International Journal of Cardiology xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Novel oral anticoagulants in acute coronary syndrome

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ARTICLE INFO

Article history:
Received 16 April 2012
Received in revised form 18 July 2012
Accepted 21 August 2012
Available online xxxx

Keywords:
Myocardial infarction
Acute coronary syndrome
Anticoagulants
Thrombin
Platelet aggregation

ABSTRACT

Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide with a prevalence that has now reached pandemic levels as a consequence of the rapid modernization of the developing world. Its presentation as an acute coronary syndrome (ACS) is a frequent reason for hospital admission and of profound implications for personal, societal and global health. Despite improvements in the management of ACS with anti-platelet and anticoagulant therapy and revascularization techniques, many patients continue to suffer recurrent ischemic events. The need to reduce future cardiovascular events has led to the development of novel therapies to prevent coronary thrombosis, targeting thrombin-mediated pathways. These include direct Xa inhibitors (apixaban, rivaroxaban and darexaban), direct thrombin inhibitors (dabigatran) and PAR 1 antagonists (vorapaxar and atopaxar). This article critically reviews the comparative mechanisms of action, the risks and benefits, together with the clinical evidence base for the use of these novel oral agents in the management of ACS patients.

1. Introduction

Cardiovascular disease is a leading cause of morbidity and mortality worldwide with acute coronary syndrome (ACS) being the most common initial presentation of this. Improvements in the diagnosis of ACS through more sensitive biomarkers and greater clinician awareness together with advances in the management of ACS have led to the reduction in the rates of ST-elevation myocardial infarction over the last decade with concomitant improvements in patient survival. Such advances have also allowed the more accurate diagnosis of non ST-elevation infarction to the extent that this now accounts for 77% of all acute infarcts [1]. Acute coronary syndrome is usually the result of atherosclerotic plaque rupture. Coronary plaques vulnerable to rupture are characterized by a lipid-laden necrotic core in which macrophage infiltration leads to the release of matrix metalloproteinases and inflammatory cytokines. This initiates a vicious inflammatory process, which involves thinning of the fibrous cap, typically around the "shoulders" of the plaque that culminates in plaque rupture and the exposure of tissue factor with the consequent activation of factor X [2,3]. Factor Xa, a key component of the prothrombinase complex then stimulates the conversion of the inactive zymogen, prothrombin to the active serine protease, thrombin. Thrombin in turn catalyzes the conversion of soluble fibrinogen to insoluble strands of fibrin which through the cleavage of protease-activated receptor 1 (PAR 1) on the platelet surface lead to platelet activation and the release of adenosine diphosphate, serotonin and thromboxane A2. This in conjunction with simultaneous platelet activation by exposed subendothelial collagen leads to platelet aggregation, fibrin and blood cell agglutination and thus thrombus formation [4,5].

Inhibition of thrombin generation, activation or both is therefore a logical target in the treatment of ACS, especially since patients may continue to suffer thrombotic events during the weeks and months

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; CAD, coronary artery disease; CrCl, creatinine clearance; DAPT, dual anti-platelet therapy; HR, hazard ratio; ISTH, International Society of Thrombosis and Haemostasis; LMWH, low molecular weight heparins; MACE, major adverse cardiac events; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; PAR 1, protease-activated receptor 1; TIMI, Thrombolysis In Myocardial Infarction definition; VKA, vitamin K antagonist; VTE, venous thromboembolism.
Trial acronyms: APPRAISE, Apixaban for Prevention of Acute Ischaemic and Safety Events trial; APPRAISE-2, Apixaban for Prevention of Acute Ischaemic Events 2 trial; ATLAS ACS-IMI 46, Anti-a 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; ATLAS ACS-IMI 51, An Efficacy and Safety Study for Rivaroxaban in Patients with Acute Coronary Syndrome; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; J-ANCELOT-CS, Safety and Tolerability of E5555 and Its Effects on Markers of Intravascular Inflammation in Subjects with Coronary Artery Disease; LANCELOT-CS, Lesson from Antagonizing the Cellular Effects of Thrombin–Acute Coronary; ONYX-rial, Factor Xa Inhibitor YM150 for the Prevention of Blood Clot Formation in Veins after Scheduled Hip Replacement; RE-EEM, Dose Finding Study for Dabigatran Etexilate in Patients with Acute Coronary Syndrome; RE-Y, Randomized Evaluation of Long Term Anticoagulant Therapy (RE-Y) with Dabigatran Etexilate; ROCKET AF, Rivaroxaban versus Warfarin in Nonvular Atrial Fibrillation trial; RUBY-rial, Study Evaluating Safety, Tolerability and Efficacy of YM150 in Subjects with Acute Coronary Syndromes; TRACER, Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome.

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0167-5273/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijcard.2012.08.014

after an ACS. In the Global Registry of Acute Coronary Events (GUSTO) Registry, nearly 40% of the deaths and 33% of MI, occurred 2 to 6 months following the initial ACS [6]. Even with dual anti-platelet therapy (DAPT) 9–11% patients with ACS continue to suffer major adverse clinical events (MACE) 1 year after the index episode [7,28]. Additional treatment to reduce future thrombosis could therefore help prevent recurrent ischemic events. Unfractionated heparin, low molecular weight heparins (LMWH), fondaparinux and more recently bivalirudin have all been shown to be of benefit in ACS [8]. The need however for parenteral administration limits the use of these agents outside the hospital setting and following discharge, and prolonged administration of LMWH has not been shown to be beneficial [9]. Long-term anticoagulation on the other hand with a vitamin K antagonist has been shown to reduce the risk of future ischemic events in patients with ACS, used alone or in combination with aspirin [10]. However, widespread and long-term use of VKAs, such as warfarin, in such patients is limited due to the variable dose–response relationship, narrow therapeutic window, need for frequent monitoring, numerous food and drug interactions and a high propensity to bleeding when used in conjunction with anti-platelet therapy [11–13]. Recently available oral anticoagulants overcome many of these issues, thus offering a new treatment strategy in patients with ACS. Ximelagatran, a direct thrombin inhibitor, was one of the first such agents to demonstrate cardiovascular benefit in post-MI patients, but had to be withdrawn from the market due to hepatotoxicity [14]. Novel oral anticoagulants recently evaluated as treatment options in ACS include the direct Xa inhibitors apixaban, rivaroxaban and darexaban, the direct thrombin inhibitor dabigatran and the thrombin receptor 1 (PAR 1) antagonists varopaxar and atopaxar (Table 1).

2. Direct Xa inhibitors

2.1. Apixaban

Apixaban (Eliquis, Bristol-Myers Squibb, Frosinone, Italy, co-marketed by Bristol-Myers Squibb/Pfizer EEIG, Uxbridge, UK) is an orally available, direct-acting, reversible and highly selective factor Xa inhibitor. Following ingestion it is rapidly absorbed and is excreted unchanged in the urine and feces, with the remaining drug being metabolized into inactive compounds partly by CYP3A4 and CYP3A5 enzymes in the liver. Thus, although apixaban itself does not induce CYP enzymes, it is susceptible to interaction with strong CYP enzyme inducers and inhibitors such as HIV protease inhibitors, azole-antimycotics, rifampicin, phenytoin and carbamazepine. Its use is not recommended in patients with creatinine clearance (CrCl) <15 ml/min or in patients with liver disease with associated coagulopathy, although it can be used with caution in patients with severe renal impairment (CrCl 15–29 ml/min) [15]. Dose modification is not required in the elderly.

Apixaban has been shown to reduce the incidence of venous thromboembolism in patients undergoing orthopedic surgery and to prevent thromboembolic events in patients with atrial fibrillation (AF) [16,17]. The role of apixaban in ACS was first examined in the phase II Apixaban for Prevention of Acute Ischemic and Safety Events trial (APPRAISE) [18]. This was a multicenter, double blind, placebo controlled, dose-finding trial in stable ACS patients within 7 days of their index event (either ST-elevation or non-ST-elevation MI), performed in two phases. In Phase A patients were randomized to placebo, apixaban 2.5 mg twice a day (b.i.d.) or apixaban once a day (o.d.). After 25% of the patients had received the study drug for at least 30 days the data were reviewed by an independent committee who recommended the inclusion of two higher apixaban doses at 10 mg b.i.d. and 20 mg o.d. Patients were assigned to placebo or 1 of 4 doses of apixaban for 6 months (2.5 mg b.i.d., 10 mg o.d., 10 mg b.i.d., 20 mg o.d.) in 3:1:1:2:2 ratio with more patients allocated to higher doses to provide more information on bleeding events at those doses. Nearly all patients received aspirin and $>75\%$ DAPT with aspirin and clopidogrel. Primary outcomes were major bleeding and non-major clinical relevant bleeding as defined by the International Society of Thrombosis and Haemostasis (ISTH) (Table 3.) with secondary outcomes being a composite of cardiovascular death, MI, severe recurrent ischemia and ischemic stroke (MACE) [19]. After the randomization of 1498 patients, the two higher apixaban (10 mg b.i.d. and 20 mg o.d.) arms were discontinued due to excess bleeding. Results showed a significant dose-dependent increase in bleeding, with apixaban 2.5 mg b.i.d. (5.7%; 95% CI 3.4–8.9) and 10 mg o.d. (7.9%; 95% CI 5.2–11.5). Bleeding rates were higher in patients receiving DAPT rather than those on aspirin alone. There was no statistical difference in adverse cardiovascular events between apixaban and placebo although patients that received apixaban had fewer ischemic events than those receiving placebo, especially those who did not receive clopidogrel. The findings of APPRAISE led to the phase III trial, Apixaban for Prevention of Acute Ischemic Events 2 trial (APPRAISE-2) examining the effect of apixaban in ACS (Table 2) [20]. Some 81% of patients were taking DAPT at the time of randomization. The study was terminated prematurely due to concerns over increased bleeding. Apixaban failed to reduce ischemic events compared to placebo (13.2 events per 100 patient-years vs. 14.0 events per 100 patient years, hazard ratio (HR) with apixaban, 0.95; 95% CI 0.80–1.11 $P=0.51$), irrespective of whether patients were receiving DAPT or aspirin alone and regardless of whether patients were managed conservatively or with revascularization. Similar findings with respect to primary end-points were seen in all key subgroups. Importantly apixaban increased bleeding, including fatal hemorrhage (5 vs. 0), intracranial bleeding (12 vs. 3) as well as ISTH major or clinical relevant nonmajor bleeding (117 vs. 45). The increased bleeding was seen both in patients taking DAPT (1.3% vs. 0.6%) and in patients taking aspirin alone (1.1% vs. 0.1%).

2.2. Rivaroxaban

Rivaroxaban (Xarelto, Bayer Schering Pharma AG, Berlin, Germany) is another highly selective, reversible, oral direct factor Xa inhibitor

Table 1
Novel oral anticoagulants recently evaluated in ACS.

Drug	Class	Half-life	Excretion	Tolerability	Interactions
Apixaban	Direct factor Xa inhibitor	8–14 h	25% Urine 25% Feces Liver	No unexpected safety concerns	Strong CYP enzyme inducers and inhibitors
Rivaroxaban	Direct factor Xa inhibitor	7–9 h	Urine, feces, biliary system	No unexpected safety concerns	Potent CYP3A4 inducers, P-gp/CYP3A4 inhibitors
Darexaban	Direct factor Xa inhibitor	14–18 h	50% Urine 50% Feces	No unexpected safety concerns	No known drug–drug interactions
Dabigatran	Direct thrombin inhibitor	12–18 h	80% Urine	Risk of MI	P-gp inhibitors and inducers
Vorapaxar	PAR 1 antagonist	126–269 h	Gastrointestinal and biliary tracts	Excess of intracranial hemorrhage in patients with PMH of stroke	CYP3A4 inducers and inhibitors
Atopaxar	PAR 1 antagonist	22–26 h	Gastrointestinal metabolism	Liver toxicity, QT prolongation	CYP3A4 inducers and inhibitors

Please cite this article as: Costopoulos C., et al., Novel oral anticoagulants in acute coronary syndrome, Int J Cardiol (2012), http://dx.doi.org/10.1016/j.ijcard.2012.08.014

Table 2
Summary of clinical trials of novel oral anticoagulants in ACS.

Name of study	Type of study	Number of patients	Drug	Primary efficacy endpoint	Secondary efficacy endpoint	Primary safety end-point
Direct factor Xa inhibitors						
APPRAISE-2 [20]	Double-blind, placebo-controlled, randomized Phase III trial	7392	Apixaban 5 mg b.i.d. (or 2.5 mg o.d. in renal impairment) vs. placebo in addition to the standard ACS therapy	Composite of cardiovascular death, myocardial infarction, or ischemic stroke 7.5% vs. 7.9%; $P=0.51$	Composite of cardiovascular death, myocardial infarction, ischemic stroke, or unstable angina; the composite of cardiovascular death, myocardial infarction, ischemic or hemorrhagic stroke, or fatal bleeding; and the composite of death from any cause, myocardial infarction, or ischemic or hemorrhagic stroke 7.2% vs. 7.5% $P=0.87$	Major bleeding (TIMI) 1.3% vs. 0.5%; $P=0.001$
ATLAS ACS-TIMI 51 [26]	Double-blind, placebo-controlled Phase III trial	15,526	Rivaroxaban (2.5 to 5 mg b.i.d.) or placebo in addition to the standard ACS protocol	Composite of death from cardiovascular causes, myocardial infarction, or stroke (ischemic, hemorrhagic, or stroke of uncertain cause) Rivaroxaban vs. placebo 8.9% vs. 10.7%, $P=0.008$,	Death from any cause, myocardial infarction or stroke 9.2% vs. 11.0%, $P=0.006$	Major bleeding (TIMI) not related to CABG 2.1% vs. 0.6%, $P<0.001$
RUBY-1 [31]	Randomized, double-blind, placebo-controlled Phase II trial	1279	Darexaban (5 mg b.i.d. 10 mg o.d. 15 mg b.i.d. 30 mg o.d.,30 mg b.i.d. or 60 mg o.d.) vs. placebo in addition to the standard ACS protocol	Composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke and severe recurrent ischemia	All-cause death, non-fatal myocardial infarction, non-fatal stroke, severe recurrent ischemia, systemic thromboembolic event and transient ischemic attack	Major or clinically relevant non-major bleeding (modified ISTH) 6.2% (10 mg), 6.5% (30 mg), and 9.3% (60 mg) vs. 3.1%; $P=0.009$
Direct thrombin inhibitors						
RE-DEEM [37]	Double-blind, placebo-controlled, phase II trial	1861	Dabigatran (50, 75, 110 and 150 mg b.i.d.) vs. placebo in addition to the standard ACS protocol	Composite of cardiovascular death, non-fatal myocardial infarction, or non-hemorrhagic stroke 4.6% (50 mg) 4.9% (75 mg), 3.0% (110 mg), 3.5% (150 mg) vs. 3.8% (placebo)	Reduction in D-dimers 81% (50 mg), 82% (75 mg), 86% (110 mg), and 89% (150 mg) $P<0.001$	Composite of major or clinically relevant minor bleeding (ISTH, TIMI, GUSTO) 3.5% (50 mg), 4.3% (75 mg), 7.9% (110 mg), and 7.8% (150 mg) vs. 2.2%; $P=0.001$
PAR 1 antagonists						
TRACER [42]	Randomized, double-blind, placebo-controlled Phase III trial	12,944	Vorapaxar (loading dose of 40 mg and a maintenance dose of 2.5 mg o.d.) vs. placebo in addition to the standard ACS protocol	Composite of death from cardiovascular causes, myocardial infarction, stroke, recurrent ischemia with re-hospitalization, or urgent coronary revascularization 18.5% vs. 19.9%; $P=0.07$ Cardiovascular death, MI, stroke, or recurrent ischemia 8.03% vs. 7.75%; $P=0.93$ Cardiovascular death, MI, or stroke 3.25% vs. 5.63; $P=0.20$	Composite of death from cardiovascular causes, myocardial infarction, or stroke 14.7% vs. 16.4%; $P=0.02$	GUSTO moderate or severe bleeding 7.2% vs. 5.2%; $P<0.001$ Significant TIMI bleeding 20.2% vs. 14.6%; $P<0.001$ Intracranial hemorrhage 1.1% vs. 0.2%; $P<0.001$
LANCELOT-ACS [43]	Randomized double-blind, placebo-controlled phase II trial	603	Atopaxar given in 1 of 3 dosing levels: 400-mg loading dose followed by 50, 100, or 200 mg daily vs. placebo			Major or minor bleeding (CURE) 3.08% vs. 2.17%; $P=0.63$ Major bleeding (CURE) 1.8% vs. 0%; $P=0.12$

capable of inhibiting both free factor Xa and factor Xa bound in the prothrombinase complex. It has >80% bioavailability, and since factor Xa is inhibited for up to 24 h once the drug is bound, it can be administered once daily [21]. Rivaroxaban is not recommended in patients with end-stage renal failure (CrCl <15 ml/min) and should be used with caution in patients with severe renal failure (CrCl 15–29 ml/min). It is contraindicated in patients with hepatic disease with associated coagulopathy but may be used with caution in cirrhotic patients with moderate hepatic impairment. Rivaroxaban is metabolized via the CYP3A4 and CYP2J2 enzyme systems as well as by CYP-independent mechanisms. Thus, the concomitant use of potent CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort)

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and P-gp/CYP3A4 inhibitors (ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir) should be avoided [21].

Rivaroxaban is effective in the prevention and treatment of venous thromboembolism. In patients with non-valvular AF, rivaroxaban was non-inferior to warfarin in the prevention of stroke and systemic embolism and also non-significantly reduce the risk of MI in the Rivaroxaban versus Warfarin in Non-valvular Atrial Fibrillation (ROCKET AF) trial [22–24]. The 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) trial evaluated rivaroxaban in ACS (Table 2) [25]. This was a dose-finding Phase II study in patients receiving aspirin alone (stratum 1, randomized to three rivaroxaban doses: 5 mg, 10 mg and 20 mg daily) or DAPT (stratum 2 randomized to four doses of rivaroxaban: 5 mg, 10 mg, 15 mg and 20 mg b.i.d.). Rivaroxaban was associated with dose-dependent increased bleeding in both stratum 1 and 2 ($P<0.0001$ and $P<0.0001$, respectively), with absolute rates of bleeding being lower in patients receiving aspirin alone, compared to those receiving DAPT. Rivaroxaban failed to reduce the occurrence of the primary efficacy endpoint (composite of death, MI, stroke and revascularization up to 6 months after enrolment) but when revascularization was excluded from the analysis, rivaroxaban was shown to be of benefit ($P=0.027$). This led to the ATLAS ACS-TIMI 51 phase III trial [26] evaluating rivaroxaban in ACS. Rivaroxaban reduced the composite primary end-point of death, MI and stroke at both doses, at the cost of increased TIMI major bleeding, which was lower with the b.i.d. regimen. Subgroup analysis demonstrated that the 2.5 mg b.i.d. dose reduced the risk of cardiovascular death (2.7% vs. 4.1%; hazard ratio, 0.66; 95% CI, 0.51 to 0.86; $P=0.002$) as well as death from any cause (2.9% vs. 4.5%; hazard ratio, 0.68; 95% CI, 0.53 to 0.87; $P=0.002$) whereas the 5 mg b.i.d. dose failed to do so.

2.3. Darexaban

Darexaban (Astellas Pharma Inc., Tokyo, Japan) is the last of the direct Factor Xa inhibitors that has been evaluated in the context of ACS. This pro-drug is rapidly absorbed in the stomach and quickly converted to its active metabolite darexaban glucuronide [27]. Unlike other direct factor Xa inhibitors examined in ACS, darexaban does not interact with CYP3A4/P-glycoprotein inhibitors and inducers [28]. The benefit of darexaban has been demonstrated in the prevention of venous thromboembolism and its role in the prevention of stroke in non-valvular AF has also been examined in the phase II OPAL-2 trial [29,30].

The role of darexaban in the treatment of ACS was examined in the phase II dose finding and safety trail, RUBY-1 [31]. Patients were randomized to either placebo or darexaban at 5 mg b.i.d., 10 mg o.d., 15 mg b.i.d., 30 mg o.d., 30 mg b.i.d. and 60 mg o.d. in 2:1:1:1:1:1:1 ratio. Darexaban was associated with significant increased bleeding in a dose-dependent manner. Astellas Pharma Inc. has now halted further development of darexaban for all indications due to difficulties in finding a partner for phase III trials and the intense market competition in the direct Xa factor inhibitor field.

3. Direct thrombin inhibitors

3.1. Dabigatran etexilate

Dabigatran (Pradaxa, Boehringer-Ingelheim, Ingelheim am Rhein, Germany) is a reversible, direct competitive inhibitor of free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. Dabigatran etexilate is a pro-drug, converted to the active metabolite by non-specific plasma and liver esterases. It has a bioavailability of 6.5% and regular anticoagulant monitoring is not required. It is metabolized by the permeability glycoprotein system (P-gp), independent of the cytochrome P450 system and thus concomitant use of potent P-gp inhibitors and inducers should be avoided [Table 1.] Information regarding its use in the elderly and in patients with severe liver impairment and moderate to severe renal failure is lacking and thus in these circumstances its use is best avoided or the dose reduced [32,33].

Dabigatran has been shown to be non-inferior to enoxaparin in the primary prevention of VTE following orthopedic surgery and as effective as warfarin in secondary VTE prevention and acute VTE treatment, with reduced major bleeding [34,35]. In the pivotal RE-LY?thyc=5?> trial in non-valvular AF, dabigatran 110 mg b.i.d. was non-inferior and dabigatran 150 mg b.i.d. was superior to warfarin in reducing the primary endpoint of stroke or systemic embolism, with the lower dose being associated with reduced major bleeding [36]. The RE-DEEM study evaluated dabigatran as an add-on therapy in patients with a recent ACS already receiving DAPT and at high risk of recurrent cardiovascular events (Table 2) [37]. Patients were initially randomized to placebo, dabigatran 50 mg b.i.d. and dabigatran 75 mg b.i.d. in 1:1:1 ratio, and following independent safety board review, 110 mg b.i.d. and 150 mg b.i.d. doses were used in newly recruited patients. Since patients with CrCl <50 ml/min are known to have higher dabigatran concentrations compared to patients with normal renal function, such patients who were randomized to the 75 mg b.i.d., 110 mg b.i.d. and 150 mg b.i.d. were assigned to the next lower dose treatment group in order to achieve similar drug exposure as patients with normal renal function. The primary safety end point was occurence of bleeding. Dabigatran increased bleeding 2–4 fold, in a dose-dependent manner, compared to placebo, with increased bleeding at the two higher dabigatran doses reaching significance ($P<0.001$). The absolute increase in bleeding however in these two groups (110 mg b.i.d. and 150 mg b.i.d.) was only ~1%. In these same groups the secondary efficacy outcome was achieved in numerically less patients (3.0% and 3.5% in the 110 mg b.i.d. and 150 mg b.i.d. groups respectively) as compared to placebo (3.8%) although this was not statistically significant. Patients receiving the 50 mg b.i.d. and 75 mg b.i.d. doses reached the secondary efficacy outcome more often (4.6% and 4.9% respectively) as compared to placebo (3.8%) with the incidence of all cause death being numerically less (2.2% and 2.7% respectively) compared to placebo (3.8%). Notably, the overall ischemic event rates were unexpectedly low in both arms of the study, and the trial was not powered to assess ischemic endpoint reduction. Dabigatran also reduced D-dimer levels at all doses, and this marker has been previously associated with cardiovascular adverse events [38]. The results are not dissimilar to other factor Xa studies and clearly, a dedicated ischemic-vent driven phase III trial is needed to fully assess the role of dabigatran in ACS.

4. PAR 1 antagonists

4.1. Vorapaxar

Vorapaxar (Merck, New Jersey, USA) is an orally-active, reversible, and selective inhibitor of the PAR-1 receptor with a very long half-life and high bioavailability (~85%). It is inactivated via the CYP3A4 enzymatic system and thus has potential interactions with CYP3A4 inducers and inhibitors. There is no significant renal metabolism [39]. The role of vorapaxar was evaluated in 3 phase II clinical trials in CAD. In an early trial of patients undergoing non-urgent PCI, vorapaxar when used in conjunction with aspirin and clopidogrel tended to reduce MACE without increasing bleeding [40]. A subsequent multi-center phase II trial study evaluated vorapaxar in 117 non-ST elevation MI patients undergoing PCI [41]. Patients within 24 h of the index event were randomized 1 h prior to catheterization to receive a loading dose of vorapaxar (20 mg or 40 mg) followed by a maintenance dose (1 mg o.d. or 2.5 mg o.d.) or placebo, continued

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for 60 days if PCI was performed. The incidence of TIMI major and minor bleeding as well as that of non-TIMI bleeding events was similar in the placebo and treatment groups. Peri-procedural MI was significantly reduced with vorapaxar (16.9% vs. 42.9%, respectively; $P=0.013$) although the majority of these events were asymptomatic increases of cardiac enzymes in the post-procedural period. There were no clinically significant ischemic events in either the treatment or control groups. These results fueled the larger TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) study [42], where ACS patients were randomized to placebo or vorapaxar. The majority of the patients received concomitant DAPT. Vorapaxar failed to reduce the primary efficacy end point of the composite of cardiovascular death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization. The secondary efficacy endpoint was reduced by vorapaxar compared to placebo (14.7% and 16.4%, respectively hazard ratio, 0.89; 95% CI, 0.81 to 0.98; $P=0.02$) and was mainly driven by a reduction in myocardial infarction (11.1% vs. 12.5% at 2 years; HR 0.88; 95% CI, 0.79 to 0.98; $P=0.02$). However, bleeding complications with vorapaxar were found to be unacceptably high which with an incremental risk over the period of treatment, which eventually led to premature termination of the study. Even prior to that, the Data Safety Monitoring Board recommended stopping vorapaxar in all patients with a prior history of stroke, due to an observed increased rate of intracranial hemorrhage with vorapaxar in these patients.

4.2. Atopaxar

Atopaxar (Eisai Co., Tokyo, Japan) is another orally active, potent, reversible PAR 1 inhibitor. It is predominantly metabolized via the CYP3A4 system with a shorter half-life than vorapaxar, and good bioavailability [39]. The role of atopaxar in ACS was assessed in the Lesson From Antagonizing the Cellular Effects of Thrombin–Acute Coronary Syndromes (LANCELOT-ACS) trial (Table 2) [43]. In this Phase II trial, most patients received DAPT with aspirin and a thienopyridine (clopidogrel or ticlodipine). The primary end point was the occurrence of significant bleeding as assessed by Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) classification criteria, with secondary endpoints of MACE (cardiovascular death, MI, stroke and recurrent ischemia), Holter-detected ischemia and effects on platelet function. Major or minor CURE bleeding (Table 3) was similar in the treatment and the control arms, although overall event rate was lower than expected making it difficult to assess the drug's effect on bleeding risk. Although there was a 34% reduction in Holter-detected ischemia in the atopaxar groups (relative risk, 0.67; 95% 0.48–0.94; $P=0.02$), this did not translate into a reduction in MACE. Thus there would appear to be a signal for ischemic event reduction, but this would need to be established in a large phase III clinical trial.

In the smaller Japanese arm of LANCELOT (J-LANCELOT-ACS) concerns were raised with regards to adverse effects of atopaxar on liver function and QTcF interval [44]. In the larger international LANCELOT-ACS trial, a statistically significant increase in alanine aminotransferase ($>3\times$ upper limit of normal) was not observed with atopaxar. When derangement in liver function did occur, this was more common with the 200 mg o.d. (5.5%) than with lower doses (50 mg o.d., 100 mg o.d. and placebo groups were 2.2%, 2.2% and 2.5% respectively). Importantly, most liver function abnormalities resolved before the end of the 12-week treatment course. Regarding QTcF, this shortened as expected during the 12-week period after the index event, but was found to shorten significantly less in the treatment groups than with placebo (−6.4 ms vs. −11.4 ms; $P=0.04$), driven by less shortening in the 100 mg and to 200 mg groups (−4.5 ms and −4.9 ms respectively). The clinical significance of this is unknown.

The findings of LANCELOT-ACS are encouraging, but this was a relatively small study compared to its competitors. Here appears a novel anticoagulant, which does not appear to increase major bleeding and may improve clinical endpoints. The 50 mg o.d. dose seemed to be particularly well tolerated, without adversely effecting QTcF and liver function, although higher dose may be required for clinical benefit. Further larger studies are thus required to assess the role of atopaxar in reducing future ischemic events in ACS.

Table 3
Bleeding classifications.

ISTH	Major bleeding 1. Fatal bleeding 2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome 3. Bleeding causing a fall in hemoglobin level of 20 g l^{-1} (1.24 mmol l^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells
Modified ISTH	Major bleeding 1. Fatal bleeding, clinically overt bleeding associated with a decrease in the hemoglobin level of >2 g/dl (1.24 mmol/l) compared with the pre-bleeding level, clinically overt bleeding leading to transfusion of two or more units of whole blood or packed cells, and symptomatic bleeding in a critical area or organ, such as retroperitoneal, intracranial, intraocular, intra-spinal, intra-articular, pericardial, or intramuscular bleeding with compartment syndrome CRNM bleeding 2. Any bleeding event considered as clinically relevant by the IAC that did not meet the criteria of a major bleeding event, e.g. any bleeding event that required medical attention or any bleeding requiring discontinuation of blinded study drug treatment All other bleeding events 3. Events not fulfilling the criteria of major or CRNM bleeding events. In addition, transfusions and the reasons behind them were tracked, and for each bleeding episode, an adjusted decrease in hemoglobin was computed by adding the number of units of packed red blood cells transfused to the decrease in hemoglobin
TIMI	Major bleeding 4. Reduction of hemoglobin of 5 g/dl or more (or >15% in hematocrit) or any intracranial bleeding Minor bleeding 5. Blood loss and a drop in hemoglobin of 3–5 g/dl (or in hematocrit from 10–15%) spontaneous gross hematuria or hematemesis (>120 ml), or unobserved loss 4 g/dl or more in hemoglobin or 12% or more in hematocrit
GUSTO	Severe or life-threatening bleeding 6. Intracerebral bleeding or resulting in substantial hemodynamic compromise requiring treatment Moderate bleeding 7. Bleeding requiring transfusion Minor bleeding 8. Other bleeding, not requiring transfusion or causing hemodynamic compromise
CURE	Severe or life-threatening bleeding 9. Fatal bleeding episode or leading to a reduction in the hemoglobin level of at least 5 g/dl or to substantial hypotension requiring the use of intravenous inotropic agents, necessitating a surgical intervention, symptomatic intracranial hemorrhage, or necessitating the transfusion of 4 or more units of blood Moderate bleeding 10. Substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least 2 units of blood Minor bleeding 11. Bleeding that led to the interruption of study medication

CRNM, clinically relevant non-major; IAC, independent adjudication committee.

5. Important considerations and future directions

Although novel anti-coagulants may be of benefit in the treatment of ACS, larger clinical trials are required to fully assess their efficacy and risk of bleeding in patients already receiving conventional ACS therapy especially since these agents, unlike VKAs, have no easily available

Please cite this article as: Costopoulos C., et al., Novel oral anticoagulants in acute coronary syndrome, Int J Cardiol (2012), http://dx.doi.org/10.1016/j.ijcard.2012.08.014

antidote. This is especially of concern in patients admitted with life threatening bleeding and in those requiring emergency invasive procedures when the drug cannot be discontinued in advance. Preclinical studies involving healthy volunteers have suggested that recombinant factor VIIa and activated prothrombin complex concentrate can be beneficial in reversing the effects of dabigatran and rivaroxaban although these may not be readily available [45]. Questions also remain with regards to the optimal timing for discontinuing these agents in patients undergoing elective invasive procedures. Data with dabigatran suggest that this should be at least 24 h prior to intervention in healthy individuals and up to 5 days in patients with renal failure or a propensity to bleeding [46]. Lack of accurate blood assays for monitoring makes such decisions even more difficult although studies have suggested that the thrombin clotting time, ecarin clotting time and APTT can be used for such purposes in the case of dabigatran with the factor Xa assay being an equivalent test for rivaroxaban and apixaban [47,48]. Thus, although the more predictable pharmacokinetics of these novel anticoagulants negates the need for frequent monitoring, there may be a disadvantage when trying to decide when to discontinue these agents and when compliance and potential toxicity need to be assessed.

There is also a need to study these drugs in greater detail in patients with renal dysfunction as in most studies patients with severe renal failure were excluded. This has to some extent been addressed in the case of dabigatran by the Hariharan et al. trial, which examined the pharmacokinetics of dabigatran in patients with varying degrees of renal impairment. In this study through the use of a simple pharmacokinetic and simulation model a dosing regime was identified for patients with severe renal failure that led the US Food and Drug Administration (FDA) to approve the use for dabigatran in patients with AF and severe renal failure [49]. Since renal failure is a risk factor for ACS in its own accord it would be logical for similar studies to be carried out for the more promising novel anticoagulants, atopaxar and rivaroxaban, if these are indeed shown to be of benefit in ACS by larger trials. Concerns also exist with regards to their effects on liver function as demonstrated by the LANCELOT-ACS trial with atopaxar and following the withdrawal of ximelagatran. In addition, over recent years newer anti-platelet agents have been increasingly used in ACS. Both prasugrel and ticagrelor have been shown to be more effective than clopidogrel as second anti-platelet agents in ACS, in the landmark TRITON and PLATO studies something that is reflected in the recent European Society of Cardiology non-ST elevation MI guidelines [50,51]. Ticagrelor in particular has been demonstrated to reduce all-cause mortality in ACS with an acceptable increase in bleeding risk and it seems that this will replace clopidogrel in the treatment of ACS. Further trials are thus required that will specifically examine the role of these agents when used as an add-on therapy to newer versions of DAPT (aspirin and ticagrelor or aspirin and prasugrel). It is possible that these agents will offer an additional benefit as unlike aspirin and thiopyridines, which inhibit cycloxygenase-2-mediated and adenosine diphosphate receptor (ADP) P2Y12 pathways respectively, they act on the highly potent thrombin-mediated pathways to inhibit platelet aggregation.

However, bleeding is a major concern with these new agents. These novel agents clearly increase the risk of bleeding, and so the clinical benefit has to outweigh the risk. The greatest benefit of these new agents is likely to be in the highest risk populations. A number of risk scores have been devised that aim to identify such patients including the GRACE (Global Registry of Acute Cardiac Events), PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) and TIMI (Thrombolysis in Myocardial Infarction) risk stratification scores. Future trials should focus on evaluating these agents in the highest risk groups, not in all-comers with ACS.

The role of platelet function and bleeding time tests in identifying 1. patients who may benefit most from such novel antithrombotic agents, such as those with anti-platelet resistance, and 2. those who are at increasing risk of bleeding with these agents, has yet to be evaluated. Furthermore the question, whether such treatment should be individualized, and given in a targeted manner to “highest risk” individuals demonstrating anti-platelet resistance and propensity to thrombosis, and whether such treatment should be guided by laboratory tests, remains to be answered.

6. Summary

Novel oral anticoagulants, used as add-on therapy, can reduce future cardiovascular events in ACS patients but the potential for increased bleeding risk has to be carefully considered. Results for various agents, even in the same class, are mixed. Darexaban and apixaban increased bleeding and darexaban has been withdrawn. Apixaban and the PAR 1 antagonist, vorapaxar, both increased major bleeding without reduction in ischemic events. Dabigatran remains to be fully evaluated. In contrast, rivaroxaban appears to reduce cardiovascular events at a cost of increased major bleeding. Atopaxar appears to improve surrogates of myocardial ischemia without increasing the risk of significant bleeding, but has not been evaluated in terms of ischemic event reduction and larger trials are required. It is likely that patients at high risk of thrombosis are the ones that will benefit the most. Close attention to bleeding and careful monitoring of renal and liver function, and perhaps platelet function tests may help identify patients at high risk of bleeding and thus target therapy at those with high thrombotic risk and low bleeding risk, making the use of these drugs more safe and efficacious.

7. Conclusion

Following an ACS, patients remain at increased risk of recurrent ischemic events despite DAPT and revascularization. Treatment targeted towards thrombin-mediated pathways of platelet aggregation and activation offer an attractive therapeutic target in minimizing such adverse events, as thrombin abundance characterizes the cellular milieu in the immediate period after ACS. This has led to the development of novel oral agents that target thrombin-mediated pathways of platelet aggregation and activation through their action on Factor Xa, thrombin and the PAR 1 receptor. Results to date have been mixed as some studies have demonstrated significant increases in bleeding risk without improvements in clinical outcomes when used in conjunction with DAPT. Of the currently available antithrombotics, the direct Xa inhibitor rivaroxaban and the PAR 1 antagonist atopaxar appear to hold the most promise in the management of patients with recent ACS.

Conflict of interest statement

The authors declared no conflicts of interest.

Acknowledgment

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [52].

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Please cite this article as: Costopoulos C., et al., Novel oral anticoagulants in acute coronary syndrome, Int J Cardiol (2012), http://dx.doi.org/10.1016/j.ijcard.2012.08.014