Low-Dose Anticoagulation for Secondary Prevention in Acute Coronary Syndrome

Freek W.A. Verheugt, MD*

After acute coronary syndrome (ACS), long-term dual antiplatelet therapy with acetylsalicylic acid and a P2Y₁₂ platelet receptor antagonist is the standard of care for secondary prevention. Despite the introduction of more potent P2Y₁₂ receptor antagonists, the risk of a recurrent vascular event within 12 months remains at approximately 10%, indicating a need for improved secondary prevention strategies. A recent phase III trial found that addition of a third antiplatelet agent, vorapaxar, in patients with atherosclerosis might benefit those who have previously experienced a myocardial infarction, although a trial in patients with ACS found this strategy led to increased bleeding without significant efficacy improvement. Previously, data from patients with ACS given vitamin K antagonists in addition to acetylsalicylic acid demonstrated significant reductions in vascular events, but this was associated with an unacceptable bleeding risk. As expected, phase II trials of newer oral anticoagulants in addition to dual antiplatelet therapy also found increased bleeding risk, with only the direct factor Xa inhibitors apixaban and rivaroxaban continuing to phase III. The phase III trial of full-dose apixaban was stopped early for safety concerns, because the major bleeding rates were significantly increased with minimal improvement in efficacy. However, the phase III trial of low-dose rivaroxaban demonstrated a significantly reduced incidence of recurrent vascular events without an increased risk of fatal bleeding. In conclusion, these trials underline the potential importance of optimal dose selection in phase III studies and suggest that the long-term use of low-dose anticoagulation, together with dual antiplatelet therapy, might have a role in secondary prevention after ACS. © 2013 Elsevier Inc. All rights reserved. (Am J Cardiol 2013;111:618–626)

The past 15 years have seen substantial advances in the short- and long-term outcomes for patients after an acute coronary syndrome (ACS) event. Improvements in therapy and adherence to guidelines have resulted in a decrease in inhospital mortality from 10.4% in 1994 to 6.3% in 2006. Approximately 17% of patients surviving an ACS event would experience recurrent events without secondary prophylaxis; however, even in recent randomized trials with newer antithrombotic agents, an ~10% risk of recurrence within 12 months remains (Table 1). The overall economic effect of ACS is high. In the United States, $150 billion is spent annually, with rehospitalization accounting for ~60% of the costs. The high rates of recurrence highlight the need for more effective secondary prevention strategies. The present review discusses recently completed clinical trials in long-term antithrombotic treatment of secondary prevention in patients with ACS and the potential implications for patient care.

Long-Term Secondary Prevention: Antiplatelet Therapy for ACS

A meta-analysis of 12 trials demonstrated the efficacy of secondary prevention with a single antiplatelet agent—mainly acetylsalicylic acid (ASA)—in ~20,000 patients with a history of myocardial infarction (MI). Patients who received a single antiplatelet agent showed a 3.5% absolute reduction in the risk of vascular events (MI, stroke, or vascular death) compared to the control group (adjusted for unequal randomization) within ~27 months’ follow-up (p <0.0001). This represents 36 fewer serious events per 1,000 patients within 2 years, highlighting the value of long-term discharge antiplatelet therapy. However, 13.5% of patients receiving antiplatelet therapy still experienced an event during that period.

Dual antiplatelet therapy: Several antiplatelet agents with different modes of action are available (Figure 1). ASA inhibits platelet activation by irreversibly acetylating cyclooxygenase-1, thereby inhibiting synthesis of the platelet activator thromboxane A₂. Clopidogrel, a thienopyridine, irreversibly inhibits the action of another platelet activator, adenosine diphosphate, by antagonizing its P2Y₁₂ receptor. The newer antiplatelet agent, prasugrel, also a thienopyridine, irreversibly inhibits the P2Y₁₂ receptor and, ticagrelor, a nonthienopyridine, is a reversible P2Y₁₂ receptor antagonist. Dual antiplatelet therapy (DAPT) with ASA/clopidogrel, and more recently ASA/prasugrel or ASA/ticagrelor, simultaneously inhibits these 2 routes to platelet activation, producing an additive effect to improve thromboprophylaxis (Table 1).

Clopidogrel: The additive benefit of DAPT was first demonstrated in 12,562 patients with non-ST-segment elevation MI (STEMI) in the 2001 Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial (Table 1). DAPT for a mean of 9 months resulted in a 20% relative
Table 1
Phase III antithrombotic trials of secondary prevention in patients with acute coronary syndrome

<table>
<thead>
<tr>
<th>Study Drug; Trial</th>
<th>Patient Characteristics</th>
<th>Primary End Point</th>
<th>CV Death</th>
<th>All-cause Death</th>
<th>Stent Thrombosis</th>
<th>Non–CABG-related TIMI Major Bleeding</th>
<th>Fatal Bleeding</th>
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<tr>
<td>Clopidogrel (irreversible P2Y₁₂ inhibitor); CURE study¹: 12,562 patients with clopidogrel 75 mg/day vs placebo for mean 9 months*</td>
<td>Median age 64 y; female 39%; STEMI 0%; NSTEMI 25%; UA 75%; diabetes 23%; stroke 4%; previous MI 32%</td>
<td>CV death, nonfatal MI, stroke at 1 y: clopidogrel 9.3%; placebo 11.4%; RRR 20% (p &lt;0.001)</td>
<td>Rate at 1 y: clopidogrel 5.1%; placebo 5.5%; RRR 7%</td>
<td>Rate at 1 y: clopidogrel 5.8%; placebo 6.2%; RRR 1%</td>
<td>NR</td>
<td>CURE, major bleeding¹ at 1 y: clopidogrel 3.7%; placebo 2.7%; ARI 1.0% (p = 0.001)</td>
<td>Rate at 1 y: clopidogrel 0.2%; placebo 0.2%; ARI 0.0%</td>
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<tr>
<td>Prasugrel (irreversible P2Y₁₂ inhibitor); TRITON-TIMI 38 study¹: 13,608 patients referred for percutaneous coronary intervention with prasugrel 10 mg/day vs 75 mg/day clopidogrel for median 15 months*</td>
<td>Median age 61 y; female 26%; STEMI 26%; NSTEMI and UA 74%; diabetes 23%; stroke/TIA 4%; previous MI 18%</td>
<td>CV death, nonfatal MI, nonfatal stroke rate at 15 months: prasugrel 2.1%; clopidogrel 2.4%; RRR 11% (p = 0.31)</td>
<td>Rate at 15 months: prasugrel 1.1%; clopidogrel 1.8%; RRR 52% (p &lt;0.001)</td>
<td>Rate at 15 months: prasugrel 2.4%; clopidogrel 2.4%; ARI 0.6% (p = 0.03)</td>
<td>Rate at 15 months: prasugrel 0.4%; clopidogrel 0.1%; ARI 0.3% (p = 0.002)</td>
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<tr>
<td>Ticagrelor (reversible P2Y₁₂ inhibitor); PLATO study¹: 18,624 patients with ticagrelor 90 mg twice daily vs clopidogrel 75 mg/day for median 15 months*</td>
<td>Median age 62 y; female 28%; STEMI 38%; NSTEMI 43%; UA 17%; diabetes 25%; nonhemorrhagic stroke 4%; previous MI 21%</td>
<td>Vascular death, MI, stroke at 1 y: ticagrelor 4.0%; clopidogrel 5.1%; RRR 21% (p = 0.001)</td>
<td>Rate at 1 y: ticagrelor 4.5%; clopidogrel 5.9%; RRR 22% (p &lt;0.001)</td>
<td>Rate at 1 y: ticagrelor 2.8%; clopidogrel 3.8%; ARI 0.6% (p = 0.03)</td>
<td>Rate at 1 y: ticagrelor 0.3%; clopidogrel 0.3%; ARI 0% (p = 0.66)</td>
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<td>Vorapaxar (PAR-1 antagonist); TRACER study¹¹: 12,944 patients with vorapaxar 2.5 mg/day vs placebo for median 12 months¹⁰</td>
<td>Median age 64 y; female 28%; NSTEMI and UA 94%; STEMI (transient) 6%; diabetes 31%; stroke 4.3%; previous MI 29%; thienopyridine 87%</td>
<td>CV death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization rate at 2 y: vorapaxar 18.5%; placebo 19.9%; RRR 8% (p = 0.07)</td>
<td>Rate at 2 y: vorapaxar 3.8%; placebo 3.8%; RRR 0% (p = 0.96)</td>
<td>Rate at 2 y: vorapaxar 6.5%; placebo 6.1%; RRI 5% (p = 0.52)</td>
<td>Rate: RRI 12% (p = 0.54)¹¹</td>
<td>Rate at 2 y: vorapaxar 2.7%; placebo 1.3%; ARI 1.4% (p &lt;0.001)</td>
<td>Rate at 2 y: vorapaxar 0.4%; placebo 0.2%; ARI 0.2% (p = 0.15)</td>
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<td><strong>Apixaban (direct factor Xa inhibitor); APPRAISE-2 study</strong>&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Median age 67 y; female 32%; STEMI 40%; NSTEMI 42%; UA 18%; diabetes 48%; cerebrovascular disease 10%; previous MI 26%; thienopyridine 81%</td>
<td>CV death, MI, ischemic stroke rate at 1 y: apixaban 4.8%; placebo 5.0%; RRI 4% (p = 0.76)</td>
<td>Rate at 1 y: apixaban 7.1%; placebo 6.6%; RRI 8% (p = 0.51)</td>
<td>Rate at 1 y: apixaban 1.6%; placebo 2.2%; RRR 27% (p = 0.15)</td>
<td>TIMI major bleeding rate&lt;sup&gt;6&lt;/sup&gt; at 1 y: apixaban 2.4%; placebo 0.9%; ARI 1.5% (p = 0.001)</td>
<td>Rate at 1 y: apixaban 0.3%; placebo 0%; ARI 0.3%</td>
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<td><strong>Rivaroxaban (direct factor Xa inhibitor); ATLAS ACS 2 TIMI 51 trial</strong>&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Mean age 61.7 y; female 25%; STEMI 50%; NSTEMI 26%; UA 24%; diabetes 32%; previous stroke/TIA 3%; previous MI 27%; thienopyridine 93%</td>
<td>CV death, MI, stroke rate at 2 y: rivaroxaban 8.9%; placebo 10.7%; RRR 16% (p = 0.002)</td>
<td>Rate at 2 y: rivaroxaban, 2.5 mg twice daily 2.7%; 5 mg twice daily 4.0%; placebo 4.1%; RRR, rivaroxaban 2.5 mg twice daily, 2.9%; 5 mg twice daily, 4.4%; placebo 4.5%; RRR rivaroxaban, 2.5 mg twice daily 32% (p = 0.005), 5.0 mg twice daily 6% (p = 0.57)</td>
<td>Rate at 2 y: rivaroxaban, 2.5 mg twice daily, 2.3%; placebo 2.9%; RRR 31% (p = 0.008)</td>
<td>Rate at 2 y: rivaroxaban 2.1%; placebo 0.6%; ARI 1.5% (p &lt;0.001)</td>
<td>Rate at 2 y: rivaroxaban 0.3%; placebo 0.2%; ARI 0.1% (p = 0.66)</td>
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ARI = absolute risk increase with study drug; CABG = coronary artery bypass grafting; CV = cardiovascular; NSTEMI = non–ST-segment elevation myocardial infarction; PAR-1 = protease-activated receptor 1; RRI = relative risk increase; RRR = relative risk reduction; TIA = transient ischemic attack; TIMI = Thrombolysis In Myocardial Infarction; UA = unstable angina.

<sup>1</sup> Patients also received ASA.

<sup>2</sup> Patients also received standard care of ASA or ASA plus thienopyridine according to guidelines; p values for ATLAS ACS 2 TIMI 51 were for intention-to-treat analysis (modified intention-to-treat for safety).

<sup>3</sup> Data for non—CABG-related TIMI major bleeding not available for CURE and APPRAISE-2.

<sup>4</sup> Calculated as sum of deaths from CV causes and deaths from non-CV causes.
factor Xa in antithrombin-dependent manner. 

Factor Xa part of prothrombinase complex, and fondaparinux targets apixaban, darexaban, and rivaroxaban directly inhibit both free factor Xa and the factor Xa part of prothrombinase complex, and fondaparinux targets factor Xa in antithrombin-dependent manner. 

Thrombin amplifies its own production and activates platelets and generates fibrin. The tissue factor (TF)/factor VIIa (FVIIa) complex initiates thrombin production by activating small amounts of factor Xa (FXa) and factor Xa (FXa), generating a small amount of thrombin from prothrombin to promote formation of the tenase and prothrombinase complexes. This leads to a burst of thrombin production at the platelet surface. Thrombin generates fibrinogen from fibrinogen and further activates platelets by cleavage of protease-activated receptors (PARs). Platelet activators adenosine diphosphate (ADP) and thromboxane (TX) also shown. Antithrombotic drug targets indicated by red blocking arrows. Note, apixaban, darezaban, and rivaroxaban directly inhibit both free factor Xa and factor Xa part of prothrombinase complex, and fondaparinux targets factor Xa in antithrombin-dependent manner. 

Thrombin initiates thrombin production by activating small amounts of factor Xa and factor Xa part of prothrombinase complex, and fondaparinux targets factor Xa in antithrombin-dependent manner. 

Thrombin generation initiates the clotting cascade, which leads to the formation of a fibrin clot. The clotting cascade involves a series of reactions that result in the conversion of prothrombin to thrombin, which is a key enzyme in the clotting process. 

**Antiplatelet agents**

Platelet inhibitors are widely used in the management of patients with cardiovascular disease. They work by blocking or slowing the activity of platelets, which are crucial for blood clotting. Common antiplatelet agents include aspirin, clopidogrel, and prasugrel. These agents are often used in combination with anticoagulants to prevent blood clots from forming and reducing the risk of heart attacks and strokes. 

**DAPT**

Dual antiplatelet therapy (DAPT) is a common treatment regimen used in patients with acute coronary syndrome (ACS). DAPT involves the concurrent use of an oral antiplatelet agent (such as aspirin or clopidogrel) and a parenteral antiplatelet agent (such as unfractionated heparin or low-molecular-weight heparin). DAPT is generally continued for at least 12 months after an ACS event. 

**Clopidogrel**

Clopidogrel is a thienopyridine antiplatelet agent that works by irreversibly inhibiting the P2Y12 receptor on platelets. It is often used in combination with aspirin as DAPT. 

**Prasugrel**

Prasugrel is a thienopyridine antiplatelet agent that works by irreversibly inhibiting the P2Y12 receptor on platelets. It is more potent than clopidogrel and is often used in combination with aspirin as DAPT. 

**Ticagrelor**

Ticagrelor is a reversible ADP receptor antagonist that works by blocking the P2Y12 receptor on platelets. It is more potent than clopidogrel and is often used in combination with aspirin as DAPT. 

**Vorapaxar**

Vorapaxar is a thienopyridine antiplatelet agent that works by irreversibly inhibiting the P2Y12 receptor on platelets. It is more potent than clopidogrel and is often used in combination with aspirin as DAPT. 

**DAPT Summary**

With the results of these cited trials, DAPT has become the standard of care for patients after an ACS event. The guidelines recommend DAPT with ASA plus clopidogrel, prasugrel, or ticagrelor for 12 months (depending on the reperfusion strategy) after either STEMI or non-STEMI ACS. However, even with the newer antiplatelet agents, a 10% 12-month risk of a recurrent vascular event remains, and improvements in efficacy have been associated with significant increases in major bleeding. Therefore, a substantial unmet need in regard to secondary prevention still exists.

**Triple antiplatelet therapy with vorapaxar**

Thrombin receptor antagonists are an emerging class of antiplatelet agents designed to inhibit thrombin-mediated platelet activation and include vorapaxar. The phase III trial, Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients with Acute Coronary Syndrome (TRACER), of vorapaxar in patients started in the acute phase and was continued in the secondary prevention setting. Compared to clopidogrel/ASA, prasugrel/ASA reduced the risk of vascular events (cardiovascular death, nonfatal MI, or nonfatal stroke) by 19% at 15 months (p < 0.001). A significant 0.6% absolute increase was seen in the risk of noncoronary artery bypass graft-related Thrombolysis In Myocardial Infarction major bleeding compared with clopidogrel/ASA (2.4% vs 1.8%; hazard ratio [HR] 1.32; p = 0.03). A post hoc analysis found that patients with previous stroke or transient ischemic attack experienced a net clinical harm with prasugrel/ASA treatment compared to clopidogrel (defined as the rate of all-cause death, nonfatal MI or stroke, and noncoronary artery bypass graft-related major bleeding; HR = 1.5; p = 0.04).

**Ticagrelor**

The Platelet Inhibition and Patients Outcomes (PLATO) trial of ticagrelor enrolled 18,624 patients with ACS, with or without ST-segment elevation (Table 1). In the acute phase (within a median of 5 hours of hospitalization), the patients were randomized to receive initial loading doses of 180 mg ticagrelor or 300 mg clopidogrel plus ASA, followed by daily doses of 90 mg ticagrelor or 75 mg clopidogrel plus ASA. Compared to clopidogrel/ASA, ticagrelor/ASA significantly reduced the risk of recurrent vascular events (vascular death, MI, or stroke) by 16% within 12 months (p < 0.001). Moreover, significant reductions in vascular (21%) and all-cause death (22%) were shown with ticagrelor/ASA compared to clopidogrel/ASA (both p ≤ 0.001). Treatment with ticagrelor/ASA did not increase the risk of the primary safety outcome of major bleeding (leading to clinically significant disability, associated with a hemoglobin decrease of 3 to 5 g/dl or requiring transfusion of 2 to 3 U of red blood cells) compared to clopidogrel/ASA (HR 1.04; p = 0.43). However, ticagrelor/ASA increased the absolute risk of noncoronary artery bypass graft-related Thrombolysis In Myocardial Infarction major bleeding by 0.6% (2.8% vs 2.2%; HR 1.25; p = 0.03) and fatal intracranial hemorrhage by 0.09% compared to clopidogrel/ASA (0.1% vs 0.01%; p = 0.02). Ticagrelor has recently been approved for clinical use for the prevention of thrombotic events in ACS in the European Union, Canada, and the United States.
with non-STEMI was stopped early after a safety review. The patients (n = 12,944) were randomized a median of 21 hours after hospitalization, in the acute care setting, to receive vorapaxar at a loading dose of 40 mg followed by 2.5 mg/day or placebo for a median of 386 days against a background of DAPT (97% ASA, 87% thienopyridine). Treatment with vorapaxar did not reduce the 2-year rate of the primary efficacy end point composite of cardiovascular death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization (HR 0.92; p = 0.07). Compared to placebo, vorapaxar also resulted in a 2% absolute increase in the 2-year rate of moderate or severe Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) bleeding (1 of 2 main safety outcomes; HR 1.35; p < 0.001).

Vorapaxar has also been evaluated in 26,449 patients with MI or ischemic stroke within the previous 2 weeks to 12 months or with peripheral arterial disease in the Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients with Atherosclerosis (TRA 2P-TIMI 50) trial. Patients were randomized to vorapaxar 2.5 mg/day or placebo (stratified by qualifying diagnosis and planned thienopyridine use), with a median follow-up of 30 months. After 2 years, patients with previous ischemic stroke were excluded, because of excess intracranial hemorrhage with vorapaxar. The primary efficacy end point was a composite of cardiovascular death, MI, or stroke; the principal safety outcome was GUSTO moderate or severe bleeding. Patients with previous MI (67%), of whom 98% received ASA and 78% a thienopyridine at baseline, demonstrated a 20% relative reduction after 3 years in the primary efficacy end point with vorapaxar compared to placebo (8.1% vs 9.7%; HR 0.80; p < 0.001). The 3-year rate of the principal safety outcome was greater in patients treated with vorapaxar than in those receiving placebo (3.4% vs 2.1%; HR 1.61; p < 0.001) but without a significant increase in intracranial bleeding (0.6% vs 0.4%; HR 1.54; p = 0.076).

**Anticoagulation in secondary prevention:** Parenteral anticoagulants (Figure 1), including unfractionated heparin, low-molecular-weight heparins, fondaparinux, and bivalirudin, are effective in the acute phase of ACS, depending on the reperfusion strategy used in STEMI and whether an invasive or conservative strategy is adopted for unstable angina and non-STEMI. Despite the efficacy of parenteral anticoagulants in the acute stages, the long-term use of parenteral agents is not practical. Oral anticoagulation represents a potential long-term solution.

**Oral vitamin K antagonists:** Warfarin is a vitamin K antagonist with a broad inhibitory action targeting several proteins in the coagulation cascade (Figure 1). Vitamin K antagonists have a narrow therapeutic window, and their effects are unpredictable because of the variable individual dose response and many food—drug and drug—drug interactions. A meta-analysis (n = 25,307) of the addition of warfarin to ASA after ACS for 3 months to 5 years showed a 27% relative risk reduction in vascular events compared to ASA alone (p < 0.001). This efficacy benefit was offset by a more than twofold increase in the relative risk of major bleeding with combination therapy compared to ASA alone (p < 0.00001). A Danish registry investigated real-world use of antithrombotic agents (ASA, clopidogrel, and vitamin K antagonists) at discharge in 40,812 patients admitted to hospital with first-time MI within a 5-year period. Nonfatal and fatal bleeding events were greater in patients receiving clopidogrel plus a vitamin K antagonist (12.3%/y) or triple therapy (12.0%/y) than in patients receiving ASA and clopidogrel (3.7%/y) or ASA monotherapy (2.6%/y).

However, the risk of all-cause mortality did not increase compared to ASA monotherapy across all subgroups determined by whether patients received 1, 2, or all 3 agents. No randomized trials of vitamin K antagonists have been performed, in addition to standard DAPT versus DAPT alone in patients with ACS. As a result of the limitations and risks associated with vitamin K antagonists, their use in patients with ACS is only recommended with caution based on clinical judgment for patients who have a clear indication, such as atrial fibrillation.

**Newer oral anticoagulants for secondary prevention:** Newer oral anticoagulants, which directly target specific molecules in the coagulation cascade (Figure 1), are in clinical development. There are 2 classes of newer oral anticoagulants: direct thrombin inhibitors and direct factor Xa inhibitors. Unlike warfarin, these agents have predictable pharmacokinetic and pharmacodynamic profiles with few drug—drug and food—drug interactions and can be given at fixed doses without the need for routine coagulation monitoring.

**Oral direct thrombin inhibitors:** Ximelagatran: In the Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Recent Myocardial Damage (ESTEEM) trial for the secondary prevention of ACS, a 24% relative reduction occurred with ximelagatran/ASA treatment for 6 months in the risk of the primary composite end point of death, nonfatal MI, and severe recurrent ischemia versus ASA alone (p = 0.036). Major bleeding increased from 0.9% with ASA to 1.8% with ximelagatran/ASA (HR 1.97; 95% confidence interval [CI] 0.80 to 4.84). Although ximelagatran has been withdrawn, the ESTEEM trial demonstrated the potential for other oral anticoagulants to be used in secondary prophylaxis.

**Dabigatran:** The phase II dose-finding Dose Finding Study for Dabigatran Etxilate in Patients with Acute Coronary Syndrome (RE-DEEM) study assessed the safety and efficacy of 4 randomized dabigatran doses ([Boehringer Ingelheim, Ingelheim am Rhein, Germany]; 50, 75, 110, and 150 mg twice daily) or placebo combined with standard DAPT for the secondary prevention of ACS. Patients with STEMI and non-STEMI (n = 1,861) were randomized a mean of 7.5 days after the index event and followed up for 6 months. The primary outcome was International Society of Thrombosis and Haemostasis major bleeding and clinically relevant minor bleeding. A dose-dependent increase was seen in the primary outcome with the addition of dabigatran to DAPT (3.5%, 4.3%, 7.9%, and 7.8% for increasing dabigatran doses and 2.2% for placebo; p < 0.001 for linear trend). No difference was found between the placebo and dabigatran groups for the composite of cardiovascular death, nonfatal MI, or stroke. This composite end point occurred in
3.8% of the placebo group and 4.6%, 4.9%, 3.0%, and 3.5% for the 50, 75, 110, and 150 mg twice daily dabigatran doses, respectively. As yet, no additional information is available from a phase III trial in ACS.

**Oral direct factor Xa inhibitors: Darexaban:** Darexaban (YM150, Astellas Pharma, Northbrook, Illinois) was recently evaluated for the secondary prevention of ACS in the phase II Study Evaluating Safety, Tolerability and Efficacy of YM150 in Subjects With Acute Coronary Syndromes (RUBY-1) trial of 1,279 patients with STEMI/non-STEMI within 7 days.\(^ {27} \) In that dose-ranging trial, patients received darexaban 5 mg twice daily, 10 mg/day, 15 mg twice daily, 30 mg/day, 30 mg twice daily, or 60 mg/day or placebo, in addition to standard antiplatelet therapy for 6 months. The primary outcome was modified International Society of Thrombosis and Haemostasis major and nonmajor clinically relevant bleeding. A dose-dependent increase was found in the primary outcome with an increasing darexaban dose (p = 0.009 for trend), with a rate of 6.2%, 6.5%, and 9.3% for the 10-, 30-, and 60-mg total daily dose, respectively, compared to 3.1% in the placebo group. Darexaban did not affect the secondary end point of all-cause mortality, nonfatal MI, nonfatal stroke, and severe recurrent ischemia. Although the secondary end point rates were numerically increased with the greater darexaban doses (7.3% to 9.3%), the rates were actually numerically decreased with the lower 10-mg/day darexaban doses (4.3% for the once and twice daily dosing) compared to placebo (5.2%). Darexaban development has been discontinued.\(^ {28} \)

**Apixaban:** Apixaban (Bristol-Myers Squibb, New York, New York) was evaluated in the phase II dose-ranging Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) study, which assessed 4 doses of apixaban (2.5 mg twice daily, 10 mg/day, 10 mg twice daily, and 20 mg/day) or placebo, in addition to standard antiplatelet therapy for the secondary prevention of ACS.\(^ {29} \) Patients (n = 1,715) with non-STEMI or STEMI within 7 days were treated for 26 weeks. The 2 greater apixaban doses were discontinued because of excess bleeding. A dose-trend was found for greater rates of International Society of Thrombosis and Haemostasis major and nonmajor bleeding (primary outcome), which occurred in 5.7% and 7.9% of patients receiving apixaban 2.5 mg twice daily and 10 mg/day, respectively, compared to 3.0% receiving placebo. Also, a promising trend was found for a reduction of the incidence of cardiovascular death, MI, severe recurrent ischemia, or ischemic stroke from 8.7% in the placebo group to 7.6% and 6.0% in patients receiving apixaban 2.5 mg twice daily and 10 mg/day, respectively (p = 0.21 and p = 0.07, respectively).

The subsequent phase III APPRAISE-2 trial evaluated the addition of apixaban 5 mg twice daily or placebo to standard therapy for the secondary prevention of ACS in 7,392 patients (Table 1).\(^ {30} \) The patients were randomized a median of 6 days after the index event and received treatment for a median of 175 days (apixaban) or 185 days (placebo). No significant difference was found in the primary efficacy end point rate (cardiovascular death, MI, or ischemic stroke) for apixaban versus placebo (13.2%/y vs 14.0%/y; HR 0.95; p = 0.51). Furthermore, the absolute rate of Thrombolysis In Myocardial Infarction major bleeding rate was 0.8% greater in the apixaban arm compared to the placebo arm (HR 2.59; p = 0.001). This increased bleeding in the apixaban arm, which was not offset by any reduction in ischemic events, led to early discontinuation of the trial by the Data Monitoring Committee.

**Rivaroxaban:** The phase II Anti-Xa Therapy to Lower cardiovascular events in Addition to standard therapy in Subjects with Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction (ATLAS ACS TIMI) 46 dose-escalation trial for the secondary prevention of ACS evaluated the addition of rivaroxaban (Bayer HealthCare Pharmaceuticals, Berlin, Germany and Janssen Pharmaceuticals, Titusville, New Jersey) to ASA (stratum 1) or ASA plus thienopyridine (stratum 2) compared to placebo in patients with recent ACS (within 7 days).\(^ {31} \) That trial included 3,491 patients who received rivaroxaban 5 to 20 mg/day, the same total dose twice daily, or placebo for 6 months. The primary safety outcome was clinically significant bleeding (Thrombolysis In Myocardial Infarction major, minor, or requiring medical attention), which increased in a dose-dependent manner with the rivaroxaban dose and thienopyridine inclusion (range 8.2% to 17.8% vs 3.3% with placebo; p < 0.0001 for both trends, respectively). In the combined rivaroxaban cohort compared to placebo, the 6-month rate of the primary efficacy end point (death, MI, stroke, or severe recurrent ischemia requiring revascularization) was numerically lower (5.6% vs 7.0%; HR 0.79; p = 0.10) and the secondary efficacy end point (death, MI, or stroke) was significantly lower (HR 0.69; p = 0.027). For the secondary efficacy end point, the rivaroxaban 2.5-mg and 5-mg twice daily doses were associated with a lower HR (HR 0.35, 95% CI 0.05 to 2.58; and HR 0.58, 95% CI 0.28 to 1.21, respectively) than the same total doses taken once daily (HR 1.04, 95% CI 0.32 to 3.39; and HR 0.84, 95% CI 0.44 to 1.59, respectively). The rates of a net clinical benefit outcome (death, MI, stroke, or Thrombolysis In Myocardial Infarction major bleeding) among patients receiving rivaroxaban 2.5 mg and 5 mg twice daily compared to placebo were associated with an HR of 0.85 (95% CI 0.47 to 1.54) in stratum 2. The 2 lower twice-daily rivaroxaban doses were selected for the phase III trial.

The phase III trial of rivaroxaban for the secondary prevention of ACS, ATLAS ACS 2 TIMI 51 (Anti-Xa Therapy to Lower cardiovascular events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome), involved 15,526 patients with all types of ACS and was recently completed (Table 1).\(^ {32} \) Stabilized patients were randomized a median of 4.7 days after the index event to receive rivaroxaban 2.5 mg or 5 mg twice daily or placebo, in addition to standard antiplatelet therapy, and were stratified according to the planned thienopyridine use. Patients received the study drug for a median of 13.1 months for a maximum of 31 months. Thienopyridines (>99% clopidogrel)\(^ {33} \) were used in 93% of patients, with a mean duration of thienopyridine treatment of 13.3 months, and the results were described for both strata combined. Rivaroxaban treatment (both doses combined) resulted in a 16% relative reduction in the rate of the primary efficacy composite of cardiovascular death, MI, or stroke compared to placebo at 2 years (8.9% vs 10.7%; HR 0.84; p = 0.002). Although an analysis of stent thrombosis was not a part of
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The addition of an anticoagulant to standard antiplatelet therapy increased major bleeding in patients with ACS compared to placebo in both the ATLAS ACS 2 TIMI 51 and APPRAISE-2 trials. This should be expected when an anticoagulant is added to DAPT; however, it might be acceptable if it results in sufficient reductions in serious vascular events. Rivaroxaban treatment in ATLAS ACS 2 TIMI 51 demonstrated a positive benefit-risk profile, although apixaban treatment in the APPRAISE-2 trial failed to show any efficacy benefit compared to placebo.

A possible reason for the different results between the APPRAISE-2 and ATLAS ACS 2 TIMI 51 trials might be the patient populations enrolled (Table 1). The ATLAS ACS 2 TIMI 51 trial excluded patients with a history of ischemic stroke or transient ischemic attack who were taking both ASA and a thienopyridine, and the APPRAISE-2 trial included patients with a history of cerebrovascular disease (which had reached 10% of those enrolled when the trial was stopped).

Apixaban treatment in patients with a history of stroke was associated with an HR of 1.32 (95% CI 0.88 to 1.99) compared to an HR of 0.89 in patients without a history of stroke (95% CI 0.74 to 1.06; p for interaction = 0.08). Similarly, in the ATLAS ACS 2 TIMI 51 trial, the treatment benefit of rivaroxaban compared to placebo was reversed in patients with a history of stroke (3% of patients; HR 1.57, 95% CI 0.75 to 3.31; p for interaction = 0.10). The addition of anticoagulation to DAPT, therefore, does not seem to be an option for these patients. It was also demonstrated in the TRITON-TIMI 38 trial that treatment with prasugrel/ASA in patients with a history of stroke resulted in a net harm compared to treatment with clopidogrel/ASA. However, because only 10% of patients included in the APPRAISE-2 trial had a history of cerebrovascular disease, other factors will have contributed to the difference in results between the APPRAISE-2 and ATLAS ACS 2 TIMI 51 trials.

The 5-mg twice daily apixaban dose in APPRAISE-2 was the same as the dose used in the phase III Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) trial of apixaban for the prevention of stroke in patients with atrial fibrillation. This level of factor Xa blockade seems to have been too great for patients with ACS in terms of both efficacy and safety. In the ATLAS ACS TIMI 46 and RUBY-1 phase II trials of patients with ACS, dose-dependent increases in major bleeding were coupled with inverse dose-dependent reductions in cardiovascular events. However, in the ATLAS ACS 2 TIMI 51 study, the total daily dose of rivaroxaban was either 1/4 or 1/2 of the 20-mg/day dose used in the An Efficacy and Safety Study of Rivaroxaban with Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients with Non Valvular Atrial Fibrillation (ROCKET AF) trial of rivaroxaban for the prevention of stroke in patients with atrial fibrillation. The favorable results of both the RUBY-1 phase II and ATLAS ACS 2 TIMI 51 trials suggest that lower—rather than greater—intensity factor Xa inhibition combined with standard antiplatelet therapy seems to be superior for both efficacy and safety in patients with ACS. This was not seen with the lower doses of the direct thrombin inhibitor dabigatran in the REDEEM study and, therefore, presently seems to be restricted to factor Xa inhibition. Furthermore, in the ATLAS ACS 2 TIMI 51 study, the lower rivaroxaban 2.5-mg twice daily dose significantly reduced both cardiovascular and all-cause mortality compared to placebo.

The ATLAS ACS 2 TIMI 51 trial compared rivaroxaban treatment and placebo in patients with ACS receiving ASA plus either clopidogrel or, in a few cases, ticlopidine. Since the ATLAS ACS 2 TIMI 51 trial was initiated, the newer antiplatelet agents prasugrel and ticagrelor have completed phase III trials in patients with ACS. Treatment with prasugrel/ASA and ticagrelor/ASA resulted in significant reductions in cardiovascular events and significant increases in noncoronary artery bypass graft-related major bleeding compared to clopidogrel/ASA in the TRITON-TIMI 38 and PLATO trials. Both agents also significantly reduced stent thrombosis compared to clopidogrel/ASA. In contrast, treatment with ticagrelor/ASA treatment resulted in significant increases in fatal bleeding but treatment with ticagrelor/ASA did not. However, ticagrelor/ASA treatment did result in increased fatal intracranial hemorrhage. Rivaroxaban treatment in the ATLAS ACS 2 TIMI 51 study did not result in increased fatal bleeding compared to placebo. Other similarities between rivaroxaban (2.5 mg twice daily) and prasugrel/ASA and ticagrelor/ASA treatment included the reductions in both cardiovascular and all-cause mortality in the ATLAS ACS 2 TIMI 51 and PLATO trials compared to placebo/clopidogrel/ASA and ticagrelor/ASA, respectively.

With the recent approval of ticagrelor, the question remains of the potential of combining ticagrelor or prasugrel with low-dose anticoagulation, with or without ASA. The mortality benefit demonstrated by both ticagrelor and rivaroxaban represents exceptional advances in both ACS and cardiology as a whole. The possibility of combining
these agents, and possibly reducing vascular events and mortality further, is therefore of great interest.

In addition, the relevance of ASA has recently been called into question. The results from the What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary StentTing (WOEST) study, in patients undergoing percutaneous coronary intervention, indicated that a DAPT strategy (adding clopidogrel only to anticoagulants and omitting ASA) causes less bleeding than triple therapy and effectively prevents thrombotic and thromboembolic complications.57

Importantly, similar to ticagrelor/ASA and prasugrel/ASA compared to clopidogrel/ASA in the PLATO and TRITON-TIMI 38 trials, respectively, rivaroxaban significantly reduced stent thrombosis compared to placebo in the ATLAS ACS 2 TIMI 51 trial (Table 1).3,12,32 This positive effect of anticoagulants on stent thrombosis suggests a role of thrombin in this definitively ischemic process. Additional reductions in stent thrombosis might be achievable by combining ticagrelor or prasugrel with low-level blockade of factor Xa.

Future studies are needed to establish the relative benefits and risks of DAPT with ticagrelor/ASA or prasugrel/ASA versus triple therapy regimens, including combinations of clopidogrel, ticagrelor, or prasugrel, with or without ASA, and low-dose anticoagulation. Such studies would provide much needed information for optimizing therapies for the prevention of secondary ACS events.

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