Reviews

New Antithrombotics for Secondary Prevention of Acute Coronary Syndrome

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ABSTRACT

Patients with acute coronary syndrome (ACS) usually receive acetylsalicylic acid plus an adenosine diphosphate (ADP) receptor inhibitor to reduce the long-term risk of recurrent events. However, patients receiving standard antiplatelet prophylaxis still face a substantial risk of recurrent events. Strategies involving 3 antithrombotic agents with different modes of action have now been tested. In Thrombin Receptor Antagonists for Clinical Event Reduction (TRA-CER), compared with standard care alone, bleeding complications including intracranial hemorrhage (ICH) were increased with the addition of vorapaxar, without efficacy benefit. In Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients With Atherosclerosis (TRA 2°P–TIMI 50), the addition of vorapaxar reduced recurrent events compared with standard care in stable patients with prior myocardial infarction. This study was terminated early in patients with prior stroke owing to excess ICH, though an increased risk of ICH or fatal bleeding was not detected in patients with prior myocardial infarction. The Apixaban for Prevention of Acute Ischemic and Safety Events 2 (APPRAISE-2) trial of standard-dose apixaban added to standard care in patients with ACS was also stopped early owing to excess serious bleeding. However, in Rivaroxaban in Combination With Aspirin Alone or With Aspirin and a Thienopyridine in Patients With Acute Coronary Syndromes (ATLAS ACS 2 TIMI 51), fatal bleeding or fatal ICH did not increase with low-dose rivaroxaban added to low-dose acetylsalicylic acid-based standard care compared with standard care alone. In that trial, a significant reduction of recurrent vascular events was shown with 3 antithrombotic regimens compared with standard care. Therefore, depending on drug dose and patient population, further reductions in recurrent vascular events after ACS may be possible in future clinical practice, with a favorable benefit-risk profile.

Introduction

Coronary artery disease (CAD) accounts for 30% of deaths worldwide.[1] The global burden of CAD is likely to worsen with an aging population and increasing obesity, cigarette smoking, and general inactivity.[1] Coronary artery disease eventually results in coronary thrombosis, leading to acute coronary syndrome (ACS) or even cardiac death.[2] These events occur when an atherosclerotic plaque ruptures[3] or is eroded,[4] resulting in partial or total occlusion of the coronary arterial tree.

Current standard care—using acetylsalicylic acid (ASA; aspirin), a thienopyridine, or both—is effective for the prevention of secondary events after ACS.[5–7] However, 12-month risk of recurrent vascular events remains at approximately 10%,[5–7] highlighting a clear need for improvement. Although the addition of other antithrombotics to standard care may be effective, the risk of serious bleeding has inhibited the adoption of this approach. Current alternative treatment strategies include platelet receptor antagonists and combining antiplatelets and anticoagulants. Results have been mixed, but encouraging data have been obtained by adding the direct factor Xa inhibitor rivaroxaban to the current standard therapy.[8] The combination of appropriate antithrombotic dosing and complementary modes of action may prevent occlusive thrombus formation while maintaining adequate hemostasis.

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Thrombus Formation in Acute Coronary Syndrome

Exposure of platelets to collagen and von Willebrand factor stimulates their adhesion at the site of plaque disruption or endothelial dysfunction (Figure 1).[9] The presence of blood-borne tissue factor and activated platelets triggers the coagulation cascade, leading to thrombin generation and conversion of fibrinogen to fibrin.[9] Simultaneously, thrombin stimulates platelet activation and aggregation mainly through G-protein-coupled protease-activated receptor 1 (PAR-1), inducing release of adenosine diphosphate (ADP) and thromboxane A_2 (TXA_2).[9]

Activation of platelets and the coagulation cascade are highly interdependent,[10,11] with thrombin playing a central role in both (Figures 1 and 2). The prothrombinase complex is assembled on the platelet surface, resulting in higher catalytic activity than that of free prothrombinase components in plasma.[12] Thrombin also behaves as an anticoagulant by activating negative-feedback regulation of its own activity via protein C activation (Figure 1).[13] Activated protein C catalyzes the inactivation of activated factors V and VIII.[13] Most thrombin is produced on the platelet surface, so platelets also have a role in both promotion and inhibition of coagulation.

Established Antiplatelet Strategies

Acetylsalicylic acid, which permanently inhibits cyclooxygenase (COX),[14,15] has been the mainstay of secondary ACS prevention for longer than 20 years. Platelet COX-1 catalyzes the conversion of arachidonic acid to prostaglandin G_2, which is converted to prostaglandin H_2, a TXA_2 precursor.[16–18] Thromboxane A_2 is released by activated platelets and induces platelet aggregation and vasoconstriction. The effects of ASA on TXA_2 synthesis are irreversible because platelets have no nuclei and are unable to continually produce COX from their limited amount of RNA.[15] Platelet COX-1 inactivation has been shown to reach saturation at 30 mg ASA daily,[19] and ASA doses ≥100 mg daily show little association with improved efficacy outcomes in ACS patients.[20,21] Furthermore, ≥100 mg daily ASA is associated with a higher risk of major gastrointestinal bleeding[20] and major bleeding in the long term.[21] European and US ACS guidelines recommend maintenance doses that reflect these data (75–100 mg daily in the European Society of Cardiology guidelines, and 75–162 mg daily in combined American College of Cardiology Foundation/American Heart Association Task Force updates).[22–25] In addition to the established mechanism of action, ASA may also prevent atherothrombosis through other COX-1–independent mechanisms, such as the cytotoxic effects of salicylate. However, these effects are neither consistent nor substantial in clinical studies.[26]

A meta-analysis of randomized trials of long-term (≥1 month) antiplatelet therapy vs control in approximately 20 000 patients with prior myocardial infarction (MI) demonstrated a 25% reduction in risk of vascular events (nonfatal MI, nonfatal stroke, and vascular death).[27] Although single antiplatelet therapy over a mean 27 months was effective, 13.5% of patients still experienced vascular events, leaving substantial room for improvement. The most widely tested regimen was ASA 75 to 325 mg, with no evidence that higher-dose ASA or an alternative antiplatelet was more effective.[27] Therefore, dual antiplatelet regimens that added a different type of antiplatelet agent to ASA were investigated.

Clopidogrel is a thienopyridine with an irreversible effect on the $P2Y_{12}$ ADP receptor (Figure 2).[18] In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, long-term ASA/clopidogrel was compared with ASA/placebo for 3 to 12 months in 12 562 patients with unstable angina (UA) or non–ST-elevation MI (NSTEMI).[7] Dual therapy resulted in a 20% reduction in cardiovascular

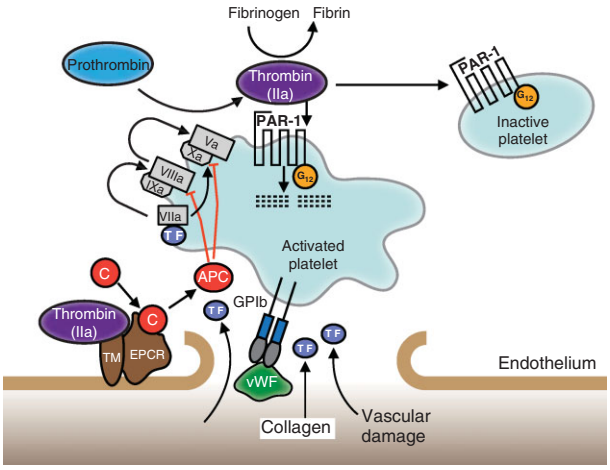

Figure 1. Interactions between platelet activation and thrombin generation in the coagulation cascade. Vascular damage exposes collagen, von Willebrand factor (VWF), and tissue factor (TF), leading to adherence and aggregation of flowing platelets and activation of coagulation to produce thrombin. Thrombin promotes platelet activation and fibrin production and acts as an anticoagulant, with thrombomodulin (TM), by activating protein C (C) bound to endothelial protein C receptor (EPCR). Activated protein C (APC) binds protein S (not shown) and inactivates the coagulation cascade, inhibiting further thrombin production. As most thrombin is produced on the platelet surface, platelet activation is linked to both promotion and inhibition of coagulation. Abbreviations: APC, activated protein C; C, protein C; EPCR, endothelial protein C receptor; PAR-1, proteinase-activated receptor 1; TF, tissue factor; TM, thrombomodulin; vWF, von Willebrand factor.

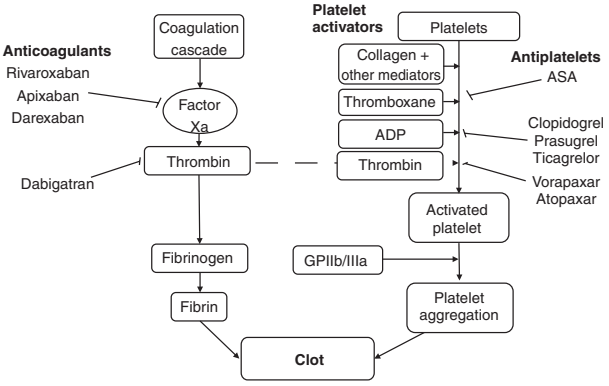

Figure 2. The central role of thrombin in platelet activation and coagulation in clot formation. Abbreviations: ADP, adenosine diphosphate; ASA, acetylsalicylic acid; GP, glycoprotein. Adapted with permission from Hamm et al.[22] Copyright © 2011 Oxford University Press.

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(CV) death, nonfatal MI, or stroke compared with ASA alone (9.3% vs 11.4%; $P < 0.001$).[7] Major bleeding (Table 1) occurred in 3.7% of patients receiving ASA/clopidogrel and 2.7% of patients receiving ASA alone (relative risk [RR]: 1.38, $P = 0.001$).[7] Antiplatelets predispose patients to bleeding by preventing platelets from repairing vessel injury. The addition of a second antiplatelet agent to ASA resulted in more bleeding events than ASA alone.

The Clopidogrel for the Reduction of Events During Observation (CREDO) study involving patients with symptomatic CAD[28] and the Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study (COMMIT/CCS-2) involving patients with ST-elevation MI (STEMI) and NSTEMI[29] also demonstrated the benefits of dual antiplatelet agents. Long-term dual antiplatelet therapy is now standard care for secondary prevention after ACS, and it is recommended for at least 12 months by practice guidelines.[22,24,25,30]

Although the effectiveness of standard clopidogrel dosing (300 mg loading, 75 mg maintenance) is well established, the Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events–Optimal Antiplatelet Strategy for Interventions 7 (CURRENT-OASIS 7) trial demonstrated a benefit for double-dose clopidogrel in reducing the risk of stent thrombosis in patients who underwent percutaneous coronary intervention (PCI) vs standard dosing (1.6% vs 2.3%; hazard ratio [HR]: 0.68, 95% confidence interval [CI]: 0.55-0.85, $P = 0.001$).[20] The American College of Cardiology Foundation/American Heart Association do not yet recommend the 600-mg dose for PCI patients, whereas the European Society of Cardiology advocates this as the preferred dosing option.[22–25]

Acute coronary syndrome treatment failure is a particular concern for ASA/clopidogrel therapy, increasing the risk of ischemic events in nonresponders.[31–34] Lack of antiplatelet effectiveness is attributed to several causes, including genetic polymorphism in key proteins such as COX-1 and COX-2 for ASA, and CYP enzymes PON-1 and the P-glycoprotein transporter for clopidogrel.[33–36] However, genetic testing is not routine in clinical practice. Dose titration in response to platelet function has been investigated minimally and has yet to reveal a clinical advantage.[37] Furthermore, the accuracy and prognostic value of available ex vivo platelet-function assays are debatable.[31] In the Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome Subjects (TRILOGY ACS) platelet-function substudy, prasugrel was associated with lower platelet reactivity than clopidogrel; however, platelet reactivity was not associated with the occurrence of ischemic outcomes over the 30-month study period.[38] Based on these data, nonresponders may be best managed by switching to alternative therapy options, with genotyping and/or platelet-function testing used selectively. Individualized dosing of clopidogrel might improve the outcome of ACS patients; however, there is currently no established method for personalized dose-adjustment strategy.

The newer antiplatelets, prasugrel and ticagrelor, also act via $P2Y_{12}$ receptor inhibition (Figure 2) but do so more quickly, consistently, and effectively than clopidogrel.[5,6,39,40] Prasugrel, a prodrug requiring hepatic conversion into an active metabolite, binds to and irreversibly inhibits the $P2Y_{12}$ platelet receptor.[22] Ticagrelor, a direct-acting cyclopentyl-triazolo-pyrimidine, reversibly binds to and inhibits the $P2Y_{12}$ receptor.

In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) trial (N = 13 608), prasugrel/ASA reduced CV death, nonfatal MI, or nonfatal stroke, compared with clopidogrel/ASA, by 19% over 15 months (9.9% vs 12.1%; $P < 0.001$).[6] Similarly, in the Platelet Inhibition and Patient Outcomes (PLATO) trial (N = 18 624), ticagrelor/ASA reduced CV death, MI, or stroke compared with clopidogrel/ASA by 16% at 12 months (9.8% vs 11.7%; $P < 0.001$).[5] Both trials included patients with UA, NSTEMI, and STEMI; patients recruited in TRITON-TIMI 38 were scheduled for PCI. Furthermore, ticagrelor/ASA reduced both all-cause and vascular death by 22% and 21%, respectively, compared with clopidogrel/ASA (both $P \leq 0.001$).[5] With both prasugrel/ASA and ticagrelor/ASA, thrombolysis in MI (TIMI) major bleeding (Table 1), not associated with coronary artery bypass graft (CABG), was 0.6% higher than with clopidogrel/ASA (2.4% vs 1.8%; RR: 1.32 for prasugrel/ASA, and 2.8% vs 2.2%; RR: 1.25 for ticagrelor/ASA; $P = 0.03$ for both).[5,6] Furthermore, prasugrel/ASA resulted in a significant increase in life-threatening and fatal bleeding compared with clopidogrel/ASA (1.4% vs 0.9%; RR: 1.52, $P = 0.01$; and 0.4% vs 0.1%; RR: 4.19, $P = 0.002$, respectively).[6] Ticagrelor and prasugrel are now included in guideline recommendations for long-term antiplatelet therapy after STEMI or NSTEMI/UA.[22,24,25,30] Considering practicalities of treatment, ticagrelor requires a twice-daily (bid) dosing regimen, whereas prasugrel is effective as a once-daily (od) treatment. Clopidogrel and ticagrelor therapy should be discontinued 5 and 7 days in advance of surgery, respectively. Ticagrelor is associated with an increased incidence of dyspnea and ventricular pauses vs clopidogrel.[5,22,41]

Different patient populations must also be considered. For example, increased bleeding has been demonstrated in patients taking antithrombotic therapy for cerebrovascular disease (rather than for CAD). In the Management of Atherothrombosis With Clopidogrel in High-Risk Patients (MATCH) trial (N = 7599), adding ASA to clopidogrel for 18 months doubled the absolute risk of life-threatening bleeding (2.6% vs 1.3%; $P < 0.0001$).[42] Also, additional ASA did not significantly reduce vascular events in these patients. Similarly, in Japanese patients with cerebrovascular disease (Bleeding With Antithrombotic Therapy [BAT] study, N = 4009), dual antiplatelet therapy was independently associated with a 2.6-fold increase in the annual incidence of life-threatening or major bleeding, compared with single antiplatelet therapy ($P = 0.036$).[43] Prasugrel is contraindicated in patients with ACS and prior stroke based on a significant increase vs clopidogrel in net clinical harm (defined as the rate of death from any cause, nonfatal MI, nonfatal stroke, or non–CABG-related nonfatal TIMI major bleeding; 23% vs 16%; HR: 1.54, $P = 0.04$) and TIMI major bleeding (5.0% vs 2.9%; HR: 2.46, $P = 0.06$) including intracranial hemorrhage (ICH; 2.3% vs 0.0%; $P = 0.02$) in the TRITON-TIMI 38 study.[6,44] In contrast, a predefined subanalysis of PLATO of patients with ACS and prior stroke/transient ischemic attack found that the primary

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Table 1. Bleeding Definitions[7,52,66]

Classification	Severity	Criteria
TIMI	Major	Intracranial or overt bleeding with a drop in hemoglobin of ≥5 g/dL or hematocrit drop ≥15%
	Minor	Spontaneous gross hematuria, spontaneous hematemesis, observed bleeding associated with a fall in hemoglobin ≥3 g/dL but a hematocrit drop ≤15%
	Clinically significant	Major or minor bleeding, bleeding requiring unplanned medical or surgical treatment or laboratory evaluation
	Insignificant	Bleeding not meeting the criteria above
ISTH	Major	Fatal bleeding or symptomatic bleeding in a critical area or organ (eg, intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular), or bleeding causing a hemoglobin decrease of >2 g/dL or requiring >2 U transfusion
CURE	Major, life threatening	Fatal, hemoglobin drop ≥5 g/dL, causing hypotension requiring administration of an inotropic agent or a surgical intervention, symptomatic ICH, necessitating transfusion of ≥4 U of blood
	Major, non–life threatening	Necessitating transfusion of ≥2 U of blood, intraocular hemorrhage leading to vision loss or causing other significant disability
	Minor	Other hemorrhages leading to study-drug interruption
GUSTO	Severe	Fatal or intracerebral bleeding, or bleeding resulting in substantial hemodynamic compromise requiring treatment
	Moderate	Bleeding requiring transfusion
	Mild	Bleeding not requiring transfusion or causing hemodynamic compromise

Abbreviations: CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; ICH, intracranial hemorrhage; ISTH, International Society on Thrombosis and Haemostasis; TIMI, Thrombolysis in Myocardial Infarction.

end point (composite of death from vascular causes, MI, or stroke) and total mortality remained consistent with the overall trial results, demonstrating improved efficacy and reduced mortality with ticagrelor as compared with clopidogrel in these high-risk patients.[45] Recommendations for ASA/clopidogrel treatment do not exclude patients with ACS and prior stroke.[25,30]

Medical management is a particularly important alternative to invasive therapy for frail patients (such as those age ≥75 years or with concurrent disease). TRILOGY ACS compared prasugrel with clopidogrel therapy in NSTEMI patients with UA or MI and not intended for invasive management. The primary end point of death from CV causes, nonfatal MI, or nonfatal stroke was similar between treatment groups. Results, therefore, failed to reflect the improved efficacy outcomes seen in TRITON-TIMI 38 for prasugrel vs clopidogrel among patients undergoing PCI.[46] A substudy of medically managed patients in the PLATO trial yielded similar benefits to the overall PLATO results.[47] This highlights that, in terms of benefit-risk profiles, in addition to variation between the different patient groups, there is also variability between the different $P2Y_{12}$ inhibitors.

Although combined in-hospital mortality from STEMI and NSTEMI has fallen from 10.4% to 6.3% (between 1994 and 2006), the 12-month risk of a recurrent vascular event with current standard therapy remains at approximately 10%,[5–7,48] emphasizing the need for further improvement.

New Antiplatelet Agents

Two thrombin receptor antagonists have also recently been investigated for secondary prevention after ACS. Thrombin activates platelets by binding and cleaving protease-activated receptors on the platelet surface (Figure 1).[9] The thrombin receptor antagonists atopaxar and vorapaxar, both competitive, reversible antagonists of PAR-1, block thrombin-induced platelet activation (Figure 2). It was hypothesized that thrombin receptor antagonist therapy might not result in excess bleeding because PAR-1 knockout mice have normal hemostasis.[49]

Atopaxar

In the Lessons From Antagonizing the Cellular Effect of Thrombin–Acute Coronary Syndrome (LANCELOT–ACS) phase II trial, 603 patients who were within 72 hours of UA or NSTEMI were randomized to receive 50, 100, or 200 mg of atopaxar or placebo plus standard care for 12 weeks.[50] The incidence of CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) major or minor bleeding (Table 1) was similar with atopaxar or placebo (3.1% [combined] vs 2.2%; $P = 0.63$) with no atopaxar dose-related trends ($P = 0.80$). The incidence of CV death, MI, stroke, or recurrent ischemia was also similar for atopaxar (combined) and placebo (8.0% vs 7.8%; $P = 0.93$). Similar results were obtained in a smaller phase II Japanese trial.[51]

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Vorapaxar

The Thrombin Receptor Antagonists for Clinical Event Reduction (TRA-CER) phase III trial evaluated vorapaxar 2.5 mg od or placebo plus standard care in 12 944 NSTEMI ACS patients.[52] At 2 years, the rate of the primary efficacy end point (composite of CV death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization) was similar in both groups (HR: 0.92, $P = 0.07$). Both main safety outcomes—moderate or severe Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) bleeding and clinically significant TIMI bleeding (Table 1)—were greater with vorapaxar (7.2% vs 5.2% and 20.2% vs 14.6%; both $P < 0.001$). Of note, ICH increased from 0.2% with placebo to 1.1% with vorapaxar (HR: 3.39, $P < 0.001$). Consequently, TRA-CER was stopped early after safety review.[52]

In the phase III TRA 2°P–TIMI 50 trial, 26 449 patients with atherosclerotic disease (67% with prior MI) were randomized to vorapaxar 2.5 mg daily or placebo, and standard care.[53] After 2 years, the trial was stopped in patients with a history of stroke because of excess ICH in the vorapaxar-treated patients. After 3 years, vorapaxar-treated patients with prior MI experienced a 20% reduction in the primary efficacy end point of CV death, MI, or stroke (8.1% vs 9.7%; HR: 0.80, $P < 0.001$), and a 1.3% absolute increase in GUSTO moderate or severe bleeding (3.4% vs 2.1%; HR: 1.61, $P < 0.001$). The risk of intracranial or fatal bleeding was similar for vorapaxar and placebo (0.6% vs 0.4%; HR: 1.54, $P = 0.076$ and 0.2% vs 0.1%; HR: 1.56, $P = 0.3$, respectively).

Anticoagulation Revisited

Thrombosis results from coagulation cascade activity, together with activation and aggregation of platelets (Figure 2). Increased byproduct levels from both factor Xa and thrombin activity persist for weeks to months after ACS events, suggesting a continued hypercoagulable state that could be mitigated by adding an anticoagulant to standard therapy for secondary prevention.[54]

A meta-analysis of ASA plus warfarin in approximately 25 000 patients with ACS indicated a 27% reduction in all-cause death, nonfatal MI, and nonfatal thromboembolic stroke vs ASA alone ($P < 0.00001$).[55] This benefit was offset by significantly increased major bleeding (ICH, bleeding events requiring transfusions, or ≥ 2 g/dL drop in hemoglobin) vs ASA alone (odds ratio: 2.32, $P < 0.00001$). The bleeding risk associated with warfarin when added to single or dual antiplatelet therapy, in addition to the difficulties associated with warfarin use (eg, the routine monitoring requirement and interactions with various drugs), has led to a reluctant use of warfarin in triple antithrombotic therapy. Although warfarin demonstrated the benefit of long-term oral anticoagulation across several indications, including ACS, the associated limitations and risks prompted development of newer oral anticoagulants.

A New Generation of Oral Anticoagulant

The direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors apixaban and rivaroxaban (Figure 2) have undergone recent evaluation for long-term secondary prevention in patients with ACS (Tables 2 and 3).

Dabigatran

Dabigatran underwent evaluation in 1861 patients with NSTEMI and STEMI in the phase II Randomised Dabigatran Etexilate Dose-Finding Study in Patients With Acute Coronary Syndromes Post–Index Event With Additional Risk Factors for Cardiovascular Complications Also Receiving Aspirin and Clopidogrel (RE-DEEM) trial (Table 2).[56] Patients received dabigatran 50 to 150 mg bid or placebo, plus standard care, for 6 months starting within 14 days of the index event. There were numerically lower rates of recurrent vascular events with high-dose dabigatran than with low-dose dabigatran, but this potential benefit was more than offset by a dose-dependent increase in ISTH (International Society on Thrombosis and Haemostasis) major or clinically relevant minor bleeding with increasing dabigatran dose ($P < 0.001$). There are currently no plans for a phase III trial of dabigatran in patients with ACS.

Apixaban

In the phase II Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial (Table 2), apixaban 2.5 mg bid, 10 mg od, 10 mg bid, 20 mg od or placebo, plus standard care, were evaluated in 1715 patients within 7 days of NSTEMI or STEMI for 6 months.[57] The 2 higher apixaban doses were discontinued early because of excess bleeding. Bleeding rates increased and recurrent vascular events decreased numerically with increasing apixaban dose. Given these results, an apixaban 10-mg total daily dose was selected for the phase III APPRAISE-2 trial.[58]

In APPRAISE-2 (Table 3), 7392 patients were randomized to apixaban 5 mg bid or placebo, plus standard care, after a median of 6 days, and median follow-up was 241 days.[58] There was no benefit with apixaban compared with placebo for the primary efficacy end point (CV death, MI, or ischemic stroke [HR with apixaban: 0.95, $P = 0.51$]). Apixaban treatment increased the rate of TIMI major bleeding more than 2-fold vs placebo (HR with apixaban: 2.59, $P = 0.001$). The rate of ICH increased significantly with apixaban vs placebo (0.3% vs 0.1%; HR: 4.06, $P = 0.03$). APPRAISE-2 was stopped early because of clinically significant increases in bleeding rate, especially ICH among apixaban-treated patients, with no efficacy benefit to offset this finding.

Rivaroxaban

A broad range of rivaroxaban od and bid doses was evaluated in the phase II Rivaroxaban in Combination With Aspirin Alone or With Aspirin and a Thienopyridine in Patients With Acute Coronary Syndromes (ATLAS ACS TIMI 46) trial (Table 2).[59] Patients (N = 3491) with STEMI, NSTEMI, or UA were randomized within 7 days of admission to rivaroxaban 5, 10, 15, 20 mg od (or the same total daily dose bid) or placebo, plus ASA, or ASA and a thienopyridine, for 6 months. Rivaroxaban 2.5 mg bid and 5 mg bid (combined) demonstrated promising efficacy and safety profiles in patients receiving ASA/thienopyridine, compared with placebo, for the net clinical outcome of

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Table 2. Results of Phase II Trials of Newer Anticoagulants in Patients With ACS

Trial	Treatment	Main Safety Outcome (%)	Main Efficacy End Point (%)
RE-DEEM (dabigatran)[56]: primary outcome = ISTH major bleeding or clinically relevant minor bleeding events; efficacy end point = CV death, nonfatal MI, or nonhemorrhagic stroke	Placebo	2.2	3.8
	50 mg bid	3.5	4.6
	150 mg bid	7.8	3.5
APPRAISE (apixaban)[57]: primary outcome = ISTH major or clinically relevant nonmajor bleeding; secondary end point = CV death, MI, severe recurrent ischemia, or ischemic stroke	Placebo	3.0	8.7
	2.5 mg bid	5.7	7.6
	10 mg od	7.9	6.0
ATLAS ACS TIMI 46 (rivaroxaban)[59]: primary safety outcome = clinically significant bleeding (TIMI major, TIMI minor, or requiring medical attention); primary efficacy end point = death, MI, stroke, severe recurrent ischemia requiring revascularization	Placebo	3.3	7.0
	2.5 mg bid	4.8	5.3
	20 mg od	16.0	5.2

Abbreviations: AF, atrial fibrillation; bid, twice daily; APPRAISE, Apixaban for Prevention of Acute Ischemic and Safety Events; ATLAS ACS TIMI 46, Rivaroxaban in Combination With Aspirin Alone or With Aspirin and a Thienopyridine in Patients With Acute Coronary Syndromes; CV, cardiovascular; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; od, once daily; RE-DEEM, Randomised Dabigatran Etexilate Dose-Finding Study in Patients With Acute Coronary Syndromes Post–Index Event With Additional Risk Factors for Cardiovascular Complications Also Receiving Aspirin and Clopidogrel; TIMI, Thrombolysis in Myocardial Infarction.

death, MI, stroke, or TIMI major bleeding (HR: 0.85, 95% CI: 0.47-1.54). These doses were selected for phase III based on the graded increase in bleeding with increasing rivaroxaban doses and the efficacy observed at lower doses.

In ATLAS ACS 2 TIMI 51, 15 526 patients with all ACS types were stratified according to thienopyridine use, then randomized to rivaroxaban 2.5 mg or 5 mg bid, or placebo plus low-dose ASA (Table 3).[8] Patients were randomized a median of 4.7 days after the index event and treated for a mean of 13.1 months. A thienopyridine was used in 93% of cases (>99% clopidogrel[60]). The rate of the primary efficacy composite of CV death, MI, or stroke at 2 years was reduced by 16% with rivaroxaban vs placebo ($P = 0.008$). Unlike APPRAISE-2, the primary efficacy end point included hemorrhagic stroke and stroke of uncertain cause, as well as ischemic stroke. Compared with placebo, rivaroxaban significantly increased the rate of TIMI major bleeding not related to CABG (2.1% vs 0.6%; $P < 0.001$), and ICH (0.6% vs 0.2%; $P = 0.009$). However, there was no significant increase in fatal bleeding (0.3% vs 0.2%; $P = 0.66$) or fatal ICH.[8,60] The 2-year rates of CV and all-cause death with rivaroxaban 2.5 mg bid were reduced by 34% and 32%, respectively, vs placebo (2.7% vs 4.1%; $P = 0.002$, and 2.9% vs 4.5%; $P = 0.002$). The 2.5-mg dose resulted in a lower rate of TIMI major bleeding not related to CABG (1.8% vs 2.4%; $P = 0.12$) and fatal bleeding (0.1% vs 0.4%; $P = 0.04$) compared with the 5-mg dose. Although not part of the formal statistical hierarchy, rivaroxaban treatment (combined) resulted in a significant reduction (31%) in stent thrombosis compared with placebo (Table 3). Overall, a dual-pathway strategy with rivaroxaban plus antiplatelet therapy significantly reduced the composite rate of CV death, MI, or stroke without increasing the risk of fatal bleeding or fatal ICH.

Apixaban and rivaroxaban are both factor Xa inhibitors; therefore, the difference in results between APPRAISE-2 and ATLAS ACS 2 TIMI 51 may be due to the differences in trial design or dosing. APPRAISE-2 included 10% of patients with a history of cerebrovascular disease; in ATLAS ACS 2 TIMI 51, patients with a history of stroke were excluded from the stratum receiving ASA/thienopyridine, and the treatment benefit of rivaroxaban compared with placebo was reversed in the 3% of patients with a history of stroke (HR: 1.57, 95% CI: 0.75-3.31, P value for interaction = 0.10).[8] In the Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients With Atherosclerosis (TRA 2°P–TIMI 50), the risk of ICH with vorapaxar was higher in patients with a history of stroke.[53] This is consistent with the excess bleeding observed in the MATCH, BAT, and TRITON TIMI 38 studies with dual antiplatelet therapy.[6,42,43]

Importantly, the dose of rivaroxaban used in ATLAS ACS 2 TIMI 51 was lower than that used in trials of stroke prevention in atrial fibrillation (AF), whereas APPRAISE-2 used the same dose of apixaban in both ACS and AF trials.[8,58,61,62] This difference arises from the phase II dose-finding strategy: Most apixaban doses investigated in APPRAISE were higher than the apixaban AF dose, whereas the rivaroxaban dose used to treat AF was the highest dose included in ATLAS ACS TIMI 46.[8,57–59] Low-dose anticoagulation might be more appropriate in patients with ACS when patients were already treated by standard antiplatelet therapy. However, in RE-DEEM, lower dabigatran doses demonstrated no efficacy benefit, although this study was not powered for efficacy.[56] These findings support the concept that low-intensity factor Xa blockade with the resulting impact on thrombin generation may be effective in the prevention of recurrent ACS, rather than direct inhibition of existing thrombin.

Now that use of low-dose rivaroxaban for secondary prevention of ACS is approved in Europe,[63] the question of how to treat patients with ACS who also develop AF, or already have AF, arises. As mentioned above, the approved dose for stroke prevention in patients with AF is 20 mg od, rather than 2.5 mg bid.[63] There is no evidence that low-dose rivaroxaban combined with dual antiplatelet therapy would reduce the risk of stroke in patients with AF and ACS, and warfarin therapy may be

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Table 3. Results of Phase III Trials of Newer Anticoagulants in Patients With ACS

Trial	Treatment	CV Death, MI, Stroke[a]	Stent Thrombosis	MI	CV Death	All-Cause Death	TIMI Major Bleeding	ICH	Fatal Bleeding	Fatal ICH
ATLAS ACS 2 TIMI 51[8,60] (rivaroxaban): 2-year rate; HR (95% CI); *P* value[b] vs placebo	Placebo	10.7	2.9	6.6	4.1	4.5	0.6[c]	0.2	0.2	0.1[d]
	2.5 mg bid	9.1; 0.84 (0.72-0.97); *P* = 0.007	2.2; 0.65 (0.45-0.94); *P* = 0.02	6.1; 0.90 (0.75-1.09); *P* = 0.09	2.7; 0.66 (0.51-0.86); *P* = 0.005	2.9; 0.68 (0.53-0.87); *P* = 0.004	1.8[c]; 3.46 (2.08-5.77); *P* < 0.001	0.4; 2.83 (1.02-7.86); *P* = 0.04	0.1; 0.67 (0.24-1.89); *P* = 0.45	0.1[d]
	5.0 mg bid	8.8; 0.85 (0.73-0.98); *P* = 0.01	2.3; 0.73 (0.51-1.04); *P* = 0.04	4.9; 0.79 (0.65-0.97); *P* = 0.008	4.0; 0.94 (0.75-1.20); *P* = 0.57	4.4; 0.95 (0.76-1.19); *P* = 0.89	2.4[c]; 4.47 (2.71-7.36); *P* < 0.001	0.7; 3.74 (1.39-10.07); *P* = 0.005	0.4; 1.72 (0.75-3.92); *P* = 0.20	0.2[d]
	Combined	8.9; 0.84 (0.74-0.96); *P* = 0.008	2.3; 0.69 (0.51-0.93); *P* = 0.02	5.5; 0.85 (0.72-1.00); *P* = 0.01	3.3; 0.80 (0.65-0.99); *P* = 0.05	3.7; 0.81 (0.66-1.00); *P* = 0.08	2.1[c]; 3.96 (2.46-6.38); *P* < 0.001	0.6; 3.28 (1.28-8.42); *P* = 0.009	0.3; 1.19 (0.54-2.59); *P* = 0.66	0.1[d]
APPRAISE-2[58] (apixaban): 1-year rate; HR (95% CI); *P* value vs placebo	Placebo	14.0[e]	2.2	9.2	5.0	6.6	0.9	0.2	NA	NA
	5.0 mg bid	13.2[e]; 0.95 (0.80-1.11); *P* = 0.51	1.6; 0.73 (0.47-1.12); *P* = 0.15	8.6; 0.93 (0.76-1.14); *P* = 0.51	4.8; 0.96 (0.73-1.25); *P* = 0.76	7.1; 1.08 (0.86-1.35); *P* = 0.51	2.4; 2.59 (1.50-4.46); *P* = 0.001	0.6; 4.06 (1.15-14.38); *P* = 0.03	0.3	NA

Abbreviations: ACS, acute coronary syndrome; bid, twice daily; APPRAISE, Apixaban for Prevention of Acute Ischemic and Safety Events; ATLAS ACS TIMI 46, Rivaroxaban in Combination With Aspirin Alone or With Aspirin and a Thienopyridine in Patients With Acute Coronary Syndromes; CABG, coronary artery bypass graft; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ICH, intracranial hemorrhage; ITT, intention to treat; MI, myocardial infarction; NA, not available; TIMI, Thrombolysis in Myocardial Infarction.
[a]Primary efficacy end point. [b]*P* values for ITT analysis (modified ITT for safety). [c]Non–CABG-related TIMI major bleeding. [d]Total event rates at end of study rather than 2-year Kaplan-Meier rates. [e]Ischemic stroke only.

preferred over any novel oral anticoagulant in this setting.[64] There is currently considerable variation in adoption of triple antithrombotic therapy in patients with coexisting AF and ACS.[65] Future studies with rivaroxaban, such as A Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI; http://www.clinicaltrials.gov: NCT01830543), may provide insight into how to treat patients with AF who develop ACS, or vice versa, and may therefore lead to rivaroxaban being an important option to treat such patients in the future. As well as rivaroxaban 15 mg od with clopidogrel alone, this study will evaluate initial triple therapy with warfarin or rivaroxaban 2.5 mg bid, followed by warfarin or rivaroxaban 15 mg od with ASA alone, in patients with AF who undergo coronary stenting.

Summary

Even with newer antiplatelet agents, patients with ACS still face a 12-month risk of recurrent vascular events of approximately 10%.[5–7] This defines a clear need for improved secondary prevention. In TRA 2°P–TIMI 50, addition of vorapaxar to standard antiplatelet therapy significantly reduced vascular events vs placebo in stable patients with prior MI,[53] suggesting further reductions in secondary vascular events after ACS are possible. In ATLAS ACS 2 TIMI 51, in addition to reductions in vascular events, treatment with low-dose rivaroxaban also reduced mortality compared with placebo.[8] Furthermore, although rivaroxaban treatment increased the rate of TIMI major bleeding not related to CABG surgery, fatal bleeding and fatal ICH were not increased compared with placebo.

Treatment with rivaroxaban in addition to standard antiplatelet therapy targets both platelet activation and coagulation, the pathways of which are highly interdependent (Figures 1 and 2). Although RE-DEEM was not powered for efficacy, comparison of ATLAS ACS 2 TIMI 51, APPRAISE-2, and RE-DEEM combining antiplatelets and anticoagulants suggests that low-dose factor Xa inhibition is required to produce the favorable efficacy benefit without increasing serious bleeding events. The numerous interactions of the regulatory pathways for both activation and inhibition of thrombosis may explain the superior efficacy of lower-dose anticoagulation, although it is unclear how modulation of factor Xa activity might achieve these differential effects.

The introduction of newer oral anticoagulants and antiplatelet agents provides an opportunity to improve secondary prevention after ACS and further reduce vascular events after ACS.

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