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Novel anti-thrombotic therapy in acute coronary syndromes

Amir Aziz, Shabeena Aziz, Stephen B. Wheatcroft

Multidisciplinary Cardiovascular Research Centre, University of Leeds, Leeds, United Kingdom

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ABSTRACT

Despite recent developments in revascularisation, anti-platelet and anti-thrombotic therapies, patients with acute coronary syndromes (ACS) remain at increased risk of recurrent atherothrombotic events. Dual anti-platelet therapy comprising aspirin and platelet $P2Y_{12}$ receptor inhibition has become the cornerstone of therapy in ACS. However, thrombin-mediated pathways, which contribute to platelet activation and are responsible for the formation of fibrin clot, remain active following initial plaque rupture. Recently, orally administered drugs which directly target thrombin, factor Xa or thrombin-mediated platelet activation have been developed. Efficacy outcomes in trials of these novel anti-thrombotic agents in ACS have yielded mixed results and their adoption in clinical practice is currently hampered due to a penalty of increased bleeding. To date, the direct Xa inhibitor rivaroxaban and the protease-activated receptor-1 antagonist atopaxar have shown most promise and require further evaluation to determine their role in ACS management.

Klíčová slova:
Akutní koronární syndrom
Antitrombotika
Trombóza

SOUHRN

Přes pokrok v oblasti revaskularizačních výkonů i protidestičkových léků a antitrombotik přetrvává u pacientů s akutními koronárními syndromy (AKS) zvýšené riziko recidivy aterotrombotických příhod. Hlavním prvkem léčby AKS se stala duální antiagregační léčba založená na podávání kyseliny acetylsalicylové a inhibici destičkového receptoru typu $P2Y_{12}$. Trombinem zprostředkované dráhy, které přispívají k aktivaci destiček a jsou odpovědné za tvorbu fibrinové sraženiny, však přetrvávají i po ruptuře plátu. V poslední době byly vyvinuty perorálně podávané léky přímo cíleně působící na trombin, faktor Xa nebo trombinem zprostředkovanou aktivaci destiček. Hodnocení účinnosti ve studiích s těmito novými antitrombotiky u AKS zatím přineslo smíšené výsledky a jejich zavedení do klinické praxe v současné době ztěžuje problém zvýšené krvácivosti. Zatím se jako nejslibnější jeví přímý inhibitor faktoru Xa rivaroxaban a proteázou aktivovaný antagonista receptoru-1 atopaxar; u nich je však nutno ještě podrobněji posoudit jejich možnou úlohu v léčbě AKS.

Address: Dr. Stephen B. Wheatcroft, PhD, FRCP, Division of Cardiovascular & Diabetes Research, LIGHT Laboratories, University of Leeds, Clarendon Way, LS2 9JT Leeds, United Kingdom, e-mail: s.b.wheatcroft@leeds.ac.uk
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Introduction

Acute coronary syndromes (ACS) represent the most common clinical manifestation of cardiovascular disease and are associated with both a short-term risk of morbidity and mortality and a substantial risk of re-admission to hospital within 6 months of the acute event [1]. Treatment costs associated with ACS represent a major drain on healthcare expenditure in economies across Europe [2]. The critical role of coronary thrombus in the pathology of ACS provides the rationale for intensive anti-platelet and anti-thrombotic therapy as cornerstones of in-hospital management. The last two decades have witnessed major advances in acute anti-thrombotic and anti-platelet pharmacotherapy and recently potent, rapidly acting oral anti-platelet agents have become established for use in ACS. Despite these important advances, however, around 10% of patients with ACS continue to experience a recurrent athero-thrombotic event in the year following the index ACS event [3–5]. Although routine treatment with aspirin and a $P2Y_{12}$ receptor inhibitor provides an effective strategy for platelet inhibition following ACS, thrombin-mediated effects including fibrin generation and thrombin-mediated platelet activation may contribute to recurrent athero-thrombotic events. Here we review the recent evaluation of orally active factor Xa inhibitors, direct thrombin inhibitors and protease activated receptor-1 (PAR 1) inhibitors as potential strategies to further reduce recurrent events in ACS.

Mechanisms of action

Acute coronary syndromes (ACS) represent potentially life-threatening consequences of atherosclerosis. Acute thrombosis is typically induced by rupture or erosion of an atherosclerotic plaque in the coronary circulation [6]. Exposure of sub-endothelial matrix proteins and tissue factor initiate thrombosis by activating platelets and factor X respectively (see Fig. 1). Platelet-derived agonists including thromboxane A_2 and adenosine diphosphate (ADP) then further contribute to a feedback cycle of platelet activation and aggregation. Factor Xa stimulates the conversion of inactive prothrombin to the active serine protease, thrombin. Thrombin then catalyses the conversion of soluble fibrinogen to form insoluble fibrin strands which contribute mechanical stability to the developing thrombus and further amplify platelet activation through cleavage of the protease-activate receptor 1 (PAR 1) on the platelet surface [7]. The rapid development of clot comprised of aggregated platelets in a fibrin mesh leads to the clinical manifestation of acute coronary syndrome through occlusion of the coronary artery (typically in the case of ST segment elevation ACS) or by inducing myocardial ischaemia through partial occlusion and micro-embolisation (typically in the case of non-ST segment ACS). The central role of thrombosis in the pathology of ACS argues for intensive inhibition of platelet activation and fibrin generation as strategies to prevent continued thrombus generation in the acute setting. Anti-platelet agents of proven efficacy in ACS include aspirin [8], glycoprotein receptor inhibitors [9] and $P2Y_{12}$ inhibitors such as clopidogrel [4], prasugrel [3] or ticagrelor [5]. Dual anti-platelet therapy (typically with aspirin and an orally administered $P2Y_{12}$ inhibitor) for up to one year is recommended by the European Society of Cardiology following ACS [10]. Thrombin generation in the acute setting is combated by short-term use of parenterally administered anti-coagulants, which may include unfractionated heparin, low-molecular weight heparin [11], fondaparinux [12] or bivalirudin [13]. However, it has been recognised for many years that pro-coagulant factors may continue to be active for long periods following ACS [14], suggesting that longer-term anti-thrombotic therapy may be beneficial.

Oral anti-thrombotics in ACS

An increased risk of recurrent ischaemic events after discontinuation of unfractionated heparin or low-molecular weight heparin has been noted in ACS patients [15,16]. Following the observation that increased levels of prothrombin fragments persist up to six months after a coronary ischaemic event [14], several trials investigated the possibility that long-term anti-coagulation with vitamin K antagonists (e.g. warfarin) could prevent recurrent atherothrombotic events following ACS. A comprehensive meta-analysis of such trials demonstrated a significant reduction in the incidence of recurrent ACS events and stroke with long-term treatment with aspirin and warfarin compared to aspirin alone [17]. However, no associated decrease in mortality was apparent and bleeding events were more than twice as common in those receiving aspirin and warfarin in combination [17]. These trials pre-dated the development of revascularisation with widespread use of coronary artery stents in ACS. Additionally, concerns over drug–drug interactions, variable bioavailability and the requirement for frequent INR monitoring limit the potential utility of warfarin in this setting.

Recently, newer anti-thrombotic agents which may overcome many of the limitations of warfarin or provide additional strategies for platelet inhibition have been developed. These agents comprise direct thrombin inhibitors, factor Xa inhibitors and PAR 1 antagonists. Collectively these agents have stable pharmacokinetic profiles, few food and drug–drug interactions and do not require regular monitoring of anti-coagulant effect. Several of the direct thrombin inhibitors and factor Xa inhibitors were initially evaluated as anti-coagulants to prevent venous thrombo-embolism or reduce the risk of stroke in non-valvular atrial fibrillation and have been approved for clinical use in these settings. Here we provide an overview of more recent phase II and phase III trials in which novel anti-thrombotic drugs have been evaluated in patients with ACS (summarised in Table 1).

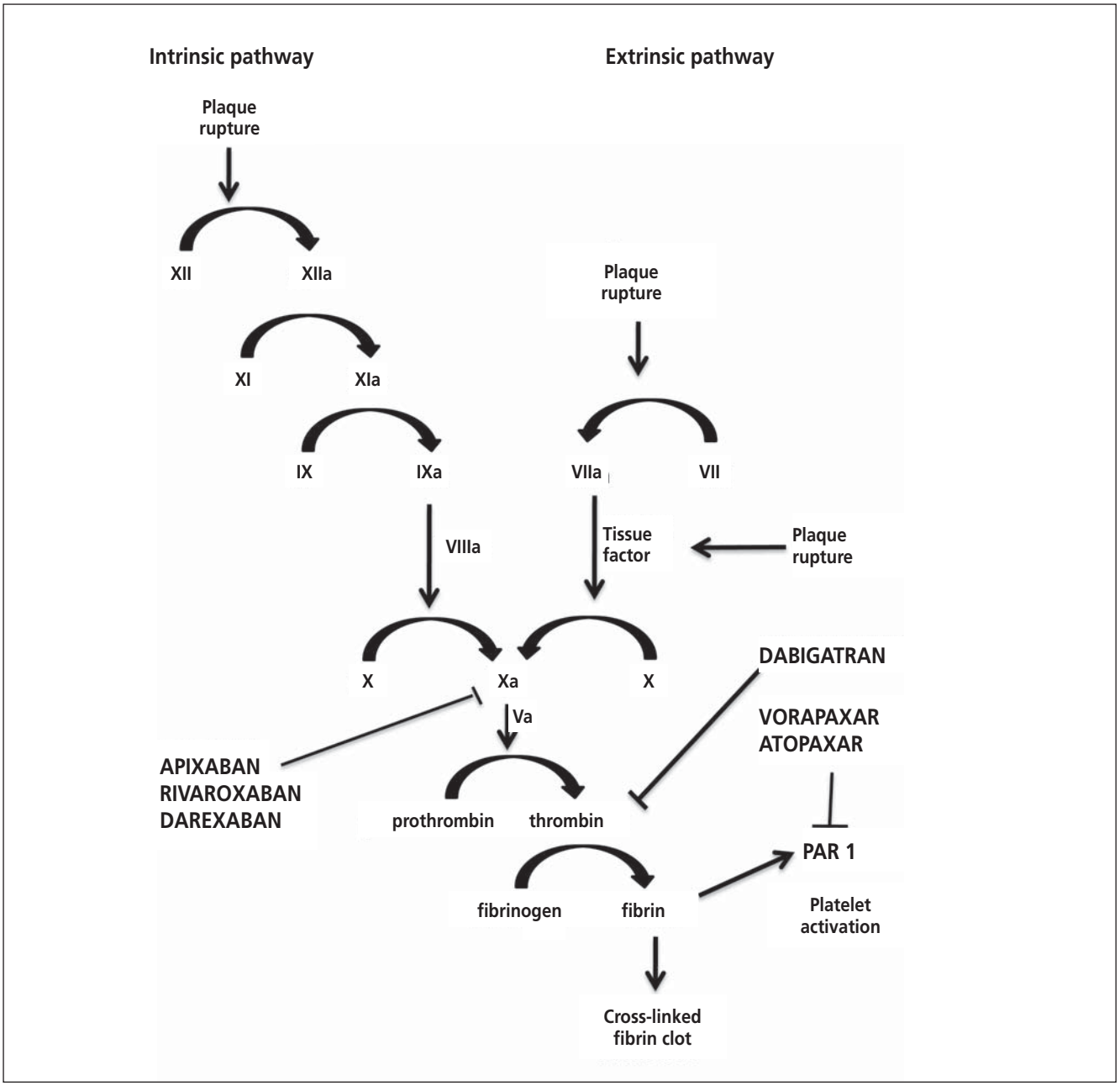

Fig. 1 – Schematic representation of activation of clotting pathways and thrombin-mediated platelet activation in acute coronary syndrome. Sites of action of novel anti-thrombotic drugs on factor Xa, thrombin and protease-activated receptor 1 (PAR 1) are indicated.

Direct thrombin inhibitors

Thrombin is a critical player in both fibrin generation and platelet activation following atherosclerotic plaque rupture. Direct thrombin inhibitors inactivate soluble and fibrin-bound thrombin and thereby limit thrombogenesis and reduce platelet activation. Ximelagatran was an early oral direct thrombin inhibitor, which demonstrated efficacy in reducing death, non-fatal myocardial infarction and severe recurrent ischaemia in ACS when used in combination with aspirin [18]. Further evaluation of ximelagatran was abandoned in 2006 after concerns arose over liver toxicity. However, the newer direct thrombin inhibitor dabigatran has subsequently been trialled in ACS.

Dabigatran

Dabigatran exelate is a competitive and reversible direct thrombin inhibitor that binds to both free and fibrin-bound thrombin, thereby reducing conversion of fibrinogen into fibrin and inhibiting thrombin-induced platelet aggregation. Dabigatran is a pro-drug which is converted to its active metabolite by plasma and liver esterases. Dabigatran has proved effective in the prevention and treatment of venous thromboembolism [19]. In non-valvular atrial fibrillation, the pivotal RE-LY trial demonstrated

Table 1 – Summary of key findings from phase II and phase III trials of novel anti-thrombotic drugs in acute coronary syndrome.

Study	Year	Sample size	Follow up	Drug	Concomitant treatment	Key findings
Direct thrombin inhibitors						
RE-DEEM (phase II)	2011	1861	6 months	Dabigatran 50 mg, 75 mg, 110 mg, 150 mg twice daily versus placebo	Dual-antiplatelet	Dose dependent increase in bleeding events. No reduction in ischaemic events.
Factor Xa inhibitors						
APPRAISE (phase II)	2009	1715	6 months	Apixaban 2.5 mg twice daily Apixaban 10 mg daily Apixaban 10 mg twice daily Apixaban 20 mg daily Placebo	Aspirin Clopidogrel	Apixaban showed dose related increase in bleeding. Dose related trend towards reduction in ischaemic events.
APPRAISE-2 (phase III)	2011	7392	8 months	Apixaban 5 mg twice daily versus placebo	Aspirin Clopidogrel	Apixaban 5 mg bd increased the number of major bleeding events. No significant reduction in recurrent ischaemic events.
ATLAS ACS-TIMI-46 (phase II)	2009	3491	6 months	Rivaroxaban 5 mg, 10 mg, 20 mg daily versus placebo	Stratum 1 – aspirin only Stratum 2 – aspirin and clopidogrel	Significant increase in bleeding. Reduced composite of death, MI, stroke.
ATLAS ACS-TIMI-51 (phase III)	2012	15,526	13 months	Rivaroxaban 2.5 mg or 5 mg twice daily versus placebo	Dual-antiplatelet	Significant reduction of composite ischemic end point. Increased risk of major bleeding and intracranial haemorrhage.
RUBY-1 (phase II)	2011	1279	6 months	Darexaban 5 mg twice daily, 10 mg once daily, 15 mg twice daily, 30 mg once daily, 30 mg twice daily, 60 mg once daily versus placebo	Dual-antiplatelet	Dose related two- to four-fold increase in bleeding. No overall decrease in ischaemic events.
PAR 1 antagonists						
Goto et al. (phase II)	2010	117	60 days	Vorapaxar (20 mg loading then 1 mg daily or 40 mg loading then 2.5 mg daily) versus placebo	Aspirin Ticlopidine	No difference in bleeding. Reduction in per-procedural MI.
TRACER (phase III)	2012	12,944	502 days	Vorapaxar (40 mg loading then 2.5 mg daily) versus placebo	Aspirin $P2Y_{12}$ inhibitor	Increased major bleeding. Increased intra-cranial bleeding. No difference in primary composite ischaemic endpoint.
J-LANCELOT (phase II)	2010	504	12–24 weeks	Atopaxar 50 mg, 100 mg or 200 mg daily versus placebo	Aspirin $P2Y_{12}$ inhibitor	No difference in bleeding. Dose dependent increase in liver enzymes and QTc.
LANCELOT ACS (phase II)	2011	603	16 weeks	Atopaxar 400 mg loading then 50 mg, 100 mg or 200 mg daily versus placebo	Aspirin $P2Y_{12}$ inhibitor	No difference in major or minor bleeding. Reduced Holter-detected ischaemia. No difference in clinical ischaemic events.

that dabigatran 110 mg twice daily was non-inferior to warfarin and 150 mg twice daily was superior to warfarin in reducing stroke or systemic embolisation [20].

The phase II dose-finding RE-DEEM trial investigated escalating doses of dabigatran in 1861 patients with ACS [21]. Patients with STEMI (60%) or NSTEMI (40%) and ≥ 1 additional risk factor for a repeat event were randomised to twice daily treatment with dabigatran 50 mg, 75 mg, 110 mg, 150 mg or placebo. 99% of patients received dual anti-platelet therapy. The primary safety end point comprised major or clinically relevant minor bleeding according to the International Society of Thrombosis and Haemostasis (ISTH) definition [22] over 6-months. Dabigatran therapy was associated with 2–4 fold, dose-dependent increased risk of bleeding with the primary endpoint occurring in 3.5%, 4.3%, 7.9% and 7.8% of patients receiving the 50, 75, 110 and 150 mg twice daily doses respectively – compared to 2.2% receiving placebo ($p < 0.001$). Although the study was not powered for efficacy, no significant reduction in ischaemic events was apparent in patients receiving dabigatran. The composite of cardiovascular death, myocardial infarction and stroke occurred in 4.6%, 4.9%, 3.0% and 3.5% of patients receiving the 50, 75, 110 and 150 mg twice daily doses respectively – compared to 3.8% in the placebo group.

Dabigatran has not been evaluated further in a phase III trial in ACS. However, potential safety concerns have emerged following recognition of a small increased risk of myocardial infarction in patients with atrial fibrillation receiving dabigatran compared to warfarin in the RE-LY trial [20] and an increased risk of acute coronary events in patients receiving dabigatran reported in a recent meta-analysis [23].

Factor Xa inhibitors

Activation of factor X plays a critical role in activation of the clotting cascade following atherosclerotic plaque rupture. Several selective, orally active factor Xa inhibitors have been developed and recently evaluated in ACS.

Apixaban

Apixaban is an orally active, selective, direct-acting, factor Xa inhibitor. Apixaban was demonstrated to reduce the incidence of venous thromboembolism in patients undergoing orthopaedic surgery [24] and to prevent thromboembolic events in patients with atrial fibrillation [25]. Apixaban has a half-life of 12 h and is eliminated predominantly through non-renal mechanisms. In the phase II APPRAISE trial, 1715 subjects within 7 days of an ACS and with ≥ 1 additional risk factor for recurrent events were randomised to placebo or to one of four doses of apixaban (2.5 mg twice daily, 10 mg once daily, 10 mg twice daily or 20 mg once daily) [26]. The two treatment arms with the higher doses were discontinued early because of excess bleeding. The primary outcome of ISTH major and clinically relevant non-major bleeding occurred in 3.0% of patients receiving placebo, 5.7% of patients receiving apixaban 2.5 mg twice daily and 7.9% of patients receiving apixaban 10 mg once daily. There was no statistically significant difference in ischaemic endpoints between patients receiving apixaban (7.6% and 6.0%) or placebo (8.7%).

The 10 mg daily dose of apixaban was selected for a phase III trial for the prevention of recurrent events in ACS. APPRAISE-2 randomised high-risk ACS patients to placebo or apixaban 5 mg twice daily in addition to dual anti-platelet therapy with aspirin and clopidogrel [27]. The trial was terminated prematurely after recruitment of 7392 patients because of an increase in major bleeding events with apixaban in the absence of a reduction in recurrent ischaemic events. Over a median follow-up of 241 days, the primary outcome of cardiovascular death, myocardial infarction, or ischaemic stroke occurred in 279 of the 3705 patients (7.5%) assigned to apixaban (13.2 events per 100 patient-years) and in 293 of the 3687 patients (7.9%) assigned to placebo (14.0 events per 100 patient-years) (hazard ratio with apixaban, 0.95; 95% confidence interval [CI], 0.80–1.11; $p = 0.51$). The primary safety outcome of major bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) definition occurred in 46 of the 3673 patients (1.3%) who received at least one dose of apixaban (2.4 events per 100 patient-years) and in 18 of the 3642 patients (0.5%) who received at least one dose of placebo (0.9 events per 100 patient-years; hazard ratio with apixaban, 2.59; 95% CI, 1.50–4.46; $p = 0.001$).

Rivaroxaban

Rivaroxaban is another selective, direct-acting factor Xa inhibitor which is effective in the prevention and treatment of venous thromboembolism [28] and in the prevention of stroke and systemic embolisation in non-valvular atrial fibrillation [29]. In the ATLAS ACS-TIMI-46 phase II dose-finding trial or rivaroxaban, 3491 high-risk patients with ACS were assigned at their physician's discretion to aspirin alone (stratum 1) or to aspirin plus a thienopyridine (stratum 2) [30]. In each stratum, patients were randomised to placebo or rivaroxaban 5 mg, 10 mg or 20 mg daily (administered once daily or in two divided doses). Rivaroxaban was associated with a significant increase in bleeding in both stratum 1 and stratum 2. The overall risk of clinically significant bleeding with rivaroxaban vs. placebo increased in a dose-dependent manner (hazard ratios [HRs] 2.21 [95% CI 1.25–3.91] for 5 mg, 3.35 [2.31–4.87] for 10 mg, 3.60 [2.32–5.58] for 15 mg, and 5.06 [3.45–7.42] for 20 mg doses; $p < 0.0001$). Rivaroxaban did not reduce the primary efficacy endpoint (a composite of death, myocardial infarction, stroke, or severe recurrent ischaemia requiring revascularisation during 6 months). However, rivaroxaban did reduce the secondary efficacy endpoint of death, MI or stroke compared to placebo (3.9% *vs*. 5.5%; HR 0.69, [95% CI 0.50–0.96], $p = 0.0270$).

The findings of this study led to the larger phase III ATLAS ACS 2-TIMI 51 trial, in which two doses of rivaroxaban (5 mg/day or 10 mg/day) were selected for evaluation [31]. In ATLAS ACS 2-TIMI 51, 15,526 patients with ACS were randomised 1:1:1 to rivaroxaban 2.5 mg twice daily, rivaroxaban 5 mg twice daily or placebo in addition to aspirin and a $P2Y_{12}$ inhibitor. Over a median follow up of 31 months, both doses of rivaroxaban decreased the primary efficacy endpoint of death from cardiovascular causes, myocardial infarction or stroke compared to placebo (2.5 mg dose 9.1% vs. 10.7%, HR 0.84, 95% CI 0.72–0.97;

5 mg dose 8.8% vs. 10.7%, HR 0.85, 95% CI 0.73–0.98). However, rivaroxaban increased the rates of major bleeding not related to coronary-artery bypass grafting (2.1% vs. 0.6%, $p < 0.001$) and intracranial haemorrhage (0.6% vs. 0.2%, $p = 0.009$), without a significant increase in fatal bleeding (0.3% vs. 0.2%, P=0.66). The twice-daily 2.5-mg dose of rivaroxaban reduced the rates of death from cardiovascular causes (2.7% vs. 4.1%, $p = 0.002$) and of death from any cause (2.9% vs. 4.5%, $p = 0.002$).

Darexaban

Darexaban is a further direct inhibitor of factor Xa which has been evaluated in ACS. Darexaban is a pro-drug which rapidly absorbed from the gut and converted to its active metabolite. It reaches maximum plasma levels at 1–1.5 h post-dose and has a terminal half-life of 14–18 h. Darexaban demonstrates predictable pharmacokinetics and pharmacodynamics. Darexaban has minimal interaction with food and, unlike the other available direct factor Xa inhibitors, has no important interactions with CYP3A4/P-glycoprotein inhibitors and inducers [32].

Darexaban has been evaluated for prevention of venous thromboembolism and for the prevention of stroke in non-valvular atrial fibrillation. In ACS, the phase II RUBY trial investigated 1279 patients in a 26-week, multi-centre, double-blind, randomized, parallel-group study [33]. Patients with recent high-risk non-ST-segment elevation ACS or ST-segment elevation ACS were randomised to one of six darexaban regimens or placebo in addition to dual anti-platelet therapy. A dose-dependent increase in bleeding events was observed in the darexaban active treatment arms (pooled HR 2.2275, 95% CI 1.13–4.60). The main efficacy outcome (a composite of death, stroke, myocardial infarction, systemic thromboembolism, and severe recurrent ischaemia) was not reduced by darexaban, although the study was under-powered to assess efficacy. The data were not sufficiently encouraging to progress to a phase III trial and it is unlikely that darexaban will be further examined in the context of ACS.

PAR 1 antagonists

Cleavage of platelet surface PAR 1 by fibrin promotes platelet activation and the release of the pro-aggregatory mediators adenosine diphosphate, serotonin and thromboxane A_2. The thrombin-induced platelet activation mediated through PAR 1 is thought to contribute to coronary thrombosis and has prompted the recent evaluation of PAR 1 inhibitors as potential therapeutic agents in ACS.

Vorapaxar

Vorapaxar is an orally active compound which mediates selective and reversible inhibition of PAR 1. Vorapaxar has high bioavailability associated with a long plasma half-life. Elimination is predominantly through metabolism by hepatic CYP3A4 enzymes, raising the possibility of interaction with CYP3A4 activators and inhibitors. Voropaxar has been evaluated in three phase II studies in patients with coronary artery disease. In the TRA-PCI study, vorapaxar in addition to aspirin and clopidogrel was evaluated in patients undergoing non-urgent PCI [34]. A reduction in major adverse cardiovascular events was noted in the absence of an increased bleeding risk. In a subsequent phase II study in ACS, 117 patients with ACS scheduled for PCI were randomised to vorapaxar (20 mg or 40 mg loading dose followed by 1 mg or 2.5 mg maintenance dose once daily) or placebo for 60 days [35]. Incidence of bleeding events was similar in placebo and vorapaxar-treated groups. A significant reduction of biochemically detected peri-procedural myocardial infarction was associated with vorapaxar administration although no clinically significant adverse ischaemic events were present in either placebo or vorapaxar treated groups. In the much larger TRACER study, 12,944 patients with non-ST segment elevation ACS were randomised to receive vorapaxar (40 mg loading and 2.5 mg daily maintenance dose) or placebo in addition to aspirin and a $P2Y_{12}$ inhibitor [36]. The trial was stopped early after a safety review identified an unacceptable increase in bleeding in vorapaxar treated patients. Rates of moderate and severe bleeding were 7.2% in the vorapaxar group and 5.2% in the placebo group (hazard ratio, 1.35; 95% CI, 1.16–1.58; $p < 0.001$). Intracranial haemorrhage occurred in 1.1% and 0.2%, respectively (HR, 3.39; 95% CI, 1.78–6.45; $p < 0.001$). The primary endpoint (death from cardiovascular causes, myocardial infarction, stroke, recurrent ischaemia with rehospitalization, or urgent coronary revascularization) was not significantly different in patients receiving vorapaxar vs. patients receiving placebo (Kaplan–Meier 2-year rate, 18.5% vs. 19.9%; HR, 0.92; 95% CI, 0.85–1.01; $p = 0.07$). However, the composite of death from cardiovascular causes, myocardial infarction, or stroke occurred less commonly in the vorapaxar group vs. the placebo group (14.7% and 16.4%, respectively; HR, 0.89; 95% CI, 0.81–0.98; $p = 0.02$).

Atopaxar

Atopaxar is an orally active, reversible PAR 1 inhibitor with high bioactivity, though with a shorter half-life than vorapaxar. It is also metabolised via the CYP3A4 enzyme system. Two small phase II trials of atopaxar conducted in Japan (reported together as J-LANCELOT) demonstrated effective platelet inhibition in the absence of increased risk of bleeding in patients with ACS or high risk coronary artery disease [37]. Dose-dependent increases in liver function abnormalities and corrected QT interval were observed in atopaxar-treated patients. Atopaxar has subsequently been evaluated in a larger international phase II study in ACS. In LANCELOT-ACS, 603 patients with non-ST segment elevation ACS were randomised to receive one of three doses of atopaxar (400-mg loading dose followed by 50, 100, or 200 mg daily) or placebo in addition to aspirin and a $P2Y_{12}$ inhibitor [38]. The primary endpoint, the incidence of Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) major or minor bleeding, did not differ significantly between the atopaxar and placebo groups (3.08% vs. 2.17%, respectively; $p = 0.63$). A signal for efficacy was provided by the finding that atopaxar significantly reduced ischaemia on continuous ECG monitoring (Holter) at 48 h compared with placebo (relative risk, 0.67; $p = 0.02$). This did not translate into a significant reduction in the incidence of cardiovascular death, myocardial infarction, or stroke (5.63% in the pla-

cebo group vs. 3.25% in the combined atopaxar group [$p = 0.20$]). However, the study was underpowered to detect clinical efficacy in reducing ischaemic events. Transient dose-dependent transaminase elevation and relative QTc prolongation were observed in patients receiving the highest doses of atopaxar. Collectively, the findings of reduced Holter-detected ischaemia in the absence of an increased bleeding risk in LANCELOT-ACS are encouraging and support the further evaluation of atopaxar in larger studies in patients with ACS.

Summary and future directions

Novel oral anti-thrombotic drugs target complementary pathways to those addressed by the current standard combination of aspirin and a $P2Y_{12}$ inhibitor in ACS, and offer a plausible strategy to reduce recurrent ischaemic events. However, efficacy outcomes in recent clinical trials of factor Xa inhibitors, direct thrombin inhibitors and PAR 1 inhibitors in ACS are mixed, even within the same class of compound, and the increased bleeding risk observed in many of the trials remains a major concern. Darexaban and apixaban were both associated with increased bleeding in ACS and darexaban has been withdrawn from further development. Dabigatran is yet to be evaluated in a phase III clinical trial in ACS; however, the signal of increased risk of myocardial infarction in the RE-LY study in non-valvular atrial fibrillation represents cause for concern in this context. Both apixaban and the PAR 1 inhibitor vorapaxar increased major bleeding in ACS without any evidence of reduction in cardiovascular ischaemic events.

To date, rivaroxaban and atopaxar represent the compounds showing most promise for risk reduction in ACS whilst maintaining an acceptable safety profile. In ATLAS ACS 2-TIMI 51, rivaroxaban demonstrated an overall 16% decrease in recurrent ischaemic events and a 32% decrease in overall mortality at the lower dose evaluated (2.5 mg) [31]. However, this efficacy benefit comes with the penalty of a significant increase in major bleeding events with rivaroxaban overall. The PAR 1 inhibitor atopaxar improved the surrogate marker of Holter-detected ischaemia in LANCELOT-ACS without increasing the risk of significant bleeding [38], but remains to be evaluated in a large-scale trial to assess its potential to reduce clinical adverse events.

Several factors may contribute to the disparate results from these trials of novel anti-thrombotic drugs in ACS and are pertinent to their interpretation. In particular, consideration of differences in patient selection, dosing and definition of bleeding events are relevant to assessing the balance between clinical efficacy and bleeding risk in the trials. The risk profile of trial participants is likely to impact both on the potential for a novel compound to demonstrate efficacy in reducing ischaemic events and on its susceptibility to increase bleeding. Baseline risk differed substantially between the trials of novel anti-thrombotic drugs in ACS. For example, APPRAISE-2 enroled older, higher risk ACS patients with at least two additional risk factors [26], whereas patients in ATLAS-ACS-2 were not required to have additional risk factors and potential participants with previous intracranial haemorrhage or stroke were excluded [31]. Bleeding is a major concern with novel anti-thrombotic drugs, not least because, unlike warfarin, effective strategies to reverse the anti-coagulant effects in serious bleeding are not readily available [39]. Additionally, disparate definitions of bleeding events used in the recent trials render it difficult to satisfactorily compare haemorrhagic outcomes between trials.

In addition to baseline population risk, the dose of novel anti-thrombotic drug selected for ACS trials is likely to be of critical importance in negotiating the balance between clinical efficacy and bleeding. This is especially pertinent in the context of dual anti-platelet therapy which itself increases the risk of bleeding complications. What is not yet clear is whether it is indeed feasible to achieve additional reduction of recurrent cardiovascular events in ACS through the use of novel anti-coagulants without incurring a penalty of increased bleeding. In future, it may be necessary to evaluate selective use of novel anti-thrombotics in those ACS patients at highest risk of recurrent ischaemic events rather than 'all-comers' with ACS. However, patients identified as being at high risk of ischaemic events by available risk scores (e.g. GRACE, PURSUIT or TIMI) are often also at high risk of bleeding. Newer bleeding risk scores in ACS [40] may be useful to weigh the risks and benefits in individual patients. It is reassuring that recent data do not suggest increasing incidence of serious bleeding over time in real-world ACS registries [41,42], suggesting that physicians may already be using more aggressive anti-thrombotic drugs selectively in their patients. Some commentators have proposed an optimal dose of anti-thrombotic, or a 'sweet-spot', at which clinical efficacy may be attained with minimum haemorrhagic exposure [43]. It is noteworthy that the dose of apixaban employed in the APPRAISE-2 trial is the same as that used for thromboembolic prophylaxis in atrial fibrillation. In contrast, the dose of rivaroxaban used in ATLAS ACS 2-TIMI 51 is one quarter of that used in atrial fibrillation. One may speculate that future trials seeking to achieve a consistent low-level anti-thrombotic effect may be able to facilitate cardiovascular event reduction with an acceptable bleeding risk in ACS patients receiving concomitant intensive anti-platelet therapy.

Uncertainty remains over how novel anti-coagulants will be positioned in the future therapeutic armamentarium for ACS. The arena of anti-platelet therapy is rapidly evolving and the landmark TRITON and PLATO studies have provided a strong rationale for the use of newer $P2Y_{12}$ inhibitors prasugrel and ticagrelor, rather than clopidogrel, in ACS [3,5]. This change has been reflected in the recent European Society of Cardiology Guidelines for the management of non-ST elevation myocardial infarction [10]. Demonstration in PLATO of reduced all-cause mortality in ACS patients with an acceptable overall bleeding risk [5] is likely to herald more widespread use of ticagrelor in particular. Most of the recent trials of novel anti-thrombotic drugs in ACS have been undertaken on a background of aspirin and clopidogrel dual anti--platelet therapy. Whether the novel anti-thrombotics have a role in patients receiving newer generation $P2Y_{12}$ inhibitors remains to be evaluated. It is feasible that no-

vel anti-thrombotic drugs could prove complimentary by antagonising thrombin-mediated platelet activation. In particular, atopaxar may offer the opportunity to inhibit thrombin-mediated platelet activation through PAR 1 antagonism without interfering with thrombin-mediated fibrin generation. It remains to be seen whether the neutral effect on bleeding risk of atopaxar in phase II trials can be maintained whilst demonstrating clinical efficacy in larger studies.

In conclusion, patients sustaining an ACS remain exposed to an unacceptable risk of subsequent recurrent events despite revascularisation and dual anti-platelet therapy. Novel approaches targeting fibrin generation and thrombin-mediated platelet activation represent important opportunities to reduce recurrent ischaemic events in ACS. The recent development of selective orally-administered direct thrombin inhibitors, factor Xa inhibitors and PAR 1 antagonists has gone some way in addressing this unmet need. However, mixed evidence of clinical efficacy and unacceptable risks of bleeding encountered with several of these agents have proved to be disappointing. The direct Xa inhibitor rivaroxaban and the PAR 1 antagonist atopaxar have demonstrated the most encouraging results to date and warrant further evaluation in the changing environment of ACS management.

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