Role of Oral Factor Xa Inhibitors after Acute Coronary Syndrome

Abhishek Sharma^a Akash Garg^c Jeffrey S. Borer^b Parasuram Krishnamoorthy^e
Jalaj Garg^f Carl J. Lavie^{h,i} Armin Arbab-Zadeh^j Debabrata Mukherjee^k
Hasan Ahmad^g Edgar Lichstein^d

^aDivision of Cardiovascular Medicine and ^bThe Howard Gilman Institute for Heart Valve Disease and the Schiavone Institute for Cardiovascular Translational Research, State University of New York Downstate Medical Center, ^cDepartment of Medicine, James J. Peters VA Medical Center, Mount Sinai School of Medicine and ^dDepartment of Medicine, Maimonides Medical Center, New York, N.Y., ^eDepartment of Internal Medicine, Mount Sinai Englewood Hospital and Medical Center Englewood, Englewood, N.J., ^fDepartment of Internal Medicine and ^gDivision of Cardiology, Westchester Medical Center, New York Medical College, Valhalla, N.Y., ^hDepartment of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School, University of Queensland School of Medicine, New Orleans, La., ⁱDepartment of Preventive Medicine, Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, La., ^jDivision of Cardiology, Johns Hopkins University School of Medicine, Baltimore, Md., and ^kDivision of Cardiology, Texas Tech University, Lubbock, Tex., USA

Key Words

Acute coronary syndrome · Factor Xa · Coagulation pathway

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.

© 2014 S. Karger AG, Basel

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 re-thrombosis [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 creatine clearance of <15 ml/min), and the dose needs to be adjusted in patients with advanced renal insufficiency (i.e. a creatine 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

Table 1. Inclusion and exclusion criteria of studies evaluating the role of oral factor Xa inhibitors in ACS

	APPRAISE 2	ATLAS ACS 2-TIMI 51
Inclusion criteria	An ACS (STEMI, NSTEMI or unstable angina) event within the previous 7 days, if clinically stable and receiving standard antiplatelet therapy (ASA or ASA + P2Y ₁₂ receptor antagonist) and ≥ 2 of the following high-risk characteristics: age ≥ 65 years, diabetes mellitus, MI within the previous 5 years, cerebrovascular disease, peripheral vascular disease, clinical heart failure or LVEF $< 40\%$ in association with the index event, impaired renal function with a CrCl < 60 ml/min and no revascularization after the index event.	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.
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	<i>Primary:</i> a composite of CV death, MI or ischemic stroke. <i>Secondary:</i> 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.	<i>Primary:</i> a composite of death from CV causes, MI or stroke (ischemic, hemorrhagic or stroke of uncertain cause). <i>Secondary:</i> 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	<i>Primary:</i> TIMI major bleeding, i.e. a reduction in Hb of ≥ 5 g/dl (or $> 15\%$ in hematocrit) or any intracranial bleeding. <i>Secondary:</i> TIMI major or minor bleeding ISTH major or clinically relevant bleeding Severe or moderate bleeding according to the GUSTO definitions.	<i>Primary:</i> TIMI major bleeding not related to CABG. <i>Secondary:</i> 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.

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

	Dose	Primary efficacy end point	CV death	All-cause death	MI	Stent thrombosis	Primary safety end point	Intracranial bleeding
Apixaban APPRAISE 2 trial	5 mg BID vs. placebo	7.5 vs. 7.9%, HR 0.95 (0.80–1.11) p = 0.51	2.8 vs. 3%, HR 0.96 (0.73–1.25) p = 0.76	4.2 vs. 3.9%, HR 1.08 (0.86–1.35) p = 0.51	4.9 vs. 5.3%, HR 0.93 (0.76–1.14) p = 0.51	0.9 vs. 1.3%, HR 0.73 (0.47–1.12) p = 0.15	1.3 vs. 0.5%, HR 2.59 (1.50–4.46) p = 0.001	0.3 vs. 0.1%, HR 4.06 (1.15–14.38) p = 0.03
Rivaroxaban ATLAS ACS 2-TIMI 51 trial	2.5 mg BID vs. placebo	9.1 vs. 10.7%, HR 0.84 (0.72–0.97) p = 0.02	2.7 vs. 4.1%, HR 0.66 (0.51–0.86) p = 0.002	2.9 vs. 4.5%, HR 0.68 (0.53–0.87) p = 0.002	6.1 vs. 6.6%, HR 0.90 (0.75–1.09) p = 0.27	2.2 vs. 2.9%, HR 0.65 (0.45–0.94) p = 0.02	1.8 vs. 0.6%, HR 3.46 (2.08–5.77) p < 0.001	0.4 vs. 0.2%, HR 2.83 (1.02–7.86) p = 0.04
	5 mg BID vs. placebo	8.8 vs. 10.7%, HR 0.85 (0.73–0.98) p = 0.03	4 vs. 4.1%, HR 0.94 (0.75–1.20) p = 0.63	4.4 vs. 4.5%, HR 0.95 (0.76–1.19) p = 0.66	4.9 vs. 6.6%, HR 0.79 (0.65–0.97) p = 0.02	2.3 vs. 2.9%, HR 0.73 (0.51–1.04) p = 0.008	2.4 vs. 0.6%, HR 4.47 (2.71–7.36) p < 0.001	0.7 vs. 0.2%, HR 3.74 (1.39–10.07) p = 0.005

Figures in parentheses are CIs. b.i.d. = Twice a day; CV = cardiovascular.

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 0.54–0.95, $p = 0.019$). This observation is consistent with the efficacy results of the entire ACS cohort. Compared with placebo, 2.5 mg rivaroxaban increased the nonbypass 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 antiplatelet 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-

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 atherosclerotic 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 sub-

jects 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.

References

- Lewis BS, Mehta SR, Fox KA, et al: Benefit of clopidogrel according to timing of percutaneous coronary intervention in patients with acute coronary syndromes: further results from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study. *Am Heart J* 2005;150:1177–1184.
- Rothberg MB, Celestin C, Fiore LD, Lawler E, Cook JR: Warfarin plus aspirin after myocardial infarction or the acute coronary syndrome: meta-analysis with estimates of risk and benefit. *Ann Intern Med* 2005;143:241–250.
- Andreotti F, Testa L, Biondi-Zoccai GG, Crea F: Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. *Eur Heart J* 2006;27:519–526.
- Karjalainen PP, Porela P, Ylitalo A, et al: Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. *Eur Heart J* 2007;28:726–732.
- Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H: Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002;347:969–974.
- van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE: Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. *Lancet* 2002;360:109–113.
- Ye Y, Xie H, Zeng Y, Zhao X, Tian Z, Zhang S: Optimal oral antithrombotic regimes for patients with acute coronary syndrome: a network meta-analysis. *PLoS One* 2014;9:e90986.
- Arbab-Zadeh A, Nakano M, Virmani R, Fuster V: Acute coronary events. *Circulation* 2012;125:1147–1156.
- Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM: Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001–2015.
- Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Harrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA: Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045–1057.
- Hoffman M, Monroe DM 3rd: A cell-based model of hemostasis. *Thromb Haemost* 2001;85:958–965.
- Yin ET, Wessler S: Investigation of the apparent thrombogenicity of thrombin. *Thromb Diath Haemorrh* 1968;20:465–468.
- Herbert J, Bono F, Herault J, Avril C, Dol F, Mares A, Schaeffer P: Effector protease receptor 1 mediates the mitogenic activity of factor Xa for vascular smooth muscle cells in vitro and in vivo. *J Clin Invest* 1998;101:993–1000.
- Cirino G, Cicala C, Bucci M, Sorrentino L, Ambrosini G, DeDominicis G, Altieri DC: Factor Xa as an interface between coagulation and inflammation. Molecular mimicry of factor Xa association with effector cell protease receptor-1 induces acute inflammation in vivo. *J Clin Invest* 1997;99:2446–2451.
- Breddin K, Loew D, Lechner K, Oberla K, Walter E: The German-Austrian Aspirin Trial: a comparison of acetylsalicylic acid, placebo and phenocoumon in secondary prevention of myocardial infarction. *Circulation* 1980;62(suppl V):V-63–V-72.
- EPSIM Research Group: A controlled comparison of aspirin and oral anticoagulants in prevention of death after myocardial infarction. *N Engl J Med* 1982;307:701–708.
- Julian DG, Chamberlain DA, Pocock SJ: A comparison of aspirin and anticoagulation following thrombolysis for myocardial infarction (the AFTER study): a multicenter unblinded randomized clinical trial. *BMJ* 1996;313:1429–1431.
- Hamm CW, Bassand JP, Agewall S, et al: ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:2999e3054.
- Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, et al: ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). *Eur Heart J* 2012;33:2569e2619.
- Oler A, Whooley MA, Oler J, Grady D: Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina: a meta-analysis. *JAMA* 1996;276:811–815.
- Murphy SA, Gibson CM, Morrow DA, Van de Werf F, Menown IB, Goodman SG, Mahaffey KW, Cohen M, McCabe CH, Antman EM, Braunwald E: Efficacy and safety of the low-molecular weight heparin enoxaparin compared with unfractionated heparin across the acute coronary syndrome spectrum: a meta-analysis. *Eur Heart J* 2007;28:2077–2086.
- Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, Budaj A, Peters RJ, Bassand JP, Wallentin L, Joyner C, Fox KA: Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006;354:1464–1476.
- Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, Budaj A, Peters RJ, Bassand JP, Wallentin L, Joyner C, Fox KA; OASIS-6 Trial Group: Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 2006;295:1519–1530.
- Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, Moses JW, White HD, Pocock SJ, Ware JH, Feit F, Colombo A, Aylward PE, Cequier AR, Darius H, Desmet W, Ebrahimi R, Hamon M, Rasmussen LH, Rupprecht HJ, Hoekstra J, Mehran R, Ohman EM; ACUTY Investigators: Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;355:2203–2216.
- Morrow DA, Antman EM, Fox KA, White HD, Giugliano R, Murphy SA, McCabe CH, Braunwald E; ExTRACT-TIMI 25 Investigators: One-year outcomes after a strategy using enoxaparin vs. unfractionated heparin in patients undergoing fibrinolysis for ST-segment elevation myocardial infarction: 1-year results of the ExTRACT-TIMI 25 Trial. *Eur Heart J* 2010;31:2097–2102.

- 26 Cohen M, Demers C, Gurfinkel EP, Turpie AG, Fromell GJ, Goodman S, Langer A, Califf RM, Fox KA, Premmureur J, Bigonzi F: A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events study group. *N Engl J Med* 1997;337:447–452.
- 27 Wallentin L: Low-molecular-weight heparin as a bridge to timely revascularization in unstable coronary artery disease – an update of the Fragmin during Instability in Coronary Artery Disease II Trial. *Haemostasis* 2000; 30(suppl 2):108–113.
- 28 Tanguer MJ1, Frison L, Weaver D, Wilcox RG, Bylock A, Emanuelsson H, Held P, Oldgren J: Effect of ximelagatran on ischemic events and death in patients with atrial fibrillation after acute myocardial infarction in the efficacy and safety of the oral direct thrombin inhibitor ximelagatran in patients with recent myocardial damage (ESTEEM) trial. *Am Heart J*. 2008;155:382–387.
- 29 Uchino K, Hernandez AV: Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. *Arch Intern Med* 2012;172:397–402.
- 30 Alexander JH, Becker RC, Bhatt DL, Cools F, Crea F, Dellborg M, Fox KA, Goodman SG, Harrington RA, Huber K, Husted S, Lewis BS, Lopez-Sendon J, Mohan P, Montalescot G, Ruda M, Ruzyllo W, Verheugt F, Wallentin L: Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. *Circulation* 2009;119:2877–2885.
- 31 Steg PG, Mehta SR, Jukema JW, Lip GY, Gibson CM, Kovar F, Kala P, Garcia-Hernandez A, Renfurm RW, Granger CB: RUBY-1: a randomized, double-blind, placebo-controlled trial of the safety and tolerability of the novel oral factor Xa inhibitor darexaban (YM150) following acute coronary syndrome. *Eur Heart J* 2011;32:2541–2554.
- 32 Mega JL, Braunwald E, Mohanavelu S, Burton P, Poulter R, Misselwitz F, Hricak V, Barnathan ES, Bordes P, Witkowski A, Markov V, Oppenheimer L, Gibson CM: Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS TIMI 46): a randomised, double-blind, phase II trial. *Lancet* 2009;374:29–38.
- 33 Goldstein S, et al: Safety evaluation of the factor Xa inhibitor TAK-442 in subjects with acute coronary syndromes: phase 2 AXIOM-ACS trial results. *Eur Heart J* 2011;32(abstr suppl):414.
- 34 Alexander JH, Lopes RD, James S, et al: Apixaban with antiplatelet therapy after acute coronary syndrome (APPRAISE-2). *N Engl J Med* 2011;365:699–708.
- 35 Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FW, Gibson CM: Rivaroxaban in patients with a recent acute coronary syndrome(ATLAS ACS 2-TIMI 51). *N Engl J Med* 2012;366:9–19.
- 36 Perzborn E, Strassburger J, Wilmen A, Pohlmann J, Roehrig S, Schlemmer KH, Straub A: In vitro and in vivo studies of the novel antithrombotic agent BAY 59-7939 – an oral, direct factor Xa inhibitor. *J Thromb Haemost* 2005;3:514–521.
- 37 Mueck W, Becka M, Kubitz D, Voith B, Zuehlendorf M: Population model of the pharmacokinetics and pharmacodynamics of rivaroxaban – an oral, direct factor Xa inhibitor – in healthy subjects. *Int J Clin Pharmacol Ther* 2007;45:335–344.
- 38 Gopalakrishnan L, Kumar V, Kohli P, Singh P, Rastogi U, Gibson CM: Pharmacokinetic evaluation of rivaroxaban for the treatment of acute coronary syndromes. *Expert Opin Drug Metab Toxicol* 2012;8:889–900.
- 39 Weinz C, Schwarz T, Kubitz D, Mueck W, Lang D: Metabolism and excretion of rivaroxaban, an oral, direct factor Xa inhibitor, in rats, dogs, and humans. *Drug Metab Dispos* 2009;37:1056–1064.
- 40 Kubitz D, Becka M, Mueck W, Halabi A, Maatouk H, Klaus N, Lufft V, Wand DD, Philipp T, Bruck H: Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban – an oral, direct factor Xa inhibitor. *Br J Clin Pharmacol* 2010;70:703–712.
- 41 Gibson CM1, Chakrabarti AK, Mega J, Bode C, Bassand JP, Verheugt FW, Bhatt DL, Goto S, Cohen M, Mohanavelu S, Burton P, Stone G, Braunwald E: Reduction of stent thrombosis in patients with acute coronary syndromes treated with rivaroxaban in ATLAS ACS 2-TIMI 51. *J Am Coll Cardiol* 2013;62:286–290.
- 42 Mega JL, Braunwald E, Murphy SA, Plotnikov A, Burton P, Kiss RG, Parkhomenko A, Tendra M, Widimsky P, Gibson CM: Rivaroxaban in patients stabilized after a ST-elevation myocardial infarction: results from the ATLAS ACS 2-TIMI 51 Trial. *J Am Coll Cardiol* 2013;61:1853–1859.
- 43 Mega JL, Braunwald E, Wiviott SD, Murphy SA, Plotnikov A, Gotcheva N, Ruda M, Gibson CM: Comparison of the efficacy and safety of two rivaroxaban doses in acute coronary syndrome (from ATLAS ACS 2-TIMI 51). *Am J Cardiol* 2013;112:472–478.
- 44 Virmani R, Burke AP, Farb A: Sudden cardiac death. *Cardiovasc Pathol* 2001;10:211–218.
- 45 Davis MJ, Thomas A: Thrombosis and acute coronary artery lesions in sudden cardiac ischemic death. *N Engl J Med* 1984;310:1138–1140.
- 46 Segev A, Strauss BH, Tan M, Constance C, Langer A, Goodman SG: Predictors and 1-year outcome of major bleeding in patients with non-ST-elevation acute coronary syndromes: insights from the Canadian Acute Coronary Syndrome Registries. *Am Heart J* 2005;150:690–694.
- 47 Mehran R, Pocock S, Nikolsky E, Dangas GD, Clayton T, Claessen BE, et al: Impact of bleeding on mortality after percutaneous coronary intervention results from a patient-level pooled analysis of the REPLACE-2 (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events), ACUTY (Acute Catheterization and Urgent Intervention Triage Strategy), and HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trials. *JACC Cardiovasc Interv* 2011;4:654–664.
- 48 Chan MY, Sun JL, Wang TY, Lopes RD, Jolicœur ME, Pieper KS, Rao SV, Newby LK, Mahaffey KW, Harrington RA, Peterson ED: Patterns of discharge antiplatelet therapy and late outcomes among 8,582 patients with bleeding during acute coronary syndrome: a pooled analysis from PURSUIT, PARAGON-A, PARAGON-B, and SYNERGY. *Am Heart J* 2010;160:1056–1064.
- 49 Karthikeyan G, Eikelboom JW: Apixaban in acute coronary syndromes. *Cardiovasc Ther* 2011;29:285–290.
- 50 Raghavan N, Frost CE, Yu Z, He K, Zhang H, Humphreys WG, Pinto D, Chen S, Bonacorsi S, Wong PC, Zhang D: Apixaban metabolism and pharmacokinetics after oral administration to humans. *Drug Metab Dispos* 2009;37:74–81.
- 51 U.S. Food and Drug Administration (FDA): FDA Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee (CRDAC). NDA: 202439/S-002. Drug: Xarelto® (Rivaroxaban) oral tablets. Silver Spring, FDA, 2012. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeeting-Materials/Drugs/CardiovascularandRenal-DrugsAdvisoryCommittee/UCM304755.pdf>
- 52 Bayer Pharma AG: Xarelto® Summary of Product Characteristics, 2013. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/000944/WC500057108.pdf (accessed December 3, 2013).
- 53 European Medicines Agency: Xarelto assessment report, London 2013. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000944/WC500144718.pdf (accessed December 4, 2013).
- 54 Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, Adriaenssens T, Vrolix M, Heestermans AA, Vis MM, Tijssen JG, van 't Hof AW, ten Berg JM: Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;381:1107–1115.