Insights into the role of thrombin in the pathogenesis of recurrent ischaemia after acute coronary syndrome

Jeffrey I. Weitz
McMaster University and the Thrombosis and Atherosclerosis Research Institute, Hamilton, Ontario, Canada

Summary
Acute coronary syndrome (ACS) is a medical emergency. Patients who survive the initial event remain at risk of recurrent cardiovascular events. In most cases, ACS is triggered by thrombosis after rupture of an atherosclerotic plaque. Key to thrombus formation at this site is the generation of thrombin, which not only converts fibrinogen to fibrin but also serves as a potent platelet agonist and induceth platelet aggregation at the site of vascular injury. Although dual antiplatelet therapy is more effective for the prevention of recurrent events than aspirin alone after ACS, there remains an approximately 10% risk of recurrent ischaemic events at one year. Recent studies have evaluated whether the addition of an anticoagulant to antiplatelet therapy reduces the risk of recurrent ischaemia after an ACS event. Rivaroxaban, an oral factor Xa inhibitor, attenuates thrombin generation. When used in conjunction with dual antiplatelet therapy in patients with stabilised ACS, rivaroxaban 2.5 mg twice daily significantly reduced the risk of the composite endpoint of cardiovascular death, myocardial infarction and stroke compared with placebo. Although it increased the risk of bleeding, rivaroxaban was associated with a reduction in mortality; a finding that supports the use of a dual-pathway approach that combines anticoagulant and antiplatelet therapy. This review explores the pathophysiology of ACS to provide perspective on the results of recent clinical trials with novel oral anticoagulants for ACS and to identify their potential role in this setting.

Keywords
Acute coronary syndrome, thrombin, thrombosis, factor Xa, rivaroxaban

Introduction
Acute coronary syndrome (ACS) is a leading cause of death and morbidity in Western countries (1). After the initial event, patients remain at risk of further life-threatening thromboembolic cardiovascular (CV) events, with up to one-third of patients dying or experiencing myocardial infarction (MI), refractory angina or hospital readmission for unstable angina within six months (2). Therefore, reducing the risk of recurrent CV events is a global priority to reduce the healthcare burden associated with ACS.

Secondary prevention of thromboembolic events after ACS has been a focus of intense research and development in recent years, resulting in advances in this therapeutic area. A better understanding of the pathways implicated in thrombus formation after ACS has not only resulted in the development of new antiplatelet drugs but also renewed interest in the potential use of anticoagulants for secondary prevention. Newer antiplatelet agents include prasugrel and ticagrelor; these are more potent inhibitors of P2Y12 (the major adenosine diphosphate [ADP] receptor on platelets) than clopidogrel (3–6). Compared with aspirin alone, dual antiplatelet therapy (DAPT) with aspirin and an ADP receptor antagonist reduces the risk of subsequent CV events or stent thrombosis after ACS (7, 8). However, even with the adoption of the newer antiplatelet agents as standard of care, there is an approximately 10% risk of recurrent events within the first year after an ACS event (5, 6).

To address this remaining unmet need, attention has turned from platelets to the coagulation pathway because thrombin generated via this pathway is implicated in recurrent ischaemia after ACS (9).

The initial evidence that inhibition of coagulation is of benefit to patients with ACS was demonstrated in studies with warfarin. When warfarin was added to aspirin in patients who had experienced an ACS event, the risk of subsequent MI and stroke was reduced (10). However, the complexity of warfarin management and the increased risk of bleeding curtailed the use of warfarin in this setting. Nonetheless, the results with warfarin provided proof-of-principle that inhibition of coagulation may be of benefit in a process previously thought to be predominantly platelet-driven. Results from recent studies support the concept that the platelet and thrombin pathways are intimately linked. This observation, together with the availability of non-vitamin K antagonist (VKA) oral anticoagulants (NOACs) that are safer and easier to administer than warfarin, has triggered further investigation into the use of anticoagulants for secondary prevention of ACS.

Financial support:
Editorial support was funded by Bayer HealthCare Pharmaceuticals and Janssen Scientific Affairs LLC.

Received: March 24, 2014
Accepted after minor revision: May 24, 2014
Epub ahead of print: July 17, 2014
http://dx.doi.org/10.1160/TH14-03-0265
Thromb Haemost 2014; 112: 924–931
of anticoagulants in conjunction with antiplatelet therapy in patients with ACS.

Focusing on advances in ACS management, this article a) explores current knowledge about the pathophysiology of ACS, b) describes the NOACs, c) reviews the results of recent clinical trials using these agents in the ACS setting and d) provides perspective on the opportunities and challenges of combined anticoagulant and antiplatelet therapy in patients with ACS. The objective of this review is to consider the benefit-to-risk profile of NOACs in the context of ACS. The literature was identified by a search of relevant keywords (rivaroxaban, dabigatran, apixaban, oral anticoagulant, acute coronary syndrome, warfarin, direct thrombin inhibitors and bleeding) on PubMed, going back to the year 2000. Additional references were sourced from reference lists of other papers, and from the author's own knowledge.

Mechanisms of thrombosis in ACS

The pathogenesis of most ACS events starts with disruption of an atherosclerotic plaque, which exposes thrombogenic material to the blood. Platelets adhere to exposed subendothelial collagen and von Willebrand factor (vWF) via constitutively expressed receptors on their surface (11). Adherent platelets become activated and release thromboxane A₂ and ADP, which activate adjacent platelets. Platelet activation not only triggers outside–inside signalling pathways but also induces conformational changes in glycoprotein (GP) IIb/IIIa, the most abundant integrin on the platelet surface (11). These changes endow GP IIb/IIIa with the capacity to bind fibrinogen and, under high shear conditions, vWF. By simultaneously binding to GP IIb/IIIa on adjacent platelets, fibrinogen and vWF bridge the platelets together, a process that results in platelet aggregation (11).

Concomitant with platelet activation and aggregation, plaque disruption exposes tissue factor (TF) in the lipid-rich core of the plaque to the blood. Exposed TF binds factor VIIa and the TF–factor VIIa complex then initiates blood coagulation, which results in the generation of thrombin. In addition to converting fibrinogen to fibrin, thrombin serves as a potent platelet agonist and feeds back to amplify its generation by activating factors V, VIII and XI (11). Thrombin also activates factor XIII, which then cross-links the fibrin to render it more resistant to degradation.

Thus, thrombus formation after ACS is driven by co-ordinated ‘platelet’ and ‘thrombin’ pathways (Figure 1). Thrombi formed under high shear conditions are platelet-rich, whereas those formed under low blood flow conditions are fibrin-rich (12). However, these two pathways intersect at several levels depending on the site and environmental conditions under which the thrombi form. For example, thrombi in the coronary arteries often have a platelet-rich head and a fibrin-rich tail. The platelet-rich head forms at the site of plaque rupture because platelets adhere to exposed collagen and vWF. Once thrombin is generated and platelet aggregation occurs, blood flow is reduced and the thrombus becomes more fibrin-rich. In addition, platelets have an important role in amplifying thrombin generation because intrinsic tenase (the complex of factor IXa bound to factor VIIIa that is critical for efficient factor Xa generation) and prothrombinase (the complex of factor Xa bound to factor Va that is responsible for the thrombin generation that induces thrombus formation) are assembled on the activated platelet surface (13). Therefore, thrombin serves as the link between vascular injury at sites of atherosclerotic plaque disruption, fibrin formation and the activation of platelets that lead to the formation of platelet-rich thrombi; the central event in the pathogenesis of ACS (14, 15).

Enhanced thrombin generation and increased thromboembolic risk

In the acute phase of ACS, antiplatelet agents (such as aspirin and clopidogrel or another P2Y₁₂ antagonist) and parenteral anticoagulants (such as heparin, enoxaparin or fondaparinux) are the mainstay of treatment (11). Antiplatelet drugs are administered to attenuate platelet activation and aggregation, whereas an anticoagulant is given to inhibit thrombin and/or reduce its generation (11).

Patients are managed medically or undergo reperfusion strategies that involve either percutaneous coronary intervention (PCI) or coronary artery bypass surgery to open blocked arteries. Typically, parenteral anticoagulation is stopped after the acute phase, leaving patients on DAPT with aspirin plus a P2Y₁₂ antagonist, with no mitigation of the potential contribution of the thrombin pathway to subsequent events. This is problematic because markers of thrombin generation, including prothrombin fragment 1 and 2 and thrombin–antithrombin complexes, remain elevated for at least one year after an MI (9) and for more than six months after an ACS event (16, 17). This period of increased thrombin generation coincides with the period of ongoing risk of recurrent ischaemic events, as evidenced by the ~10% rate of CV death, MI or stroke in the first year after an ACS event despite administration of antiplatelet agents (5, 6, 18). Consequently, because DAPT alone is insufficient to fully address the residual risk of recurrence, the existing evidence provides a scientific rationale for a ‘dual-pathway’ approach, targeting both the ‘thrombin pathway’ with anticoagulants as well as the ‘platelet pathway’.

Targeting thrombin in the chronic phase of ACS

Long-term suppression of thrombin generation or thrombin activity requires oral therapy. Until recently, VKAs – e.g. warfarin – were the only oral anticoagulants available. However, recently, orally active direct inhibitors of factor Xa, such as rivaroxaban and apixaban, of thrombin, such as dabigatran, have been licensed for certain indications. Unlike VKAs, which attenuate thrombin generation by reducing the synthesis of the vitamin K-dependent clotting factors, the NOACs attenuate thrombin generation by blocking the active site of factor Xa or inhibit thrombin activity by blocking the active site of thrombin (Table 1, Figure 2) (38).
In the setting of prevention, preclinical evidence suggests that inhibition of factor Xa may have advantages over targeting thrombin, because one molecule of factor Xa has the potential to generate 1,000 molecules of thrombin (19, 20).

**Clinical studies with VKAs**

The potential benefits of anticoagulants after an ACS event were demonstrated years ago with VKAs. The first study reporting a reduction in mortality with VKA administration after MI was published in 1949 (21), and many subsequent trials have confirmed these findings. Meta-analysis of 10 such trials revealed that, compared with aspirin alone, the combination of warfarin plus aspirin reduces the annual rate of recurrent MI by 44% and the annual rates of stroke and revascularisation by 54% and 20%, respectively (10). However, these benefits are offset by a 2.5-fold increase in the incidence of major bleeding (10). The results of an indirect meta-analysis also suggest that the combination of warfarin plus aspirin has similar benefits over aspirin plus clopidogrel, but at the expense of a two-fold increase in major bleeding (22). Although the studies adding warfarin to single or DAPT provide proof-of-principle that attenuation of thrombin generation is of benefit, the complexity of warfarin management and the increased risk of bleeding has restricted its use in this setting.

**Clinical studies with NOACs**

A number of clinical trials have been performed to evaluate the potential benefit of NOACs in addition to standard of care after an ACS event. A summary of relevant trials is provided (Table 2).

**Dabigatran**

In the phase II RE-DEEM trial, patients receiving DAPT after an ACS event were randomised to twice-daily dabigatran (in doses ranging from 50 mg to 150 mg) or to placebo for six months (23). The primary endpoint, the composite of major and non-major clinically relevant bleeding, was increased in a dose-dependent fashion with dabigatran from 1.8-fold to 4.3-fold with the 50 mg and 150 mg dose regimens, respectively. D-dimer levels were reduced with all doses of dabigatran (23). The study was underpowered to assess efficacy, but there was no clear signal for a reduction in the incidence of death, MI or stroke with any dose of dabigatran and development of the drug for this indication was halted.

**Darexaban**

In the phase II RUBY-1 study, patients receiving DAPT after an ACS event received darexaban, an oral direct factor Xa inhibitor (at doses ranging from 10 to 60 mg/day) or placebo for six months...
Bleeding events (the primary endpoint) were more frequent in the darexaban arms than in the placebo arm (pooled hazard ratio [HR] 2.28; 95% confidence interval [CI] 1.13–4.60; p=0.022), and the incidence of bleeding events across the darexaban arms was dose-related. Although there were no other safety concerns, there was no signal of efficacy (24), and the agent was not taken forward into phase III trials.

**TAK-442**

In a randomised phase II study of TAK-442, another oral, direct factor Xa inhibitor, in patients with a recent ACS event and currently receiving aspirin or DAPT, TAK-442 doses of 10–120 mg twice daily or 40–160 mg once daily were compared with placebo. Using sensitive bleeding scales, the rate of bleeding was increased with higher doses of study drug. There was no clear evidence of a reduction in CV events with TAK-442 and the agent was not developed further (25).

**Apixaban**

In the phase II APPRAISE study, patients with stabilised ACS (N=1,715) were randomised to apixaban (at doses of 2.5 or 10 mg twice daily, or 10 or 20 mg once daily) or to placebo; most patients

---

**Table 1: Characteristics of vitamin K antagonists and of direct thrombin and factor Xa inhibitors.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Agents</th>
<th>Principal mechanism of action</th>
<th>Requires routine coagulation monitoring</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKAs</td>
<td>Warfarin Phenprocoumon Acenocoumarol</td>
<td>Inhibition of synthesis of vitamin K–dependent coagulation factors (factors II, VII, IX and X)</td>
<td>Yes</td>
<td>Delayed onset and offset of action, Unpredictable dose response, Narrow therapeutic window, Multiple drug and food interactions</td>
</tr>
<tr>
<td>Thrombin inhibitor</td>
<td>Darexaban</td>
<td>Inhibition of thrombin activity</td>
<td>No</td>
<td>Twice-daily dosing for most indications, Renal excretion, No reversal agent</td>
</tr>
<tr>
<td>Factor Xa inhibitors</td>
<td>Rivaroxaban Darexaban Apixaban Edoxaban Betrixaban</td>
<td>Inhibition of factor Xa activity, thereby attenuating thrombin generation</td>
<td>No</td>
<td>Once- or twice-daily dosing (twice-daily for rivaroxaban in ACS), Partial renal excretion, No reversal agent</td>
</tr>
</tbody>
</table>

aNot approved for use in secondary prevention of atherothrombotic events post-ACS. ACS, acute coronary syndrome; VKA, vitamin K antagonist.

---

**Figure 2: Pathways for thrombus formation and targets for antithrombotic agents.** For clarity, only key activation pathways are shown. TF = tissue factor; VKA = vitamin K antagonist. Adapted from (38).
were receiving concomitant aspirin and clopidogrel (26). The two higher-dose apixaban regimens were stopped early because of excess bleeding (26). Although the 2.5 mg twice-daily and 10 mg once-daily regimens were associated with 1.8-fold and 2.5-fold increases in bleeding, respectively, rates of ischaemic events were reduced; this was more frequently observed in patients who were taking aspirin alone (26). Based on these results, patients with stabilised ACS were randomised in the phase III APPRAISE-2 trial to apixaban (5 mg twice daily) or placebo, in addition to DAPT with aspirin and clopidogrel in most patients (27). The study was

Table 2: Summary of trials of non-Vitamin K antagonist oral anticoagulants in acute coronary syndrome.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study drug and doses</th>
<th>Duration</th>
<th>Mechanism of action</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-DEEM (23) (2011):</td>
<td>Dabigatran 50 mg bid; 75 mg bid; 110 mg bid; 150 mg bid vs placebo, in patients hospitalised with an ACS in previous 14 days and receiving DAPT</td>
<td>6 months</td>
<td>Oral direct thrombin inhibitor</td>
<td>Composite of major and NMCR bleeding; RR (95 % CI) vs placebo: Dabigatran 50 mg: 1.77 (0.70–4.50) Dabigatran 75 mg: 2.17 (0.88–5.31) Dabigatran 110 mg: 3.92 (1.72–8.95) Dabigatran 150 mg: 4.27 (1.86–9.81)</td>
</tr>
<tr>
<td>1,861 patients</td>
<td>(Phase II)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RUBY-1 (24) (2011):</td>
<td>Darexaban 5 mg bid; 10 mg od; 15 mg bid; 30 mg od; 30 mg bid; 60 mg od vs placebo, in patients with recent STE-ACS/NSTE-ACS</td>
<td>26 weeks</td>
<td>Oral direct factor Xa inhibitor</td>
<td>Composite of major and NMCR bleeding; HR (95 % CI) vs placebo: Darexaban pooled analysis: 2.28 (1.13–4.60), p=0.022</td>
</tr>
<tr>
<td>1,279 patients</td>
<td>(Phase II)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AXIOM-ACS (25) (2011):</td>
<td>TAK-442 Stage 1: 10 mg bid; 20 mg bid; 40 mg od Stage 2: 40 mg bid; 80 mg od; 80 mg bid Stage 3: 160 mg od; 120 mg bid (in addition to usual care) vs placebo, in patients with recent ACS</td>
<td>24 weeks</td>
<td>Oral direct factor Xa inhibitor</td>
<td>Incidence of major bleeding (TIMI) Not increased in TAK-442 patients compared with placebo. However, when a more sensitive bleeding scale was employed, bleeding increased in a dose-dependent manner</td>
</tr>
<tr>
<td>2,753 patients</td>
<td>(Phase II)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APPRAISE (26) (2009):</td>
<td>Apixaban 2.5 mg bid; 10 mg od; 10 mg bid; 20 mg od, in stabilised patients who experienced an ACS in the previous 7 days</td>
<td>6 months</td>
<td>Oral direct factor Xa inhibitor</td>
<td>Composite of major and NMCR bleeding; HR (95 % CI) vs placebo: Apixaban 10 mg bid and 20 mg od discontinued due to excess total bleeding Apixaban 2.5 mg bid: 1.78 (0.91–3.48), p=0.09 Apixaban 10 mg od: 2.45 (1.31–4.61), p=0.005</td>
</tr>
<tr>
<td>1,715 patients</td>
<td>(Phase II)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APPRAISE-2 (27) (2011):</td>
<td>Apixaban 5 mg bid, in patients hospitalised with an ACS in the previous 7 days</td>
<td>241 days (early termination)</td>
<td>Oral direct factor Xa inhibitor</td>
<td>CV death, MI or ischaemic stroke; HR (95 % CI) vs placebo: 0.95 (0.80–1.11), p=0.51 Primary safety outcome of major bleeding: 2.59 (1.50–4.46), p=0.001</td>
</tr>
<tr>
<td>7,392 patients</td>
<td>(Phase III)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATLAS ACS-TIMI 46 (28)</td>
<td>Rivaroxaban Range of od and bid doses (5–20 mg), in stabilised patients with ACS, 1–7 days post-index event, with aspirin alone or aspirin plus a thienopyridine</td>
<td>6 months</td>
<td>Oral direct factor Xa inhibitor</td>
<td>Death, MI, stroke or severe recurrent ischaemia; HR (95 % CI) vs placebo: 0.79 (0.60–1.05); p=0.10 Death, MI or stroke; 0.69 (0.50–0.96); p=0.027 Primary safety outcome of major bleeding; Clinically significant bleeding was increased with rivaroxaban in a dose-dependent manner</td>
</tr>
<tr>
<td>(2009): 3,491 patients</td>
<td>(Phase II)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATLAS ACS 2-TIMI 51 (29, 30) (2012): 15,526 patients</td>
<td>Rivaroxaban 2.5 mg bid; 5 mg bid, in hospitalised patients with symptoms suggestive of ACS</td>
<td>Maximum follow-up of 31 months (mean: 13 months)</td>
<td>Oral direct factor Xa inhibitor</td>
<td>CV death, MI or stroke; HR (95 % CI) vs placebo: 0.84 (0.74–0.96); p=0.008 Primary safety outcome of non-CABG major bleeding; Increased rate compared with placebo (2.1 % vs 0.6 %, p&lt;0.001)</td>
</tr>
<tr>
<td>(Phase III)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACS = Acute coronary syndrome; bid = Twice daily; CABG = Coronary artery bypass graft; CI = Confidence interval; CV = Cardiovascular; DAPT = Dual antiplatelet therapy; HR = Hazard ratio; MI = Myocardial infarction; NMCR = Non-major clinically relevant; NSTE-ACS = Non-ST-elevation acute coronary syndrome; od = Once daily; RR = Relative risk; STE-ACS = ST-elevation acute coronary syndrome; TIMI = Thrombolysis in myocardial infarction.
stopped early (after recruitment of 7,392 of the planned 10,800 patients) because of excessive bleeding with apixaban that was not offset by a reduction in ischaemic events (27). Apixaban has not been studied further in this setting.

**Rivaroxaban**

The phase II ATLAS ACS–TIMI 46 trial randomised 3,491 patients with stabilised ACS to a wide range of once- or twice-daily rivaroxaban regimens (up to a total dose of 20 mg/day) or to placebo. All patients received aspirin and most were also given a thienopyridine (28). Compared with placebo, rivaroxaban produced a dose-dependent increase in clinically relevant bleeding events; this increase was offset by a reduction in the rate of death, MI or stroke from 5.5% to 3.9% (HR=0.69; 95% CI 0.50–0.96; p=0.027) (29). Based on analysis of net clinical benefit, the two lowest doses of rivaroxaban (2.5 and 5 mg twice daily) were carried forward into phase III testing (29).

In the double-blind, placebo-controlled, phase III ATLAS ACS 2–TIMI 51 trial, the efficacy and safety of rivaroxaban 2.5 and 5 mg twice daily were compared with those of placebo in 15,526 patients with stabilised ACS (30). After a mean treatment duration of 13 months, rivaroxaban significantly reduced the primary efficacy outcome – a composite of CV death, MI or stroke – from 10.7% to 8.9% (HR=0.84; 95% CI 0.74–0.96; p=0.008). In patients given the 5 and 2.5 mg twice-daily regimens, the rates were 8.8% (p=0.03) and 9.1% (p=0.02), respectively (30). Compared with placebo, rivaroxaban produced a statistically significant increase in the rates of major bleeding (from 0.6% to 2.1%; p<0.001) and intracranial haemorrhage (from 0.2% to 0.6% in the combined analysis; p=0.009). In the subdivision of treatment arms, rates of intracranial haemorrhage were 0.2% with placebo, and 0.4% and 0.7% with the 2.5 and 5 mg twice-daily doses of rivaroxaban, respectively. Rates of TIMI major bleeding not associated with coronary artery bypass graft surgery were significantly higher with the 2.5 mg and 5 mg doses of rivaroxaban than with placebo (1.8%, 2.4% and 0.6%, respectively), representing three- and fourfold increases, respectively. Importantly, however, there was no significant increase in the rate of fatal bleeding (from 0.2% to 0.3%; p=0.66) (30). Rivaroxaban also reduced the rate of stent thrombosis from 2.9% to 2.3% (p=0.02). This observation is particularly noteworthy because it challenges the prevailing wisdom that stent thrombosis is a platelet-driven phenomenon. Although both doses of rivaroxaban reduced the rate of the primary efficacy endpoint, the lower-dose regimen was not only associated with less fatal bleeding than the higher (5 mg twice daily) dose (0.1% and 0.4%, respectively; p=0.04) but also reduced the rate of death from CV causes compared with placebo, from 4.1% to 2.7% (p=0.002) (30). Based on these results, rivaroxaban 2.5 mg twice daily was the first of the NOACs to receive regulatory approval in the European Union for secondary prevention in patients with elevated cardiac biomarkers after an ACS event (31). Although approved for use in conjunction with aspirin and/or clopidogrel, rivaroxaban is not licensed for use in conjunction with ticagrelor or prasugrel (31) because rivaroxaban in combination with these agents was not evaluated in the ATLAS ACS–TIMI 46 and ATLAS ACS 2–TIMI 51 trials.

**Wider implications and next steps**

Why did dabigatran, darexaban, TAK-442 and apixaban fail to demonstrate a reduction in CV death, MI or stroke compared with placebo? Firstly, the phase II studies of dabigatran, darexaban and TAK-442 were small and underpowered to show an efficacy advantage. Secondly, the dose of anticoagulant is critical, as highlighted by the results of the ATLAS trials, in which lower doses were associated with a greater net clinical benefit than higher doses. Therefore, the 2.5 mg twice-daily dose of rivaroxaban that is licensed for the ACS indication in the European Union is not only lower than the 20 mg once-daily dose that is approved for reduction of stroke in patients with atrial fibrillation and for treatment of acute venous thromboembolism but is also lower than the 10 mg once-daily dose licensed for prevention of venous thromboembolism after elective hip or knee replacement surgery. Third, patient selection is likely to be relevant. Patients with a history of ischaemic stroke or transient ischaemic attack have an increased risk of intracranial bleeding (6, 32), and the ATLAS ACS 2–TIMI 51 study excluded such patients (30). In contrast, this patient group was not excluded from the APPRAISE-2 study (26). Finally, the failure of dabigatran to show a benefit in the ACS setting may reflect mechanistic limitations of the drug. With plaque rupture, there is a rapid generation of thrombin, and the local concentrations of thrombin may exceed those of dabigatran.

Although the results of ATLAS ACS 2–TIMI 51 give rise to speculation regarding drug mechanisms, they also offer new insights into the pathophysiology of atherothrombosis. The reduction in the incidence of recurrent ischaemic events that is achieved by adding an anticoagulant to DAPT supports the notion that increased thrombin generation after ACS has a role in the pathogenesis of subsequent ischaemic events, thereby validating a combined anticoagulant–antiplatelet approach to risk reduction post-ACS. The reduction in stent thrombosis with rivaroxaban observed in the ATLAS trials alters the current paradigm that this is a platelet-driven phenomenon and offers a novel strategy for reducing the risk of this potentially fatal complication. The ATLAS ACS 2–TIMI 51 study was a long-term secondary prevention study, with antiplatelet therapy initiated in the acute phase and rivaroxaban therapy initiated sub-acutely. Although there is a preference for ticagrelor or prasugrel over clopidogrel in the guidelines, all three antiplatelet agents are recommended (33, 34), and clopidogrel remains in widespread use globally. On the basis of the findings of ATLAS ACS 2 TIMI 51, the most recent European guidelines for ST-segment elevation myocardial infarction (STEMI) also recommend that rivaroxaban 2.5 mg twice daily be considered for patients at low bleeding risk who are receiving aspirin and clopidogrel (33). Ongoing studies, such as PIONEER AF-PCI (see below), are evaluating the efficacy and safety of rivaroxaban in combination with the newer antiplatelet agents, albeit in a clinical context different from that of the ATLAS trials.
An ongoing phase III trial with rivaroxaban (the COMPASS trial; NCT01776424) is evaluating the role of rivaroxaban for secondary prevention of CV death, MI and stroke in 19,500 patients with coronary artery disease or peripheral arterial disease (35). This three-arm study is comparing aspirin alone, rivaroxaban alone at a dose of 5 mg twice daily, and the combination of aspirin plus rivaroxaban at a dose of 2.5 mg twice daily. If rivaroxaban reduces the risk of recurrent ischaemic events in this broad population of patients, the findings will provide further support for the role of thrombin in the pathogenesis of atherothrombosis.

Now that the benefit of combining antiplatelet and anticoagulant therapy for reduction of recurrent ischaemic events after ACS has been established, the challenge lies in identifying patients who are suitable for intensified treatment and determining whether the platform antiplatelet therapy can be modified to lower the bleeding risk. Although most of the recent advances in antithrombotic therapy have focused on combining antiplatelet drugs and replacing clopidogrel with more potent P2Y12 inhibitors, we now need to concentrate on reducing bleeding. In this regard, the results of the WOEST study are intriguing. In this open-label study, 573 patients receiving VKAs and undergoing PCI were randomised to aspirin plus clopidogrel (triple therapy) or to clopidogrel alone (dual therapy) for one year after the procedure (36). Dual therapy was associated with significantly fewer bleeding events than triple therapy (19.4% and 44.4%, respectively; HR=0.36; 95% CI 0.26–0.50; p <0.0001). Additionally, all-cause mortality was lower with dual therapy than with triple therapy (2.5% and 6.3%, respectively; p=0.027) and, with dual therapy, there was no increase in any of the other secondary efficacy endpoints, including MI, target vessel revascularisation, stroke and stent thrombosis (36). Although these findings require confirmation in larger studies, they set the stage for comparing dual therapy (rivaroxaban plus clopidogrel) with triple therapy (rivaroxaban, aspirin and a P2Y12 inhibitor [clopidogrel, prasugrel or ticagrelor]). It is hoped that the results of an ongoing study, PIONEER AF-PCI (NCT01830543), will provide insights into the potential of these novel combinations (37). This study compares triple therapy with rivaroxaban or VKAs in patients with atrial fibrillation who undergo PCI and also explores the safety and efficacy of rivaroxaban in combination with prasugrel or ticagrelor. Results of this study are expected in 2015 (37).

Conclusions

Recent studies have provided additional evidence that thrombin has an important part in the pathogenesis of recurrent ischaemic events and stent thrombosis after ACS; these findings render thrombin an attractive target for therapeutic intervention. It is likely that the benefit of thrombin inhibition in this setting reflects not only attenuation of coagulation but also suppression of thrombin-mediated platelet activation and aggregation. Although the results of studies evaluating the addition of warfarin to aspirin for secondary prevention after MI supported the use of agents that suppress thrombin generation, the complexities of warfarin management and its narrow therapeutic index limit its utility. Furthermore, with the advent of DAPT as the platform for post-ACS management, there are more concerns regarding warfarin because of the increased risk of bleeding associated with its use. Rivaroxaban is the first NOAC to demonstrate an acceptable benefit-risk profile when used in combination with DAPT in this setting. With the approval of rivaroxaban for post-ACS management in the European Union, we are now poised to answer additional questions about the role of the thrombin pathway in atherothrombosis, thereby offering new possibilities for improving clinical outcomes.

Acknowledgements

The author would like to thank Abigail Macleod and John Bull, who provided editorial support with funding from Bayer Healthcare Pharmaceuticals and Janssen Scientific Affairs LLC. Dr Weitz holds the Canada Research Chair (Tier 1) in Thrombosis and the Heart and Stroke Foundation/J. Fraser Mustard Chair in Cardiovascular Research.

Conflicts of interests

Editorial support was funded by Bayer Healthcare Pharmaceuticals and Janssen Scientific Affairs LLC. Dr Weitz has served as a consultant and received honoraria from Bayer, Janssen, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Takeda and Daiichi Sankyo.

References