation of their heart failure. The primary efficacy outcome is the composite of cardiovascular death, myocardial infarction or stroke and the primary safety outcome is the composite of fatal bleeding or bleeding into a critical space with a potential for permanent disability. Treatment will be administered for 7–31 months until the requisite number of outcome events is reached.

**Venous thromboembolism**

Many ongoing studies of NOACs for VTE treatment in children, adults and cancer patients are registered through clinicaltrials.gov. Only one is comparing a NOAC with aspirin for extended VTE treatment. When compared with placebo in patients with unprovoked VTE who had received 6–12 months of anticoagulation therapy, aspirin reduced the risk of recurrence by 32% and was associated with a low risk of major bleeding (27). The three-arm EINSTEIN Choice study randomised 3,396 VTE patients who had completed 6–12 months of anticoagulation and had ongoing risk factors for recurrence to rivaroxaban 20 mg once daily, rivaroxaban 10 mg once daily or to aspirin (28). Therefore, this will be the first study to compare the efficacy and safety of anticoagulant and antiplatelet strategies for secondary thromboprophylaxis.

Although the NOACs have been compared with VKAs for VTE treatment in a limited number of patients with active cancer, they have not been compared with LMWH. The open-label HOKUSAI VTE-cancer study randomised 1,050 patients with cancer-associated VTE to edoxaban 60 mg once daily or to dalteparin after at least five days of initial dalteparin treatment (29). In addition to patients with symptomatic VTE, those with incidental VTE also were included because the risk of recurrence with incidental VTE appears to be similar to that with symptomatic VTE. The primary outcome is the composite of recurrent VTE and major bleeding during the 12-month study period. Therefore, this study will be the first to compare a NOAC with LMWH for treatment of cancer-associated VTE.

While these studies may reveal new indications for the NOACs alone or in combination with aspirin, pursuit of novel targets may be necessary to further reduce the risk of bleeding with anticoagulant therapy.
FXII and FXI, components of the contact system (Figure 2), have emerged as new targets for potentially safer anticoagulants (4, 30). Although dispensable for hemostasis, the contact system is essential for thrombus stabilisation and growth because thrombi formed at sites of arterial or venous injury in mice deficient in FXII or FXI are small and prone to embolisation (31). FXII deficiency is not associated with bleeding, and patients with FXI deficiency rarely experience spontaneous bleeding (32, 33). Therefore, inhibition of these factors may attenuate thrombosis with little or no effect on haemostasis.

Strategies to target FXII and FXI include a) antisense oligonucleotides (ASOs) that reduce hepatic synthesis of the clotting proteins (34–36), b) monoclonal antibodies that block activation or activity (36–39), c) aptamers (40), and d) small molecules that block the active site or induce allosteric inhibition (41–45).

The FXI-directed ASO is the first agent to reach phase II. A total of 300 patients undergoing elective knee arthroplasty were randomised to receive the ASO at doses of 200 or 300 mg starting 35 days prior to surgery or enoxaparin at a dose of 40 mg once daily starting after surgery (46). After at least 10 days of treatment, bilateral venography was performed. The primary efficacy outcome was VTE, while the principal safety outcome was bleeding. At the time of surgery, mean FXI levels were reduced to 38% and 28% of baseline values with the 200 and 300 mg ASO doses, respectively. The primary efficacy outcome occurred in 36 of 134 patients (27%) and in 3 of 71 patients (4%) who received the 200 and 300 mg doses of ASO, respectively, as compared with 21 of 69 patients (30%) who received enoxaparin. The 200 mg ASO regimen was non-inferior and the 300 mg ASO regimen was superior to enoxaparin (p<0.001). The rates of the composite of major or clinically relevant non-major bleeding were 3% in both ASO groups and 8% in the enoxaparin groups (46). Therefore, lowering FXI levels reduced the risk of postoperative VTE to a greater extent than enoxaparin without increasing the risk of bleeding. Additional studies are needed to confirm these findings and to explore the efficacy and safety of FXI and FXII inhibitors in other clinical settings.

Conclusions
Anticoagulation has progressed exponentially in the past 20 years with the development of LMWH and fondaparinux for out-patient prevention and treatment of thrombosis, bivalirudin for use in PCI and the NOACs as replacements for VKAs. Present efforts are directed at ensuring the NOACs are dosed correctly and are more widely used to reduce the risk of stroke in AF patients. The future lies with licensing of reversal agents for rivaroxaban, apixaban and edoxaban, identifying new indications for the NOACs and exploring FXI and FXII as targets for anticoagulants that may be even safer than those available today.

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Conflicts of interest
J.I.W.: consultant and honoraria from Bristol-Myers Squibb, Pfizer, Daiichi Sankyo, Bayer, Janssen, Boehringer Ingelheim, IONIS Pharmaceuticals, Merck, Portola and Perosphere. J.H.: consultant, honoraria and travel support from Bayer Health Care, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Doasense, Novartis, and Pfizer.

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Weitz, Harenberg: Developments in anticoagulants


