REVIEW

Cardiovascular Therapeutics

The "Dual-Pathway" Strategy after Acute Coronary Syndrome: Rivaroxaban and Antiplatelet Agents in the ATLAS ACS 2-TIMI 51 Trial

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SUMMARY

Acute coronary syndrome (ACS) is a medical emergency often associated with an occlusive coronary event with consequent myocardial underperfusion. Patients require immediate antiplatelet therapy and long-term antithrombotic prophylaxis to reduce the risk of recurrence. Acetylsalicylic acid (ASA) alone or in combination with a platelet $P2Y_{12}$ inhibitor (dual antiplatelet therapy [DAPT]) has become the clinically accepted antithrombotic prophylaxis for patients post-ACS. Historically, studies assessing the utility of adding oral anticoagulants (OACs) have not demonstrated a clinical benefit with regard to acceptable bleeding risk. Studies with vitamin K antagonists (VKAs) such as warfarin demonstrated a potential to reduce the risk of subsequent death by reinfarction but this benefit was offset by increases in bleeding. Results from studies of two targeted non-VKA OACs also proved disappointing, with little or no apparent reduction in the rate of ischemic events seen. However, the recent ATLAS studies assessing rivaroxaban (an oral factor Xa inhibitor) in patients with ACS demonstrated a reduction in the composite endpoint of deaths from cardiovascular causes, myocardial infarction (MI), or stroke, and a reduction in the rate of stent thrombosis. This review provides an overview of the pivotal studies in which the addition of OACs to antiplatelet therapy (the so-called "dual-pathway" approach) has been investigated for the management of patients post-ACS and considers the results of the ATLAS studies and their potential impact on the management of patients after an acute event.

Introduction

Acute coronary syndrome (ACS) represents a medical emergency encompassing several acute myocardial ischemic states. ACS events are categorized based on electrocardiogram (ECG) and cardiac biomarker findings. The more severe ACS event, ST-elevation MI, is characterized by ST-segment elevation on ECG and increased cardiac biomarkers and is associated with total coronary artery occlusion and subsequent myocardial necrosis [1]. Events associated with partial or intermittent coronary occlusion are referred to as non-ST-elevation ACS events and are further subdivided into non-ST-elevation MI (i.e., with no ST-segment elevation on ECG but with an increase in cardiac biomarkers) or the milder unstable angina (i.e., with neither ST-segment elevation nor increase in cardiac biomarkers). In all cases, the underlying pathophysiology involves partial or complete thrombotic coronary artery occlusion, myocardial underperfusion, and the potential tissue necrosis. In any form, ACS represents a life-threatening condition.

After an ACS event, patients remain at increased risk of recurrent cardiovascular events, and long-term DAPT is the current standard of care [2–4]. Recommended DAPT regimens consist of ASA in combination with clopidogrel or newer antiplatelets (prasugrel or ticagrelor) [2–4]. This approach is supported by large-scale trials, such as CURE, which demonstrated a reduction in the risk of cardiovascular death, nonfatal MI, or stroke among patients with ACS who received both clopidogrel and ASA [5]. Subsequently, findings from the TRITON-TIMI 38 and PLATO trials demonstrated benefits of prasugrel and ticagrelor, respectively, to further reduce the risk of cardiovascular death, nonfatal MI, or stroke in patients with ACS versus clopidogrel [6,7]. However, even with newer antiplatelet agents, approximately 10% of patients had a residual 1-year risk of cardiovascular death, nonfatal MI, or stroke. This suggests that the benefits of platelet inhibition alone, even with DAPT, may have reached a plateau. The addition of the thrombin receptor antagonist vorapaxar to DAPT in the TRACER study identified a small additional reduction in ischemic events, but at the cost of more serious bleeding events [8]. Additionally, the question of the impact of the "hypercoagulable" state that can persist after an ACS event remains (discussed later). The need to improve long-term outcomes for these patients has prompted a re-evaluation of anticoagulant therapy combined with long-term antiplatelet therapy. Effective and well-tolerated combinations of antiplatelet and

anticoagulant ("dual-pathway") therapy have the potential to improve outcomes in patients with ACS [9]. However, there is a (well-founded) perception that this approach carries too high a bleeding risk. Data from the ATLAS program, including the phase III ATLAS ACS 2-TIMI 51 trial [10,11], suggest that it may be possible to improve outcomes without excessively increasing the risk of major bleeding in patients post-ACS who are receiving dual antiplatelet–anticoagulant therapy.

This review discusses the rationale, development, and potential adoption of a "dual-pathway" approach in clinical practice, within the context of historical and recent clinical trial data. The potential barriers to this approach are also covered.

Combined Antiplatelet and Anticoagulant Therapy in Acute Coronary Syndrome: The "Dual-Pathway" Strategy

The rationale for the "dual-pathway" approach, aimed at reducing the risk of subsequent adverse cardiovascular events, lies in the nature of the thrombi associated with ACS. Such thrombi have both platelet and fibrin components [12], requiring targeting of both components to ensure effective prevention of thrombus formation. Additionally, patients with ACS exhibit persistent hypercoagulability as a result of ongoing thrombin generation [13–15], which provides further support for targeting both pathways simultaneously. Indeed, the "dual-pathway" strategy is already employed in the acute hospitalization phase following an ACS event, in which parenterally administered anticoagulant therapy (e.g., unfractionated heparin) combined with antiplatelet agents is usually the standard treatment. However, this is not continued in the outpatient setting.

Antiplatelet Therapy Plus Oral Anticoagulants

Investigations into combined antiplatelet and OAC therapy after an ACS event began in the 1990s with the evaluation of vitamin K antagonists (VKAs) and ASA. Various regimens were evaluated, including a fixed-dose combination of a VKA and ASA (e.g., CARS [16]); low-intensity VKA therapy plus low-dose ASA (e.g., CHAMP [17]); moderate-intensity VKA plus ASA (ATACS, OASIS, and APRICOT-2 [18–20]); and high-intensity VKA therapy alone versus moderate-intensity VKA plus ASA (e.g., ASPECT-2 and WARIS-2 [21,22]).

Several meta-analyses of these and similar trials have been conducted [23–25]. Andreotti et al. [23] identified 14 relevant studies including 25,307 patients with follow-up ranging from 3 months to 5 years (Figure 1). There was no significant advantage of adding VKA (any intensity) to ASA versus ASA alone, in terms of the risk of death (all-cause), nonfatal MI, and nonfatal thromboembolic events (odds ratio [OR] 0.96; 95% confidence interval [CI] 0.90–1.03; $P = 0.30$). They reported a benefit only when moderate-intensity VKA therapy (target or measured international normalized ratio [INR] 2.0–3.0) was compared with ASA alone (OR 0.73; 95% CI 0.63–0.84; $P < 0.0001$). However, there was an accompanying increase in the risk of major bleeding events with the combined regimen (OR 1.77; 95% CI 1.47–2.13; $P < 0.0001$). Testa et al. [25] extended these results by focusing on studies comparing moderate-intensity VKA plus ASA versus clopidogrel plus ASA. Their analysis included 13 studies with 69,741 patients and concluded that neither regimen offered a benefit over ASA alone with respect to all-cause death, acute MI, thromboembolic stroke, major bleeding, and overall stroke risk.

In summary, these earlier studies indicated that any clinical benefit of antiplatelet–VKA therapy for reduced ischemic risk was mostly offset by increased bleeding risk. Successful implementation of a "dual-pathway" approach in ACS requires a better balance between benefit and bleeding risk.

Nonvitamin K Antagonist Oral Anticoagulants

Although effective, VKAs such as warfarin are not ideal for routine clinical use because of variability of dose response in individual patients (necessitating regular monitoring and dose adjustment), slow onset of action, and narrow therapeutic window [26,27]. One contributing factor is their action at multiple sites in the coagulation pathway, preventing the conversion of several clotting factors from their inactive to active states [26]. The advent of "next-generation" novel OACs, selectively targeting individual clotting factors, allows for a more predictable inhibition of coagulation [28]. The selective activity of novel agents enables more predictable pharmacokinetics/pharmacodynamics and simplified dose management without the need for regular coagulation monitoring and dose adjustment. Therefore, novel OACs have a potential role as a longer-term treatment strategy.

Several novel OACs have been evaluated in the ACS setting, including dabigatran (a direct thrombin inhibitor) and the direct factor Xa inhibitors apixaban, darexaban, and rivaroxaban (Tables 1 and 2). Another direct thrombin inhibitor, ximelagatran, was previously evaluated in ACS in the phase II ESTEEM trial [29] (Table 1), in which patients were randomized within 14 days of the index event to oral ximelagatran at doses of 24, 36, 48, or 60 mg twice daily (bid), or placebo for 6 months. Although a reduction in cardiovascular events and accompanying small increase in bleeding was reported, its development was halted because of liver toxicity concerns [30]. A phase II dose-escalation study of dabigatran bid in 1861 patients with ACS in addition to DAPT, over a 6-month period, revealed a dose-dependent increase in bleeding events with no appreciable difference in the rate of MI, stroke, or cardiovascular death (3.8% of patients who received placebo versus 3.0–4.9% of those who received dabigatran) [31] (Table 1). Similarly, in the APPRAISE trial, a phase II clinical evaluation of apixaban (n = 1715) in patients with ACS, a dose-dependent increase in bleeding events was noted; however, a trend toward a reduction in ischemic events was reported for both 2.5 mg bid (hazard ratio [HR] 0.73; 95% CI 0.44–1.19; $P = 0.21$) and 10 mg once-daily (od) regimens (HR 0.61; 95% CI 0.35–1.04; $P = 0.07$) [32]. The subsequent phase III study (APPRAISE-2) with apixaban 5 mg bid was terminated early because of increased major bleeding events, with no appreciable reduction in ischemic events [33] (Table 1). Finally, in the RUBY-1 trial (a phase II dose-escalation study of darexaban with a

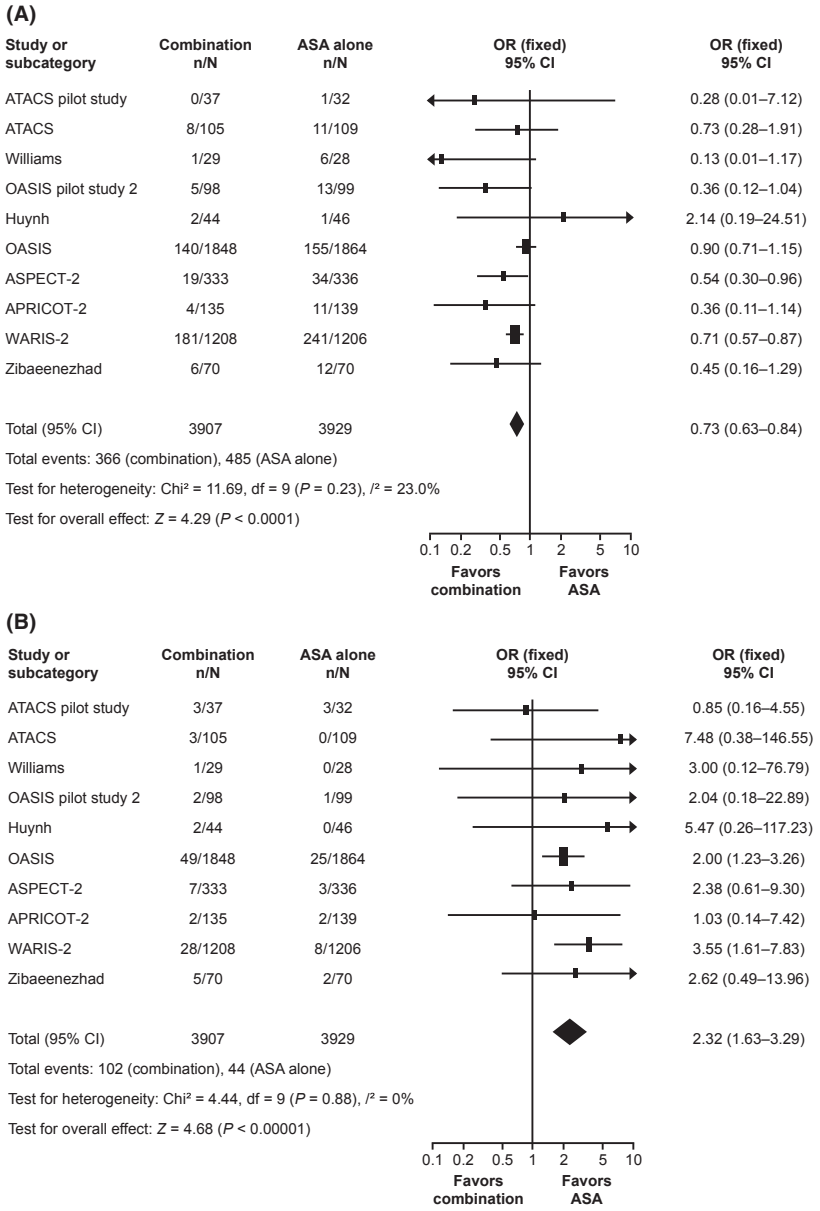

Figure 1 Comparative risk for (**A**) major adverse events (all-cause death, nonfatal myocardial infarction, nonfatal thromboembolic stroke) and (**B**) major bleeding events for moderate-intensity VKA plus ASA versus ASA alone [23]. Analysis restricted to those studies with a target or measured international normalized ratio 2.0–3.0. ASA, acetylsalicylic acid; CI, confidence interval; OR, odds ratio; VKA, vitamin K antagonist.

6-month follow-up period), there was a dose-dependent increase in bleeding events in 1279 patients after ACS, but no reduction in ischemic events [34] (Table 1).

Underlying differences between the phase III ATLAS ACS 2-TIMI 51 (rivaroxaban) and APPRAISE-2 (apixaban) trials should be considered. ATLAS patients had a lower median age than those in APPRAISE-2 [11,33], and patients with prior stroke or transient ischemic attack (TIA) who were receiving DAPT were excluded from ATLAS. Additionally, the rivaroxaban doses selected for evaluation in ATLAS ACS 2-TIMI 51 were established via the phase II ATLAS ACS-TIMI 46 study and were much lower than the dose used in the stroke prevention trial in patients with atrial fibrillation (ROCKET AF). By contrast, the same apixaban dose was used in APPRAISE-2 as in the stroke prevention trial, ARISTOTLE. Thus, the poor results obtained in APPRAISE-2 may have been a result of inappropriately high dose selection.

Rivaroxaban: The ATLAS Program of Trials

In contrast to the aforementioned findings, more positive clinical trial data for the oral, direct factor Xa inhibitor rivaroxaban have been published [10,11].

Table 1 Overview of the pivotal "dual-pathway" studies in patients post-ACS (excluding the ATLAS trials [see Figure 2 and Table 2])

Study	Regimen	Efficacy endpoints	Bleeding outcomes
ESTEEM (phase II) [29]	ASA 160 mg od plus either Ximelagatran bid (24, 36, 48, or 60 mg) (n = 1245) or Placebo	All-cause death, nonfatal MI, or severe recurrent ischemia: Placebo: 16.3% Ximelagatran combined: 12.7% (HR 0.76; 95% CI 0.59–0.98; $P = 0.036$)	Major bleeding events: Placebo: 0.9% Ximelagatran combined 1.8% (HR 1.97; 95% CI 0.80–4.84)
RE-DEEM (phase II) [31]	DAPT plus either Dabigatran bid (50, 75, 110, or 150 mg) (n = 1490) or Placebo (n = 371)	Cardiovascular death, MI, or stroke: Placebo: 3.8% Dabigatran 50 mg: 4.6% Dabigatran 75 mg: 4.9% Dabigatran 110 mg: 3.0% Dabigatran 150 mg: 3.5%	Major or clinically relevant minor bleeding events: Placebo: 2.2% Dabigatran 50 mg: 3.5% (HR vs. placebo 1.77; 95% CI 0.70–4.50) Dabigatran 75 mg: 4.3% (HR vs. placebo 2.17; 95% CI 0.88–5.31) Dabigatran 110 mg: 7.9% (HR vs. placebo 3.92; 95% CI 1.72–8.95) Dabigatran 150 mg: 7.8% (HR vs. placebo 4.27; 95% CI 1.86–9.81; $P < 0.001$ for a linear trend)
APPRAISE-2 (phase III) [33]	Standard antiplatelet therapy (ASA alone or DAPT) plus Apixaban 5 mg bid (2.5 mg bid in patients with CrCl <40 mL/min) (n = 3705) or Placebo (n = 3687)	Cardiovascular death, MI, or ischemic stroke: Placebo overall: 7.9% Apixaban overall: 7.5% (HR vs. placebo 0.95; 95% CI 0.80–1.11; $P = 0.51$) ASA alone + apixaban: 9.0% (HR vs. placebo 0.92; 95% CI 0.66–1.29) ASA alone + placebo: 9.8% DAPT + apixaban: 7.2% (HR vs. placebo 0.95; 95% CI 0.79–1.15) DAPT + placebo: 7.5%	TIMI major bleeding events per 100 patient-years: Placebo: 0.9 Apixaban: 2.4 (HR vs. placebo 2.59; 95% CI 1.50–4.46; $P = 0.001$) Fatal bleeding events per 100 patient-years: Apixaban: n = 5 Placebo: n = 0
RUBY-1 (phase II) [34]	Standard antiplatelet therapy (ASA alone or DAPT) plus Darexaban (5, 15, or 30 mg bid or 10, 30, or 60 mg od) (n = 939) or Placebo (n = 324)	All-cause death, MI, stroke, or severe recurrent ischemia: Placebo: 4.4% Darexaban 5 mg bid: 3.8% Darexaban 10 mg od: 3.8% Darexaban 15 mg bid: 6.3% Darexaban 30 mg od: 6.4% Darexaban 30 mg bid: 5.9% Darexaban 60 mg od: 7.8%	Major and clinically relevant nonmajor bleeding events (*P* vs. placebo): Placebo: 3.1% Darexaban 5 mg bid: 6.8% ($P = 0.129$) Darexaban 10 mg od: 5.6% ($P = 0.238$) Darexaban 15 mg bid: 7.5% ($P = 0.075$) Darexaban 30 mg od: 5.6% ($P = 0.213$) Darexaban 30 mg bid: 11.3% ($P = 0.002$) Darexaban 60 mg od: 7.3% ($P = 0.054$)

ACS, acute coronary syndrome; ASA, acetylsalicylic acid; bid, twice daily; CI, confidence interval; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; HR, hazard ratio; MI, myocardial infarction; od, once daily; TIMI, Thrombolysis In Myocardial Infarction.

In the large, dose-ranging, phase II ATLAS ACS-TIMI 46 study, 3491 patients were recruited [10]. This large patient cohort permitted a thorough evaluation of the rivaroxaban dose required to achieve the optimal balance between reduced ischemic risk and increased bleeding risk. Rivaroxaban doses of 5, 10, 15, and 20 mg od or bid were compared with placebo, with separate analyses performed in patients receiving ASA alone (stratum 1) and in patients receiving ASA and a thienopyridine antiplatelet agent (clopidogrel or ticlopidine; DAPT; stratum 2). The primary safety and efficacy endpoints for both strata were clinically significant bleeding (Thrombolysis In Myocardial Infarction [TIMI] criteria), and time to first episode of death, MI, stroke, or severe recurrent ischemia requiring revascularization, respectively. As expected, the bleeding risk increased dose dependently from an HR of 2.21 (95% CI 1.25–3.91) for rivaroxaban 5 mg daily to 5.06 (95% CI 3.45–7.42) for rivaroxaban 20 mg daily versus pooled placebo across both strata ($P < 0.0001$; Figure 2). Compared with placebo, treatment with rivaroxaban had similar outcomes for clinically significant bleeding in stratum 1 (HR 3.96; 95% CI 1.40–11.23) and stratum 2 (HR 3.66; 95% CI 2.54–5.27; $P = 0.90$). There was a trend toward a reduction in the rate of the primary efficacy endpoint with rivaroxaban versus placebo (5.6% vs. 7.0%; HR 0.79; 95% CI 0.60–1.05; $P = 0.10$; Figure 2) and a statistically significant reduction in the secondary efficacy endpoint of death, MI, or stroke with rivaroxaban (3.9% vs. 5.5% [pooled placebo]; HR 0.69; 95% CI 0.50–0.96; $P = 0.027$) [10]. The relative risk reductions of death, MI, or stroke demonstrated with rivaroxaban versus placebo in stratum 1 (6.6% vs. 11.9%, HR 0.54; 95% CI 0.32–0.89) and stratum 2

Table 2 The ATLAS ACS 2-TIMI 51 trial [11]

Study design	Population	Regimen	Efficacy endpoints	Bleeding outcomes	Conclusions
ATLAS ACS 2-TIMI 51 Phase III, double-blind, placebo-controlled, randomized trial Median time to randomization after the index event was 4.7 days Followed for up to 31 months	Post-ACS	Standard medical therapy plus Rivaroxaban 2.5 mg or 5 mg bid (n = 5174 and n = 5176, respectively) or Placebo (n = 5176)	Death from cardiovascular causes, MI, or stroke: Placebo: 10.7% Rivaroxaban 2.5 mg bid: 9.1% (HR vs. placebo 0.84; 95% CI 0.72–0.97; $P = 0.02$) Rivaroxaban 5 mg bid: 8.8% (HR vs. placebo 0.85; 95% CI 0.73–0.98; $P = 0.03$) Death from cardiovascular causes: Placebo: 4.1% Rivaroxaban 2.5 mg bid: 2.7% (HR vs. placebo 0.66; 95% CI 0.51–0.86; $P = 0.002$) Rivaroxaban 5 mg bid: 4.0% (HR vs. placebo 0.94; 95% CI 0.75–1.20; $P = 0.63$) MI: Placebo: 6.6% Rivaroxaban 2.5 mg bid: 6.1% (HR vs. placebo 0.90; 95% CI 0.75–1.09; $P = 0.27$) Rivaroxaban 5 mg bid: 4.9% (HR vs. placebo 0.79; 95% CI 0.65–0.97; $P = 0.02$) Stroke: Placebo: 1.2% Rivaroxaban 2.5 mg bid: 1.4% (HR vs. placebo 1.13; 95% CI 0.74–1.73; $P = 0.56$) Rivaroxaban 5 mg bid: 1.7% (HR vs. placebo 1.34; 95% CI 0.90–2.02; $P = 0.15$) Stent thrombosis: Placebo: 2.9% Rivaroxaban 2.5 mg bid: 2.2% (HR vs. placebo 0.65; 95% CI 0.45–0.94; $P = 0.02$) Rivaroxaban 5 mg bid: 2.3% (HR vs. placebo 0.73; 95% CI 0.51–1.04; $P = 0.08$)	Clinically relevant bleeding event (non-CABG-related): Placebo: 0.6% Rivaroxaban 2.5 mg bid: 1.8% (HR vs. placebo 3.46; 95% CI 2.08–5.77; $P < 0.001$) Rivaroxaban 5 mg bid: 2.4% (HR vs. placebo 4.47; 95% CI 2.71–7.36; $P < 0.001$) Intracranial hemorrhage Placebo: 0.2% Rivaroxaban 2.5 mg bid: 0.4% Rivaroxaban 5 mg bid: 0.7% Rivaroxaban combined: 0.6% ($P = 0.009$) Fatal bleeding event: Placebo: 0.2% Rivaroxaban 2.5 mg bid: 0.1% (HR vs. placebo 0.67; 95% CI 0.24–1.89; $P = 0.45$) Rivaroxaban 5 mg bid: 0.4% (HR vs. placebo 1.72; 95% CI 0.75–3.92; $P = 0.20$)	Significant reduction in death from cardiovascular causes, MI, or stroke (both doses), and in the incidence of stent thrombosis (lower dose only) compared with placebo Significant increase in the rate of clinically relevant bleeding events but not in the rate of fatal bleeding events

ACS, acute coronary syndrome; bid, twice daily; CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

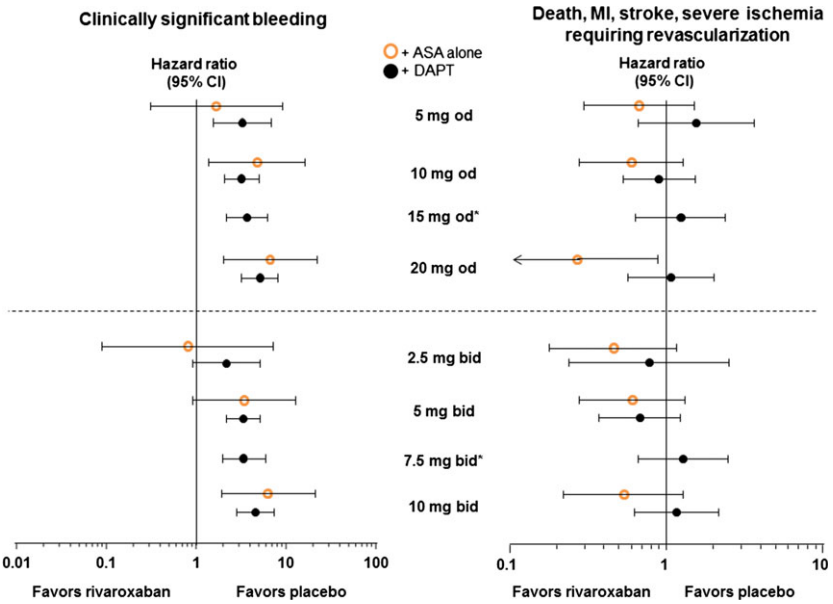

Figure 2 Comparative risk for clinically significant bleeding or death, MI, stroke, or severe ischemia requiring revascularization with a range of rivaroxaban daily doses in combination with ASA in the ATLAS ACS-TIMI 46 trial [10,11]. *Tested only in stratum 2 (rivaroxaban + DAPT). ASA, acetylsalicylic acid; bid, twice daily; CI, confidence interval; DAPT, dual antiplatelet therapy (ASA + thienopyridine); MI, myocardial infarction; od, once daily.

(3.1% vs. 3.8%, HR 0.83; 95% CI 0.54–1.28) were directionally consistent ($P = 0.19$).

In ATLAS ACS-TIMI 46, the rivaroxaban 2.5 mg and 5 mg bid doses were associated with a trend toward fewer ischemic events. In patients treated with these two doses plus ASA alone, the risk of TIMI major bleeding increased from 0% to 1.2% ($P = 0.17$), and in patients treated with these two doses plus DAPT, TIMI major bleeding increased from 0.2% to 1.2% ($P = 0.03$) versus placebo [35]. In a subsequent exploratory net clinical benefit analysis (i.e., with a composite endpoint of death, MI, stroke, or TIMI major bleeding), these two low rivaroxaban doses resulted in an HR of 0.72 (95% CI 0.46–1.12) across both strata, 0.59 (95% CI 0.30–1.16) in patients on ASA alone, and 0.85 (95% CI 0.47–1.54) in patients on DAPT compared with placebo [10].

Based on these results, the phase III ATLAS ACS 2-TIMI 51 study evaluated the efficacy of rivaroxaban 2.5 mg bid and 5 mg bid in 15,526 patients with recent ACS [11]. Patients were randomly assigned to receive either rivaroxaban (one of two regimens) or placebo in addition to standard medical therapy consisting of ASA with/without a thienopyridine. DAPT was the intended therapy for most patients (93%). Compared with placebo, rivaroxaban 2.5 mg bid (with ASA ± thienopyridine) significantly reduced the composite endpoint of cardiovascular death, MI, or stroke by 16% ($P = 0.02$) (Figure 3A) and cardiovascular death alone by 34% (HR 0.66; 95% CI 0.51–0.86; $P = 0.002$). A similar reduction was apparent for the composite endpoint (cardiovascular death, MI, or stroke) with the 5 mg bid dose (Figure 3B), but not for cardiovascular death alone (HR 0.94; 95% CI 0.75–1.20; $P = 0.63$). With the exception of patients with a history of stroke or TIA, outcomes for rivaroxaban were consistent across all major patient subgroups, including patients diagnosed with ST-elevation MI, non-ST-elevation MI, or unstable angina, and those receiving ASA alone or DAPT.

In terms of safety, although rivaroxaban was associated with an increased rate of TIMI major bleeding events not associated with coronary artery bypass grafting, compared with placebo (2.1% vs. 0.6%, respectively; $P < 0.001$), the rate of fatal bleeding events (including fatal intracranial hemorrhage) compared with placebo was very low and not significantly different (0.3% vs. 0.2%, respectively; $P = 0.66$). When both rivaroxaban doses were evaluated separately, the absolute rate of clinically significant bleeding (not related to coronary artery bypass grafting) was numerically lower for the 2.5 mg bid versus the 5 mg bid dose (1.8% vs. 2.4%; $P = 0.12$) [11]. Finally, rivaroxaban 2.5 mg bid reduced the risk of (Academic Research Consortium definition of definite, probable, or possible) stent thrombosis (a life-threatening complication) by 35% versus placebo (HR 0.65; 95% CI 0.45–0.94; $P = 0.02$); the risk reduction was not statistically significant for the 5 mg bid group ($P = 0.08$) [36].

Despite these results, in May 2012, the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the US Food and Drug Administration (FDA) did not approve rivaroxaban for an expanded ACS indication, primarily owing to the high rate of missing data in the ATLAS ACS 2-TIMI 51 study. In total, vital status was not determined in 1117 of the 1294 patients who withdrew consent, a number that was lower in other ACS trials [37]. There were concerns that the missing data may have amplified or obscured any true difference in endpoints; however, subanalyses across different patient populations showed consistent results for the primary efficacy endpoint [37]. Although the FDA is yet to approve rivaroxaban in this indication, in March 2013, the European Medicines Agency Committee for Medicinal Products for

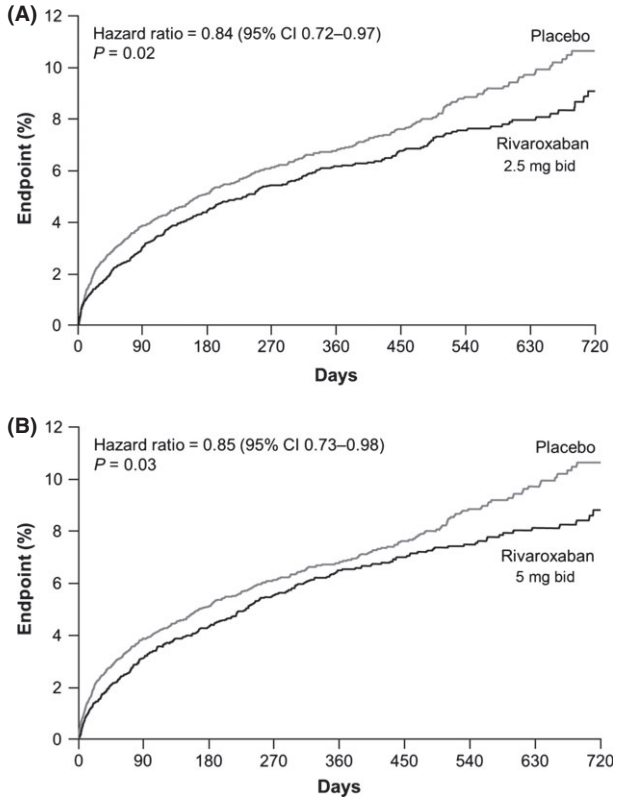

Figure 3 Cumulative incidence of death from cardiovascular causes, myocardial infarction, or stroke with (**A**) rivaroxaban 2.5 mg twice daily (bid) and (**B**) rivaroxaban 5 mg bid compared with placebo in patients with acute coronary syndrome in the ATLAS ACS 2-TIMI 51 trial [11]. CI, confidence interval.

Human Use granted an ACS indication for rivaroxaban 2.5 mg bid when coadministered with ASA alone or with ASA plus clopidogrel or ticlopidine, for the prevention of atherothrombotic events in adult patients after an ACS with elevated biomarkers [37,38]. The decision to approve this dose in patients with elevated cardiac biomarkers was based on a *post hoc* analysis of the ATLAS ACS 2-TIMI 51 data, which revealed that patients at high risk of a recurrent ischemic event (with elevated cardiac biomarker status) were most likely to benefit from the addition of rivaroxaban to standard antiplatelet therapy [39].

Implications of ATLAS ACS 2-TIMI 51 Trial Findings for Clinical Practice

The positive outcomes of ATLAS ACS 2-TIMI 51 have suggested that a balance between efficacy and safety can be achieved in patients with ACS using low-dose anticoagulant (rivaroxaban 2.5 mg bid) plus DAPT [11]. Proponents of warfarin use post-ACS may point to studies demonstrating the beneficial effects of warfarin, with tightly controlled INR, in combination with ASA, but the associated increase in bleeding risk and practical challenges surrounding warfarin have limited the use of warfarin-containing regimens [40]. Notwithstanding the ongoing discussions around optimal dosing for OACs and antiplatelet agents, rivaroxaban 2.5 mg bid can provide a reduced treatment burden compared with warfarin in this setting and is supported by a larger body of evidence than any other novel OAC. The addition of rivaroxaban 2.5 mg bid to standard therapy (ASA alone or with a thienopyridine) reduced the risk of cardiovascular death, MI, or stroke without increasing the risk of fatal bleeding events.

Even with these positive clinical trial results, however, implementation of a "dual-pathway" approach for the secondary prevention of ischemic events in patients with ACS into clinical practice will be difficult. Several clinically relevant questions remain to be addressed. Firstly, which patients should be considered for this approach? As mentioned previously, rivaroxaban 2.5 mg bid, coadministered with ASA alone or with ASA plus clopidogrel or ticlopidine, is approved in the EU for the prevention of atherothrombotic events in adult patients after an ACS event with elevated cardiac biomarkers—that is, high-risk patients [38]. However, patients with a creatinine clearance of <30 mL/min, clinically significant gastrointestinal bleeding within the past 12 months, prior intracranial hemorrhage, ischemic stroke, or TIA were also excluded from the ATLAS ACS 2-TIMI 51 study (prior stroke/TIA is in fact a contraindication for rivaroxaban in the EU) [38]. Secondly, over 90% of patients had a creatinine clearance of ≥50 mL/min and most were aged <75 years [11]. Therefore, a "dual-pathway" approach with rivaroxaban and antiplatelet therapy should undoubtedly be targeted toward specific patient types with lower bleeding potential. Findings from a recent meta-analysis of seven published phase II and III ACS studies with novel OACs reported that although there was a modest reduction in ischemic events with these agents relative to antiplatelet standard of care alone, they were associated with a substantial increase in bleeding risk [41]. Although not encouraging in themselves, these findings relate not only to more than one novel agent but also to a very broad range of patients. The findings suggest, therefore, that the balance of benefit against risk depends on both the anticoagulant agent and the patient type, and they support the need for a targeted approach.

Future studies should be conducted to determine whether routine and careful assessment of bleeding risk is required before low-dose rivaroxaban is administered. Thus, risk stratification for future ischemic and bleeding events may be appropriate to guide patient selection. For example, it may be appropriate to only implement a "dual-pathway" strategy in patients at high risk of a recurrent event and at low risk of bleeding, identified using risk scores such as GRACE and CRUSADE [2]. In the EU, although risk stratification of patients before treatment is not currently required, rivaroxaban 2.5 mg bid is contraindicated in patients with ACS and with hypersensitivity to the active substances; active clinically significant bleeding; a lesion or condition that presents a significant major bleeding risk (e.g., recent intracranial hemorrhage); hepatic disease associated with coagulopathy and clinically relevant bleeding risk; concomitant treatment with other anticoagulants (except when switching to or from rivaroxaban or when unfractionated heparin is given at doses needed to maintain an open central venous or arterial catheter); and concomitant treatment with antiplatelets in patients with a prior stroke or TIA [38].

The optimal time for introducing rivaroxaban also remains to be determined. ATLAS ACS 2-TIMI 51 trial was a secondary

prevention study rather than an acute treatment study. As a result, patients were randomized to treatment from 24 h up to 7 days after hospitalization for the index ACS event, once the patient had been stabilized and after parenteral anticoagulants had been stopped. Enrollment occurred as soon as possible after the initial treatments, including revascularization procedures for the index event [42]. Consequently, the median time from index event to randomization was 4.7 days (interquartile range 3.2–6.0 days) for rivaroxaban and 6 days (interquartile range 4–7 days) for apixaban in APPRAISE-2 [11,33]. In both studies, this was longer than for the introduction of ASA plus ticagrelor at approximately 11 h from the index event in the PLATO study—a study where the specific intention was to investigate the treatment benefits of DAPT initiated in the acute setting [7].

Finally, practical issues such as the requirement for and frequency of patient monitoring will need to be addressed, as well as the potential for combining rivaroxaban with the newer antiplatelets prasugrel or ticagrelor, plus ASA in patients with ACS.

Further clinical trial data will be required before treatment recommendations can be made with regard to antiplatelet regimens including the newer thienopyridines.

Conclusions

Bleeding is an undesirable yet unavoidable consequence of using antithrombotics. Cardiologists must weigh the benefits to patients post-ACS of avoiding subsequent ischemic events (with all their associated complications, including death) versus the risk of bleeding while receiving "dual-pathway" therapy.

Trials evaluating the efficacy of long-term warfarin in combination with ASA after ACS found promising efficacy when a target INR of 2.0–3.0 was used. However, an associated increase in bleeding and the practical difficulties of managing warfarin limited its introduction to routine practice. The success of the novel OACs in other indications in which warfarin has traditionally been used, such as atrial fibrillation, led to their evaluation in this setting. However, phase II/III trials of dabigatran, apixaban, and darexaban proved disappointing with limited or no reduction in ischemic events and an increase in bleeding events. The phase III APPRAISE-2 trial of apixaban was terminated early because of an increase in bleeding events. The reasons for this continue to be debated, but dose selection and the inclusion of a relatively high-risk patient population are likely to have contributed. However, ATLAS ACS 2-TIMI 51 data have shown that a balance between reduction in risk of death and rate of bleeding events can be achieved by the addition of rivaroxaban 2.5 mg bid to DAPT. Fourteen different regimens were evaluated in the phase II ATLAS ACS-TIMI 46 study, including four different daily doses given od or bid in addition to DAPT. The results of the phase II study provided a rationale for evaluating low-dose rivaroxaban bid combined with DAPT for long-term prophylaxis in patients post-ACS. The results of ATLAS ACS 2-TIMI 51 demonstrated an impressive reduction in both all-cause and cardiovascular mortality and stent thrombosis for rivaroxaban 2.5 mg bid plus DAPT. Although rates of clinically relevant bleeding events were higher for DAPT plus rivaroxaban 2.5 mg bid versus DAPT alone, there was a lower rate of fatal bleeding events among the DAPT plus rivaroxaban arm. However, these results emphasize the importance not only of using the right dose of novel OAC but also of treating the right patient. Subsequent analyses of the ATLAS ACS 2-TIMI 51 data revealed a greater benefit–risk profile in patients at high ischemic risk but reduced bleeding risk. Therefore, combination therapy should be tailored for patients most likely to benefit; other factors such as age, renal function, and previous history of bleeding may need to be taken into account to reduce the risk of fatal bleeding events.

Although many questions remain, findings from ATLAS ACS 2-TIMI 51 suggest that an antiplatelet–anticoagulant "dual-pathway" strategy for secondary prevention can produce clinically meaningful improvements in outcomes for patients with ACS.

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Conflict of Interest

MC has participated in speaker bureaus for Merck, Bristol-Myers Squibb, Janssen, and Boehringer Ingelheim. DI declares no potential conflict of interest.

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