Role of Oral Factor Xa Inhibitors after Acute Coronary Syndrome

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Abstract

Despite an early invasive strategy and the use of dual antiplatelet therapy, patients with acute coronary syndrome (ACS) continue to be at substantial risk for recurrent ischemic events. It is believed that this risk is, at least in part, due to an intrinsic coagulation pathway that remains activated for a prolonged period after ACS. Earlier studies using warfarin showed a reduction in ischemic events, but the overall benefits were offset by increased bleeding complications. Recently, there has been increased interest in the potential role of new oral anticoagulants, some of which target factor Xa, after ACS. Factor Xa is important for the coagulation pathway and also plays a role in cellular proliferation and inflammation. It may thus be an attractive target for therapeutic intervention in ACS. Recently, various oral factor Xa inhibitors have been studied as potential treatment options for ACS. This review will focus on currently available data to evaluate the possible role of factor Xa inhibitors in the management of patients with ACS.

Introduction

Antiplatelet therapy has significantly reduced the morbidity and mortality associated with acute coronary syndrome (ACS), the most important potentially lethal complication of coronary artery disease [1–8]. Platelet aggregation plays an important role in the pathogenesis of atherothrombosis. Hence, the administration of platelet adenosine diphosphate receptor antagonists has been a major advance in treating patients with ACS. Recently, two particularly potent nonthienopyridine adenosine di...
phosphate receptor antagonists, prasugrel and ticagrelor, have been evaluated for their efficacy relative to clopidogrel [7, 9, 10]. However, despite dual antiplatelet therapy (DAPT) with aspirin (ASA), the risk of major adverse cardiovascular events after ACS remains as high as 10%, and is attributed to a relatively hypercoagulable state which persists even months after the index event [1, 2]. ACS is likely the result of atherosclerotic plaque rupture leading to platelet activation and then activation of the coagulation cascade, which culminates in thrombus formation [8]. Factor Xa is central in the coagulation cascade, being involved in the initiation, amplification and propagation phases of clot formation [11]. Exposure to tissue factor following plaque rupture or erosion activates factor Xa, which catalyzes the conversion of prothrombin to active thrombin. Moreover, on a molar basis, factor Xa is more thrombogenic than thrombin (factor IIa) [12], and is important for cellular proliferation [13] and the inflammatory pathway [14].

For synergy in preventing thrombus formation and inflammation, antithrombin therapy in addition to platelet inhibition has been proposed. Warfarin, for many decades the only oral anticoagulant available, has produced mixed results in patients with ACS. In some trials, it was shown to reduce cardiac ischemic events [5, 6], but in others, no difference was observed when it was compared to ASA alone [15–17]. An increased risk of bleeding, a narrow therapeutic index, the need for regular monitoring and drug and food interactions all limit the use of warfarin. In addition, warfarin manifests a relative long-time action relationship, complicating dosing. Thus, the search has continued for an anticoagulant with more predictable pharmacokinetics, and perhaps providing a convenient fixed-dose administration option. New oral anticoagulants, like factor Xa inhibitors (apixaban and rivaroxaban) have been evaluated as treatment options for ACS. In this review, we examine the evidence for factor Xa inhibitors playing a role in the management of patients with ACS.

Current Anticoagulation Therapy

Early in the course of ACS, the short-term use of parenteral anticoagulants, such as unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), fondaparinux and bivalirudin, have reduced the incidence of thrombotic events [18–24]. A meta-analysis of randomized trials using UFH and ASA in patients with unstable angina pectoris showed a 33% reduction in myocardial infarction (MI) and cardiovascular mortality compared to placebo [20]. Subsequently, enoxaparin, a LMWH used in patients with MI who had been treated with fibrinolysis, proved to be more effective than UFH and was associated with a lower rate of rethrombosis [21, 25]. However, this benefit was achieved with an increase in minor (but not major) bleeding complications and greater treatment costs [26]. UFH and LMWH inhibit both factor IIa and factor Xa, whereas fondaparinux selectively inhibits factor Xa by potentiating antithrombin III. The role of fondaparinux in ACS was studied in the Organization to Assess Strategies in Acute Ischemic Syndromes trials 5 and 6 [22, 23]. A significant reduction in both bleeding risk and mortality occurred among patients with non-ST segment elevation MI (non-STEMI, NSTEMI) treated with fondaparinux when compared to enoxaparin. However, there was no statistically significant difference in cardiovascular events between the two arms [22]. Subsequently, patients with STEMI who were treated with fondaparinux had a significant decrease in cardiovascular events and mortality without an increase in bleeding complications in comparison with those treated with UFH. This benefit was not found in patients undergoing primary percutaneous intervention [23]. Thus, fondaparinux may be a useful option in patients who do not undergo reperfusion therapy, given the reduced bleeding and reduced mortality compared to with enoxaparin. The main limitation with these agents is the need for parenteral administration, which makes their use impractical after hospital discharge if continued anticoagulation is desired. Moreover, in a study investigating prolonged LMWH use following discharge, no benefit was shown [27]. Nonetheless, the encouraging results with fondaparinux raise hope for long-term oral factor Xa inhibition being beneficial.

In a multinational, randomized controlled trial, the addition of the direct thrombin inhibitor ximelagatran in patients with ACS reduced the risk of death, MI or stroke by 70%. However, these positive results were overshadowed by the liver toxicity associated with ximelagatran [28], and ultimately led to the removal of the drug from the European market as well as failure to achieve Food and Drug Administration (FDA) approval in the USA. Dabigatran was the first FDA-approved direct thrombin inhibitor for the prevention of stroke and systemic embolism in nonvalvular atrial fibrillation. However, concerns have also been raised about its safety, as it has been reported to be associated with a higher risk of ACS than alternative anticoagulant schemes [29].
Review Methods

We systematically searched the PubMed, CINAHL, Cochrane CENTRAL, Scopus and Web of Science databases for studies evaluating the role of oral factor Xa inhibitors in patients with ACS. All relevant combinations of the following keywords: ‘novel oral anticoagulants’, ‘oral factor Xa inhibitors’, ‘rivaroxaban’, ‘apixaban’, ‘darexaban’ and ‘acute coronary syndrome’ were included in the search. It was conducted from the inception of these databases up till the 31 August 2014 without applying any language restrictions.

Oral Factor Xa Inhibitors in ACS

Factor Xa inhibitors directly inhibit the enzyme-catalyzing generation of thrombin. Four of these agents, apixaban, darexaban, rivaroxaban and letaxaban, have been assessed in phase II studies in ACS [30–33], but so far only apixaban and rivaroxaban have been studied in phase III trials [34, 35] (tables 1, 2).

Rivaroxaban

Rivaroxaban is an oral, selective, direct-acting factor Xa inhibitor that leads to the inactivation of free, fibrin-bound Xa and also factor Xa within the prothrombinase complex [36]. It has dose-proportional pharmacokinetics with an oral bioavailability of approximately 80% [37]. The half-life is 5–13 h (5–9 h in the young and 11–13 h in the elderly) and the time to peak concentration in plasma is 2–4 h, which correlates well with the time for maximum inhibition of factor Xa [38]. The inhibition of factor Xa persists for up to 24 h after administration of a dose of rivaroxaban. Rivaroxaban is eliminated via both the kidneys and liver, with approximately one third eliminated as unchanged active drug in the urine. The other two thirds are metabolized in the liver mainly by the CYP3A4 and CYP2J2 enzyme systems, with half being eliminated via the hepatobiliary route in the feces and the other half via the kidneys [39]. Rivaroxaban is not recommended for cirrhotic patients with concomitant coagulopathy and end-stage renal failure (i.e. a creatinine clearance of <15 ml/min), and the dose needs to be adjusted in patients with advanced renal insufficiency (i.e. a creatinine clearance of 15–29 ml/min) [38, 40].

ATLAS ACS TIMI 46 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin with or without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 46) was a phase II, multicenter, double-blind, dose-escalation, randomized controlled trial of 3,491 patients designed to evaluate the efficacy and safety of rivaroxaban for secondary prevention in patients with ACS [32]. The trial found that rivaroxaban tended to outperform placebo, a result that failed to reach statistical significance, however. Patients who had stabilized after ACS were enrolled within 7 days of hospital admission and doses of 5–20 mg of rivaroxaban once or twice daily were administered. Patients were grouped into two strata at the discretion of investigators, to receive either ASA alone (stratum 1) or DAPT (stratum 2). Within each stratum, randomization was done on a 1:1:1 basis to either a rivaroxaban dose (5–20 mg once or twice daily) or placebo.

The results showed a nonstatistically significant decrease in the occurrence of the primary efficacy end point (death, MI, stroke or recurrent ischemia requiring revascularization) in patients receiving rivaroxaban compared to placebo [5.9 vs. 7.0%, hazard ratio (HR) 0.79 and 95% confidence interval (CI) 0.60–1.05, p = 0.10]. The secondary efficacy end point of death, MI or stroke was significantly lower in patients who received rivaroxaban (3.9 vs. 5.5%, HR 0.69 and 95% CI 0.50–0.96, p = 0.027). A dose-dependent increase in clinically significant bleeding was seen in both strata [HR 2.21 (95% CI 1.25–3.91) for 5-mg doses, 3.35 (2.31–4.87) for 10-mg doses and 5.06 (3.45–7.42) for 20-mg doses daily (p < 0.0001)], with absolute rates being higher in stratum 2 (ASA + thienopyridine) than in stratum 1 (ASA only). The net clinical outcome, i.e. death, stroke, MI or TIMI major bleeding was favorable in patients receiving 2.5 or 5 mg twice daily (HR 0.72 and 95% CI 0.46–1.12). Though the trial was not powered to demonstrate the reduction in efficacy end points, it did show a positive trend, suggesting a role for rivaroxaban in ACS.

On the basis of the findings of this trial, the low-dose regimens (i.e. 2.5 and 5 mg twice daily) were selected for further evaluation in a further randomized double-blind, multicenter, phase III trial, ATLAS ACS 2-TIMI 51 [35]. For this trial, 15,526 ACS patients (50.3% with STEMI, 25.6% with non-STEMI and 24.0% with unstable angina) were enrolled within 7 days after the index event (tables 1, 2). Randomization was done on a 1:1:1 basis to receive either rivaroxaban (2.5 or 5 mg twice a day) or placebo within each stratum (i.e. ASA vs. DAPT). The primary efficacy end point was a composite of cardiovascular death, MI or stroke. The secondary efficacy end point was death from any cause, MI or stroke. TIMI major bleeding not related to bypass surgery was designated as the primary safety end point.
point. The baseline characteristics of patients in the assigned groups were well matched and patients were followed for a mean treatment period of 13.1 months.

Rivaroxaban reduced the primary efficacy end points in comparison to placebo with rates of 9.1 versus 10.7% for 2.5 mg (HR 0.84 and 95% CI 0.72–0.97, p = 0.02) and 8.8 versus 10.7% for 5 mg (HR 0.85 and 95% CI 0.73–0.98, p = 0.03), respectively (table 2). Overall, a 16% relative risk reduction was observed in the primary efficacy composite with rivaroxaban. The results also showed a significant decrease in secondary efficacy end points among patients who received rivaroxaban (9.2 vs.11%, HR 0.84 and 95% CI 0.74–0.95, p = 0.006). Rivaroxaban lowered the rate of stent thrombosis significantly (2.3 vs. 2.9%, HR

<table>
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<tr>
<th>Inclusion criteria</th>
<th>APPRAISE 2</th>
<th>ATLAS ACS 2-TIMI 51</th>
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<tr>
<td>An ACS (STEMI, NSTEMI or unstable angina) event within the previous 7 days, if clinically stable and receiving standard antiplatelet therapy (ASA or ASA + P2Y12 receptor antagonist) and ≥2 of the following high-risk characteristics:</td>
<td>Patients aged ≥18 years diagnosed with ACS (STEMI, NSTEMI or unstable angina) in the past 7 days. Clinically stabilized. Receiving medical therapy with ASA or ASA + thienopyridine. Patients aged 18–54 years with either diabetes mellitus or previous MI.</td>
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<td>age ≥65 years, diabetes mellitus, MI within the previous 5 years, cerebrovascular disease, peripheral vascular disease, clinical heart failure or LVEF &lt;40% in association with the index event, impaired renal function with a CrCl &lt;60 ml/min and no revascularization after the index event.</td>
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| Key exclusion criteria | |
| Active bleeding or a high risk of bleeding. Known coagulopathy. Ischemic stroke within 7 days. History of intracranial bleeding. NYHA class IV heart failure. Hb <9 g/dl. Platelet count <100,000/ml. CrCl <20 ml/min. Persistent, severe hypertension. Ongoing treatment with a parenteral or oral anticoagulant. Severe comorbid condition with a life expectancy of ≤6 months. | Previous ischemic stroke or transient ischemic attack in patients taking both ASA and a thienopyridine. A history of intracranial hemorrhage. Significant gastrointestinal bleeding within the last 12 months. Hb <10 g/dl. Platelet count <90,000/ml. CrCl <30 ml/min. |

| Efficacy end points | Primary: a composite of CV death, MI or ischemic stroke. Secondary: a composite of: CV death, MI, ischemic stroke or unstable angina or CV death, MI, ischemic or hemorrhagic stroke or fatal bleeding or death from any cause, MI or ischemic or hemorrhagic stroke. | Primary: a composite of death from CV causes, MI or stroke (ischemic, hemorrhagic or stroke of uncertain cause). Secondary: a composite of: death from any cause, MI or stroke or CV death, MI, ischemic stroke or a non-CABG TIMI major bleeding event or CV death, MI, stroke or severe recurrent ischemia requiring revascularization. |

| Safety end points | Primary: TIMI major bleeding, i.e. a reduction in Hb of ≥5 g/dl (or >15% in hematocrit) or any intracranial bleeding. Secondary: TIMI major or minor bleeding ISTH major or clinically relevant bleeding Severe or moderate bleeding according to the GUSTO definitions. | Primary: TIMI major bleeding not related to CABG. Secondary: Other bleeding events, i.e. TIMI minor bleeding, TIMI bleeding requiring medical attention or intracranial hemorrhage. Serious adverse events. |

CABG = Coronary artery bypass graft surgery; CrCl = creatinine clearance; CV = cardiovascular; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; Hb = hemoglobin; ISTH = International Society on Thrombosis and Haemostasis; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.
0.69 and 95% CI 0.51–0.93, p = 0.02). In the subgroup analysis, the dose of 2.5 mg twice a day reduced all-cause mortality by 32% (2.7 vs. 4.1%, HR 0.66 and 95% CI 0.51–0.86, p = 0.002) and cardiovascular mortality by 34% (2.9 vs. 4.5%, HR 0.68 and 95% CI 0.53–0.87, p = 0.002) whereas the 5-mg twice a day regimen was associated with a significant decrease in recurrent MI (4.9 vs. 6.6%, p = 0.02). Although there was no increase in the rate of fatal bleeding (0.3 vs. 0.2%, p = 0.66), the incidence of TIMI major bleeding (unrelated to bypass surgery) was higher among those who received rivaroxaban (2.1 vs. 0.6%, HR 3.96 and 95% CI 2.46–6.38, p < 0.001). The rate of intracranial hemorrhage in the rivaroxaban group also increased significantly compared with placebo (0.6 vs. 0.2%, HR 3.28 and 95% CI 1.28–8.42, p = 0.009). However, low-dose rivaroxaban (2.5 mg twice daily) was associated with a lower risk of bleeding events compared with the 5-mg dose, including TIMI major bleeding (1.8 vs. 2.4%), intracranial hemorrhage (0.4 vs. 0.7%) and bleeding requiring medical attention (12.9 vs. 16.2%; table 2).

A subanalysis of the ATLAS ACS 2-TIMI 51 trial showed that rivaroxaban reduced stent thrombosis among patients who had had a stent placed either before or during the ACS event [41]. Compared to placebo, a significant reduction of probable or definite stent thrombosis was observed in both the pooled (HR 0.65, p = 0.017) and lower-dose (2.5 mg) groups (HR 0.61, p = 0.023), but not in the group receiving the 5-mg dose (HR 0.70, p = 0.089). Another subanalysis of ATLAS ACS 2-TIMI 51 in STEMI patients showed results consistent with the overall study [42]. The primary end point of cardiovascular death, MI or stroke was reduced by 19% with rivaroxaban compared to with placebo (8.4 vs. 10.6%, HR 0.81 and 95% CI 0.67–0.97, p = 0.019). The dose of 2.5 mg twice a day resulted in a significant decrease in cardiovascular death (2.5 vs. 4.2%, HR 0.60 and 95% CI 0.42–0.87, p = 0.006) and all-cause mortality (3 vs. 4.7%, HR 0.63 and 95% CI 0.45–0.89, p = 0.008); 5 mg twice a day failed to show a mortality benefit, but showed a nominally significant reduction in MI (4.8 vs. 6.7%, HR 0.72 and 95% CI 0.51–0.95, p = 0.008); 5 mg twice a day failed to show a mortality benefit, but showed a nominally significant reduction in MI (4.8 vs. 6.7%, HR 0.72 and 95% CI 0.51–0.95, p = 0.019). This observation is consistent with the efficacy results of the entire ACS cohort. Compared with placebo, 2.5 mg rivaroxaban increased the non-bypass TIMI major bleeding (1.7 vs. 0.6%, HR 3.63 and 95% CI 1.73–7.61, p < 0.001).

The divergent impact on the components of the primary end point with the 2 doses of rivaroxaban has raised concerns. The results relative to the primary efficacy composite were consistent across the pooled and individual dose groups as well as in the different major subgroups based on the index ACS event and antithrombotic therapy (ASA alone vs. DAPT). However, a significant reduction in all-cause mortality (2.9 vs. 4.5%, p = 0.002) and cardiovascular mortality (2.7 vs. 4.1%, p = 0.002) was associated only with the lower dose of 2.5 mg, not with the 5-mg dose [35]. In addition, only the 5-mg dose significantly decreased the rate of recurrent MIs (4.9 vs. 6.6%, p = 0.02). Making a direct comparison, the two treatment arms differed significantly regarding the risk of cardiovascular death (both ischemic and hemorrhagic events) and total mortality, with lower rates being seen with the 2.5-mg dose [2.7 vs. 4% (p = 0.009) and 2.9 vs. 4.4% (p = 0.009), respectively] [43]. This inconsistency has also led to questions about the mechanism of the mor-

Table 2. Summary of results: outcomes of studies evaluating role of oral factor Xa inhibitors in ACS

<table>
<thead>
<tr>
<th>Dose</th>
<th>Primary efficacy end point</th>
<th>CV death</th>
<th>All-cause death</th>
<th>MI</th>
<th>Stent thrombosis</th>
<th>Primary safety end point</th>
<th>Intracranial bleeding</th>
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<tr>
<td>Rivaroxaban</td>
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<tr>
<td>2.5 mg BID vs. placebo</td>
<td>HR 0.70 &amp; 0.65 (0.73–0.98)</td>
<td>p = 0.03</td>
<td>HR 0.63 &amp; 0.66</td>
<td>p = 0.02</td>
<td>HR 0.70 &amp; 0.65 (0.75–1.20)</td>
<td>HR 0.70 &amp; 0.65 (0.75–1.20)</td>
<td>HR 0.70 &amp; 0.65 (0.75–1.20)</td>
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<td>5 mg BID vs. placebo</td>
<td>HR 0.85</td>
<td>HR 0.94</td>
<td>HR 0.79</td>
<td>HR 0.73</td>
<td>HR 0.73</td>
<td>HR 4.47</td>
<td>HR 3.74</td>
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<td></td>
<td>(0.73–0.98)</td>
<td>(0.75–1.20)</td>
<td>(0.65–0.97)</td>
<td>(0.51–1.04)</td>
<td>p = 0.008</td>
<td>(2.71–7.36)</td>
<td>(1.39–10.07)</td>
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<td></td>
<td>p = 0.03</td>
<td>p = 0.63</td>
<td>p = 0.02</td>
<td>p = 0.008</td>
<td>p &lt; 0.001</td>
<td>p = 0.005</td>
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<tr>
<td>Apixaban</td>
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<tr>
<td>APPRAISE 2 trial</td>
<td>HR 0.80</td>
<td>HR 0.95</td>
<td>HR 0.89</td>
<td>HR 0.93</td>
<td>HR 0.73</td>
<td>HR 2.59</td>
<td>HR 4.06</td>
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<td></td>
<td>(0.80–1.11)</td>
<td>(0.73–1.25)</td>
<td>(0.66–1.13)</td>
<td>(0.76–1.14)</td>
<td>p = 0.05</td>
<td>(1.50–4.46)</td>
<td>(1.15–14.38)</td>
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<td></td>
<td>p = 0.51</td>
<td>p = 0.76</td>
<td>p = 0.51</td>
<td>p = 0.01</td>
<td>p = 0.03</td>
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Figures in parentheses are CIs. b.i.d. = Twice a day; CV = cardiovascular.
tality benefit with the 2.5-mg dose. One explanation for this mortality benefit could be a decrease in the risk of sudden deaths, which are largely thrombotic in origin [44, 45]. There was a significantly decreased incidence of sudden deaths with rivaroxaban 2.5 mg twice daily compared with placebo (55 vs. 81, p = 0.0047). In addition, the lack of mortality benefit with the 5-mg dose may have been due to the significantly higher rate of bleeding in this group, including an increase in fatal bleeding (0.4% vs. 0.1%, p = 0.04) [35, 43, 46, 47]. The possibility of an increased frequency of intraplaque bleeding leading to more fatal cardiovascular events can also not be totally ruled out. In the analysis that directly compared the two doses of rivaroxaban, the incidence of overall fatal cardiovascular events (112 vs. 82, p = 0.025) was significantly greater with the 5-mg dose than with the 2.5-mg dose, while the difference in fatal MIs trended toward significance (30 vs. 18, p = 0.074) [43]. Furthermore, bleeding events can result in the discontinuation of concomitant antithrombotic drugs, leading to an increased risk of subsequent ischemic events [48]. Specifically, a significantly greater proportion of subjects in the 5-mg group (than in the 2.5-mg group) prematurely discontinued the drug (29.4 vs. 26.9%, p = 0.004) [43].

Apixaban

Apixaban is a highly selective, reversible, oral factor Xa inhibitor. It has a high oral bioavailability of approximately 50% and a half-life of 8–14 h [49]. It is partly excreted in the urine (25%), with the remainder (75%) being cleared via the hepatobiliary route [50]. APPRAISE 2 (Apixaban for Prevention of Acute Ischemic and Safety Events), a randomized, double-blind, multicenter, phase II study, evaluated apixaban in doses from 2.5 mg twice a day to 20 mg once a day [30]; 1,715 patients were enrolled after stabilization, within 7 days after the ACS event. The primary end point was major bleeding and clinically relevant nonmajor bleeding according to the International Society of Thrombosis and Haemostasis definitions. A borderline significant, dose-dependent increase in bleeding was shown with apixaban at both a dose of 2.5 mg twice a day (5.7 vs. 3.0%, HR 1.78 and 95% CI 0.91–3.48, p = 0.09) and a dose of 10 mg once daily (7.9 vs. 3.0%, HR 2.45 and 95% CI 1.31–4.61, p = 0.05) compared to placebo. The use of apixaban was associated with a trend towards a decrease in the incidence of cardiovascular death, MI, severe recurrent ischemia or ischemic stroke, but this did not achieve statistical significance (HR 0.73 and 95% CI 0.44–1.19, p < 0.21 with 2.5 mg twice daily; HR 0.61 and 95% CI 0.35–1.04, p < 0.07 with 10 mg once daily).

The selection of baseline antiplatelet therapy also influenced the results: the increment in bleeding rate was more evident and reduction in ischemic events was less pronounced in patients receiving DAPT than in those who received ASA therapy only.

On the basis of these results, a phase III trial was then conducted to test the effect of apixaban 5 mg twice daily or placebo added to antiplatelet therapy [34]. This was a double-blind, multicenter, randomized study which enrolled 7,392 patients with ACS. The primary efficacy end point was the composite of cardiovascular death, MI or ischemic stroke. The primary safety outcome was defined as TIMI major bleeding (tables 1, 2). There was no statistically significant difference between apixaban and placebo for the incidence of the primary efficacy end point (7.5 vs. 7.9%, HR 0.95 and 95% CI 0.80–1.11, p = 0.51). Importantly, apixaban led to an absolute increase of 0.8% over placebo in TIMI major bleeding (1.5 vs. 0.8%, HR 2.59 and 95% CI 1.50–4.46, p = 0.001; table 2). As a result, the apixaban arm of the study was prematurely discontinued.

Darexaban

Darexaban is an oral, direct factor Xa inhibitor. The metabolite, darexaban glucuronide, is the active principle responsible for the anticoagulant effect [31]. The safety and efficacy of darexaban for secondary prevention in ACS was tested in a phase II trial of 1,279 patients [32]. In this dose-finding, randomized, double-blind, placebo-controlled study, patients received darexaban (5 mg 2× daily, 10 mg 1× daily, 15 mg 2× daily, 30 mg 1× daily, 30 mg 2× daily and 60 mg 1× daily) or placebo in a 1:1:1:1:1:2 ratio. The primary outcome, i.e. major bleeding, was increased in a dose-dependent manner in the darexaban group (p = 0.009) compared to placebo (pooled HR 2.275 and 95% CI 1.13–4.60, p = 0.022), and there was no decrease in the incidence of adverse cardiovascular events with darexaban compared to placebo. Based on the increased bleeding risk with no trend of efficacy, further development of darexaban has been discontinued.

Discussion

Despite an early invasive strategy, the use of anticoagulation (administration of warfarin or heparin in the early phase of ACS treatment) and DAPT, patients with ACS continue to have a residual risk of ischemic complications. Therefore, the use of novel oral anticoagulants to inhibit the generation or activity of thrombin provides a new and potentially useful therapeutic approach for improving
outcomes in ACS. Both apixaban and rivaroxaban are selective factor Xa inhibitors which have demonstrated trends towards a reduction in major cardiovascular events in phase II trials. However, a dose of 2.5 mg rivaroxaban twice daily has been the only agent to show a significant benefit with regard to recurrent cardiovascular events and mortality [35]. The phase III trial, evaluating apixaban, was terminated due to a high rate of bleeding without any increase in efficacy versus placebo. This difference in the results with the two factor Xa inhibitors, apixaban and rivaroxaban, may be explained by the doses used in the phase III trials. In the APPRAISE 2 trial, the dose of apixaban was the same as that used for atrial fibrillation, while the dose used in the ATLAS ACS 2-TIMI 51 trial was only a quarter to half of the dose used in the secondary prevention of complications of atrial fibrillation. Differences between the patient populations may also have contributed to the discrepancy in efficacy that was observed. Patients with a history of ischemic stroke or transient ischemic attack constituted 10% of the total sample size in the APPRAISE 2 trial, but only 2.8% in the ATLAS ACS 2-TIMI 51 trial. These patients with a history of cerebrovascular disease had net harm with apixaban due to an increase in intracranial hemorrhage [34].

The ATLAS ACS 2-TIMI 51 trial showed a significant reduction in death from cardiovascular causes, all-cause mortality and recurrent MI at the cost of an increase in bleeding risk. Furthermore, the 2.5-mg dose of rivaroxaban was associated with survival benefit and a lower risk of bleeding (compared to a dose of 5 mg), presenting a potential therapy for patients with ACS when added to DAPT. Since increased bleeding risk is expected with any anticoagulant, the use of rivaroxaban will need to be personalized for each individual, balancing the benefit of anticoagulation with the risk of bleeding. The ATLAS ACS 2-TIMI 51 trial excluded patients at a high risk for bleeding, i.e. patients with recent significant gastrointestinal hemorrhage, prior intracranial hemorrhage, ischemic stroke or transient ischemic attack [35]. Thus, it is advisable to avoid rivaroxaban in patients who have an identifiably high risk of bleeding. Further studies are required to define the subgroup of patients with 'high thrombotic risk' for whom rivaroxaban may provide the greatest benefit. This includes those with a history of atherothrombotic disease at multiple sites, high levels of lipidemia and a positive family history of death from cardiovascular causes.

In May 2012, on the basis of high rates of missing data [51] which may have impacted the efficacy results of the trial, the FDA (USA) withheld the approval of rivaroxaban for secondary prevention in ACS. Out of 1,294 subjects who withdrew their consent, investigators could confirm the vital status of only 177 patients who were still alive. In other words, the vital status of the other 1,117 patients remained unknown at the end of the trial. In addition, there were discrepancies regarding missing data in the combined rivaroxaban and placebo groups (12.4 vs. 11%). The Cardiovascular and Renal Drugs Advisory Committee concluded that the proportion of patients with unknown vital status was greater than the difference in efficacy outcomes between the treatment and placebo arms, precluding the credibility of the apparent mortality benefit. The sponsors addressed the issue of missing data, and the vital status data of 843 patients were recently submitted to the FDA (USA). As of January 2014, approval had not yet been granted. In contrast, the European Medicines Agency has granted approval for rivaroxaban 2.5 mg twice a day in conjunction with standard antiplatelet therapy for use in post-ACS patients with no history of stroke or transient ischemic attack [52]. The selection of this specific patient population was based on a post hoc analysis which demonstrated improved mortality benefit in patients who were at a greater risk of recurrent ischemic events (i.e. elevated cardiac enzymes) and a lower risk of bleeding (i.e. without prior stroke or transient ischemic attack) [53].

Further complicating the evaluation of ACS treatments is the use of the more potent P2Y12 inhibitors, prasugrel and ticagrelor, since these have shown improved efficacy when compared to the standard treatment with clopidogrel [9, 10]. Though the European guidelines recommend the use of these drugs rather than clopidogrel, the FDA in the USA has kept a neutral stance regarding the newer antiplatelet drugs. Guidelines for the use of rivaroxaban also need to be clearly defined, keeping in mind the increasingly complex sphere of antithrombotic therapy in ACS, with the introduction of prasugrel/ticagrelor as well as protease-activated receptor-1 antagonists (e.g. vorapaxar). Large trials aimed at directly comparing these agents as DAPT (ticagrelor/prasugrel + ASA) with triple therapy (rivaroxaban + clopidogrel + ASA) could help to define new guidelines for the management of ACS. Future studies should also be aimed at testing rivaroxaban as an alternative to the current drugs (e.g. ASA or clopidogrel), rather than as an add-on to DAPT. In WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting?), a recent multicentric trial, patients on anticoagulant drugs undergoing percutaneous coronary interventions were randomized to receive clopidogrel alone or DAPT (ASA + clopidogrel) [54]. The triple therapy (DAPT + an-
ticoagulant) was associated with a significantly higher rate of bleeding compared to the double therapy (clopidogrel + anticoagulant), with no difference in the rate of thrombotic events between the 2 groups.

We conclude that factor Xa inhibitors may play a role in preventing major adverse cardiovascular events when used in patients with ACS. However, optimal dosing, careful selection of patients in terms of bleeding risk and the concurrent use of DAPT must be established before recommendations can be made for the widespread use of these drugs.

Conflict of Interest
The authors have no conflicts of interest to declare.

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Sharma et al. 2013:1;381:1107–1115.