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REVIEW ARTICLE

Anticoagulants for secondary prevention after acute myocardial infarction: lessons from the past decade

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ABSTRACT

The impact of an acute coronary syndrome (ACS) event, such as an acute myocardial infarction (MI), is not limited to the acute management phase; patients face an elevated risk of residual atherothrombotic events that commonly requires chronic management for months or even years. Significant advances have been made in both the acute and chronic management of patients with acute MI over the past decade, resulting in improved prognoses. One of the hallmarks of modern treatment strategies is more aggressive antiplatelet treatment regimens. However, the risks of further ACS events, stroke and premature death remain elevated in these patients, and addressing this residual risk is challenging owing to interpatient variability, differences in management strategies between centres and countries, incomplete understanding of the specific pathophysiology of post-ACS thrombosis and limitations of current therapeutic approaches. The recent approval in Europe of the direct oral anticoagulant rivaroxaban for use in this setting in combination with clopidogrel and acetylsalicylic acid offers another strategy to consider in the management of these patients, and clinical strategies in this area continue to evolve. In this review, we chart the progress made over the past decade in reducing the burden of secondary thromboembolic events after acute MI and discuss the current position of and future perspectives on the inclusion of oral anticoagulants into care pathways in this setting.

INTRODUCTION

Acute coronary syndrome (ACS) comprises myocardial infarction (MI) and unstable angina (UA) arising from the obstruction of the coronary arteries, usually as a result of a coronary thrombosis [1]. After the acute management of an ACS event, patients remain at increased risk of secondary atherothrombotic events, including recurrent ACS events and stroke, and continue to face an increased risk of premature death [2,3].

Preventing a recurrence of life-threatening thrombotic events is a critical part of the ongoing management of these patients [1,4]. However, prevention of secondary thrombotic events after an ACS event remains challenging, owing to interpatient variability, differences in management strategies between centres and countries, incomplete understanding of the specific pathophysiology of post-ACS thrombosis and limitations of current therapeutic approaches.

A decade ago, standard care involved an approach targeted primarily at inhibiting platelet activation – using acetylsalicylic acid (ASA) or the emerging $P2Y_{12}$ inhibitors – in some patients [5–7]. Anticoagulation with warfarin was also recommended for some patient

subgroups. At that time, death rates in the year after an ACS event were high [8]: a prospective registry for the period 2002–2003 found that 9% of all patients had died in the 12 months after an acute ischaemic event and almost 16% experienced a secondary MI or died [9]. Since then, the benefits of a dual-pathway (anticoagulation + antiplatelet) approach to secondary prevention after ACS have become more evident and this approach is now recommended in evidence-based guidelines [1,10], but the increased risk of bleeding and the practical management challenges associated with warfarin use have continued to limit the implementation of this approach.

During the same period, major advances have been made with antiplatelet agents, in both optimizing the use of clopidogrel and introducing newer platelet-targeted drugs. This optimization of dual antiplatelet (DAPT) regimens has contributed to the marked reductions in post-ACS event rates and deaths in more recent years [11–15]. However, there remains a sizeable unmet need in secondary prevention of ischaemic events after ACS, with estimates suggesting that up to 14% of patients will experience a recurrent cardiovascular (CV) event in the year after an acute ACS event [16]. This residual recurrence rate has fuelled the continued evaluation of the dual-pathway approach to secondary prevention in this setting.

The aim of this review is to examine the rationale for oral anticoagulation after an MI with the aim of preventing secondary thrombotic events, thereby reducing the wider burden of ACS.

THE DUAL-PATHWAY APPROACH TO PREVENTING RECURRENT EVENTS AFTER MYOCARDIAL INFARCTION

Prevention of thrombotic events after an acute ACS event, such as an MI, is a critical component of the ongoing care for these patients. An understanding of the biologic processes that underlie the persistent risk of thrombus formation after an acute ACS event provides a rationale for incorporating inhibition of thrombin generation or activity into the pharmacologic management regimen for such patients.

Acute coronary syndrome events are most often a result of thrombus formation after atherosclerotic plaque disruption (either plaque rupture or plaque erosion) [17,18]. Passing platelets adhere to the exposed subendothelial proteins, resulting in their aggregation; tissue factors released by these newly formed plaques initiate coagulation and thrombin generation (*Figure 1*) [19,20]. Increased thrombin levels result in further thrombus growth (as platelet aggregation continues) and the stabilization of the resulting thrombi (through the conversion of fibrinogen to fibrin). The increasing thrombin levels trigger further thrombus growth, which in turn drives further thrombin generation. In addition to these localized events, thrombus formation

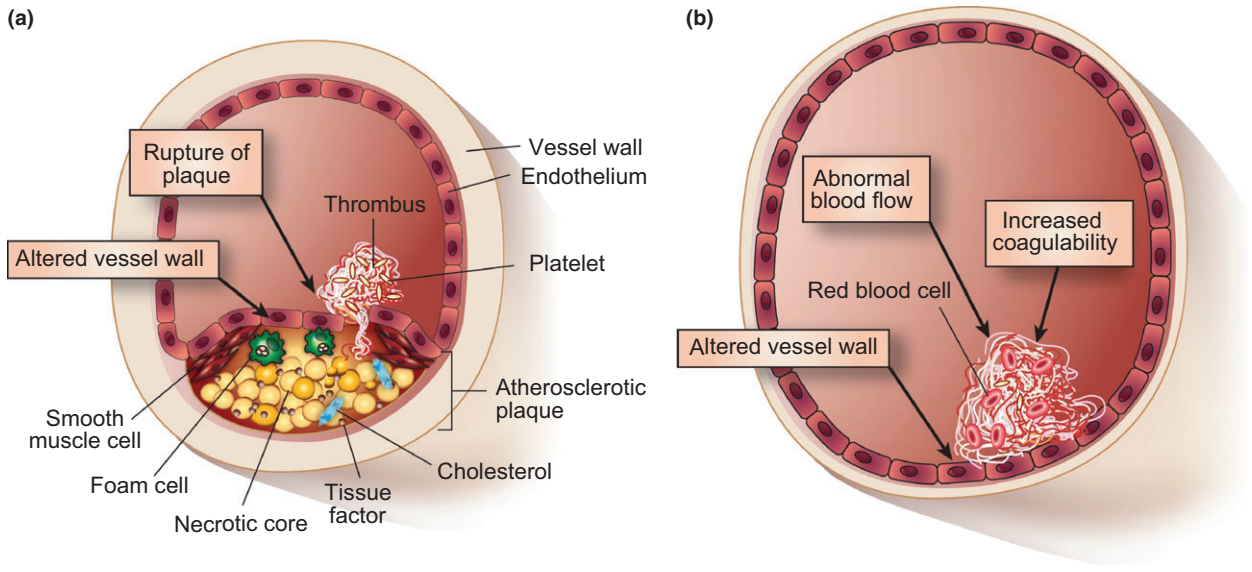

Figure 1 Triggers of (a) arterial thrombosis and (b) venous thrombosis [20].

is accompanied by systemic persistent thrombin generation that lasts much longer than the residual platelet activation that typically follows an MI [20].

Clinical studies have shown that long-term DAPT with ASA and an antiplatelet such as clopidogrel, prasugrel or ticagrelor reduces the risk of death from CV causes, nonfatal MI or stroke after an acute ACS event [21–23]. The first of the antiplatelets to demonstrate a benefit was clopidogrel. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, 12 562 patients who presented within 24 h of the onset of ACS symptoms were randomly assigned to receive either clopidogrel (300 mg loading dose then 75 mg once daily) or placebo, in addition to ASA [23]. During the 12 months of follow-up, significantly fewer patients assigned to the clopidogrel + ASA arm experienced the composite endpoint of nonfatal MI, stroke or death from CV causes than patients assigned to the ASA-only arm [9.3% vs. 11.4%; relative risk 0.80; 95% confidence interval (CI) 0.72–0.90; $P < 0.001$]. In 2007, the results of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 study were reported [22]. In this study, 13 608 patients with moderate- to high-risk ACS scheduled for percutaneous coronary intervention received either clopidogrel (300 mg loading dose then 75 mg once daily) or prasugrel (60 mg loading dose then 10 mg once daily) in addition to ASA. Fewer patients in the prasugrel arm experienced the composite endpoint of nonfatal MI, nonfatal stroke or death from CV causes than patients in the clopidogrel arm (9.9% vs. 12.1%; hazard ratio [HR] 0.81; 95% CI 0.73–0.90; $P < 0.001$). Most recently, the results of the Study of Platelet Inhibition and Patient Outcomes (PLATO) of ticagrelor in 18 624 patients hospitalized with an ACS showed that the same composite endpoint as in the CURE trial (nonfatal MI, stroke or death from CV causes) occurred significantly less frequently among patients treated with ASA + ticagrelor (loading dose 180 mg then 90 mg twice daily) than among those treated with ASA + clopidogrel (loading dose 300–600 mg then 75 mg once daily) for up to 1 year (9.8% vs. 11.7%; HR 0.84; 95% CI 0.77–0.92; $P < 0.001$) [21]. All three antiplatelets offer significant benefits to patients after an ACS event compared with ASA alone in terms of reducing the risk of nonfatal MI, nonfatal stroke or death from CV causes; however, even with a DAPT approach, a residual risk of these adverse outcomes persists for a significant proportion of patients. Therefore, it would seem that although antiplatelet-only regimens address the platelet activation that occurs after an acute MI, they are insufficient to eliminate the increased risk of subsequent thrombus formation. A likely reason for this may be that even the newer antiplatelet agents do not address the persistent procoagulant state owing to the prolonged elevation of thrombin generation that is apparent after an acute MI.

Interfering in the thrombin pathway, either directly or indirectly, has emerged as an approach that may have an impact on the formation of thrombi and may also influence platelet activation to some extent – a so-called dual-pathway approach. However, despite evidence that anticoagulation in addition to platelet inhibition is effective and that the combination of the two is more effective than either treatment alone in non-ST-elevation MI, many patients continue to be discharged from hospital after an ACS event without a prescription for an oral anticoagulation agent [24–26]. The reasons for this may be related to the key limitations of the vitamin K antagonists (VKAs) that complicate their use, which include an increased risk of bleeding and logistical challenges in managing these drugs [26]. The situation in patients suffering ST-elevation MI is even more challenging, and evidence of the benefit of VKAs in these patients is limited [10].

The development of novel oral anticoagulants (OACs) in recent years may go some way to overcoming the limitations of VKA-based anticoagulant therapy. During the past decade, several novel OACs have been studied in patients with ACS and the first of these, rivaroxaban, received marketing authorization from the European Commission in May 2013 [27].

STUDIES OF ORAL ANTICOAGULANTS FOR SECONDARY PREVENTION AFTER AN ACUTE CORONARY SYNDROME EVENT

Vitamin K antagonists

The evaluation of oral anticoagulant therapy alongside antiplatelet therapy after an acute ACS event began in the 1990s with studies of VKAs + ASA, either alone or in combination with clopidogrel. The initial challenge was to establish an optimal regimen, because many of the early studies that evaluated fixed-dose or low-intensity VKA regimens failed to demonstrate a benefit associated with the addition of anticoagulant therapy to ASA, compared with ASA alone [28,29]. However,

studies utilizing a moderate-intensity VKA regimen (target international normalized ratio 2.0–3.0) did reveal a modest benefit compared with ASA alone [30–34]. In 2006, the results of a meta-analysis of data from 14 trials that included >25 000 patients were reported [35]. Although the analysis failed to demonstrate a benefit for VKA (of any intensity) + ASA over ASA alone, analysis of the subset of studies that evaluated moderate-intensity VKA therapy did indicate a benefit for the combination regimen (odds ratio [OR] 0.73; 95% CI 0.63–0.84; $P < 0.0001$). However, this benefit was accompanied by an increased risk of major bleeding events (OR 1.77; 95% CI 1.47–2.13; $P < 0.00001$).

A further meta-analysis reported in 2007 included data from >69 000 patients who had taken part in 13 studies comparing either moderate-intensity VKA + ASA or clopidogrel + ASA with ASA alone [36]. Although both regimens were associated with significant reductions in major adverse events (all-cause death, acute MI, thromboembolic stroke, major bleeding events and overall risk of stroke) compared with ASA alone, there was no apparent benefit for one regimen over the other in terms of the overall rate of major adverse events. When individual events were examined, the addition of a VKA to ASA was associated with a significantly reduced risk of any type of stroke (OR 0.58; 95% CI 0.35–0.94; $P = 0.038$) and more specifically of thromboembolic stroke (OR 0.53; 95% CI 0.31–0.88; $P = 0.03$). However, this beneficial effect was accompanied by an increase in the risk of major bleeding events with ASA + VKA compared with ASA + clopidogrel (OR 1.9; 95% CI 1.2–2.8; $P = 0.005$).

Direct thrombin inhibitors

The oral, direct thrombin inhibitors ximelagatran and dabigatran have also been evaluated in the management of patients post-ACS. Ximelagatran was evaluated in the phase II dose-finding Efficacy and Safety of the oral direct Thrombin inhibitor ximelagatran in patients with recent Myocardial damage (ESTEEM) study [37], in which CV events were significantly reduced but bleeding events were increased compared with ASA alone. This agent was subsequently withdrawn from development owing to drug-related liver toxicity [38].

The 6-month phase II dabigatran RE-DEEM study, which compared twice-daily doses of dabigatran (50, 75, 110, or 150 mg) in combination with ASA and either clopidogrel or ticlopidine with a standard DAPT regimen, failed to reveal a reduction in the rate of MI, stroke or CV death, although, compared with the DAPT regimen, a significant reduction in coagulation activity was noted [39]. At the time of writing, phase III evaluation of dabigatran in ACS has not been initiated.

Direct Factor Xa inhibitors

Factor Xa is upstream of prothrombin in the coagulation cascade and Factor Xa inhibition downregulates thrombin generation [20]. Oral direct Factor Xa inhibitors have, therefore, been investigated as potential partners for antiplatelet therapy after an acute ACS event.

Data from two placebo-controlled studies have been reported for the oral, direct Factor Xa inhibitor apixaban: the phase II Apixaban for Prevention of Acute Ischaemic Events (APPRAISE)-1 study and the phase III APPRAISE-2 study [40,41]. In APPRAISE-1 (which studied 1715 patients with ACS), doses ranging from 2.5 mg twice daily to 20 mg once daily were evaluated. A trend towards a reduction in ischaemic events with the addition of apixaban to DAPT was accompanied by a dose-related increase in bleeding events; treatment with the two higher doses of apixaban was discontinued because of an excess of total bleeding events. Rates of ischaemic events (CV death, MI, severe recurrent ischaemia or ischaemic stroke) compared with placebo were nonsignificantly reduced with apixaban 2.5 mg twice daily (HR 0.73; $P = 0.21$) and apixaban 10 mg once daily (HR 0.61; $P = 0.07$). In APPRAISE-2, the subsequent phase III study (which included >7000 patients with ACS), addition of a 5 mg dose of apixaban twice daily to ASA alone or to a DAPT regimen (predominantly ASA + clopidogrel) was terminated early owing to an excess of major bleeding events and failure to achieve a significant reduction in ischaemic events compared with either ASA or DAPT alone. The primary efficacy endpoint (CV death, MI or ischaemic stroke) occurred in 7.5% of patients treated with apixaban vs. 7.9% of those who received placebo + antiplatelet therapy (HR 0.95; $P = 0.51$; *Figure 2*). However, it is worth noting that this study recruited a population of patients who were already at high risk of recurrent CV events and included a high proportion of patients with diabetes, prior MI and cerebrovascular disease, as well as patients who had not undergone revascularization for their index event.

More positive data have emerged for another oral, direct Factor Xa inhibitor: rivaroxaban. Data from the phase II Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects

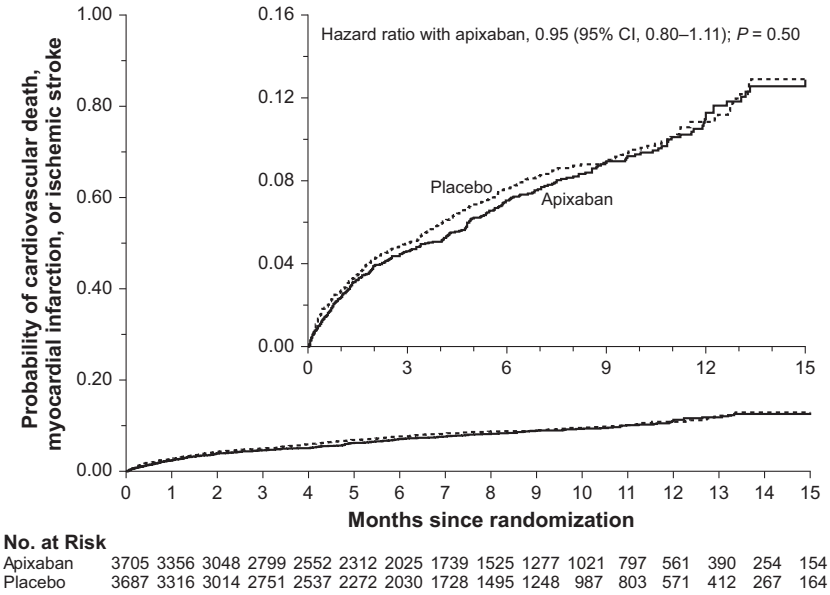

Figure 2 The probability of CV death, MI or ischaemic stroke during 15 months of follow-up among patients treated with apixaban or placebo after an ACS event [41]. ACS, acute coronary syndrome; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.

with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction-46 (ATLAS ACS TIMI 46) study and the phase III ATLAS ACS 2 TIMI 51 trial are available [42,43]. The phase II ATLAS ACS TIMI 46 study was a comprehensive dose-finding exercise in which total daily doses of rivaroxaban ranging from 5 to 20 mg, administered as once- or twice-daily regimens, were evaluated in a cohort of 3491 patients with ACS when added either to ASA alone (Stratum 1) or to DAPT (principally ASA + clopidogrel; Stratum 2) [42]. Patients were randomized within each stratum to receive either rivaroxaban or placebo. Consistent with the observations from trials of other direct Factor Xa inhibitors, a dose-dependent increase in bleeding events was noted. In general, lower rates of bleeding events were observed when rivaroxaban was administered in twice-daily divided doses rather than as a single, once-daily dose. In terms of efficacy, with the addition of rivaroxaban (all doses pooled), a trend towards a reduction in the time to the first episode of death, MI, stroke or severe recurrent ischaemia requiring revascularization was noted (5.6% vs. 7.0%; HR 0.79; 95% CI 0.60–1.05; $P = 0.10$). To determine the most appropriate doses for phase III evaluation, an exploratory net clinical benefit analysis was conducted and showed that the two lowest doses (2.5 and 5 mg twice daily) were associated with a reduced risk for the composite endpoint of death, MI, stroke or Thrombolysis in Myocardial Infarction major or minor bleeding events. The analysis also showed that the two lowest doses (2.5 and 5 mg twice daily) in combination with ASA alone or DAPT alone were associated with a trend towards a net clinical benefit compared with placebo in combination with ASA alone (HR 0.59; 95% CI 0.30–1.16) or DAPT alone (HR 0.85; 95% CI 0.47–1.54); these were the doses that were selected for further evaluation in the phase III ATLAS ACS 2 TIMI 51 study [44].

The phase III ATLAS ACS 2 TIMI 51 study randomized 15 526 patients, 15 350 of whom received one of the two rivaroxaban dose regimens or placebo, in addition to standard medical therapy of ASA with (Stratum 2) or without (Stratum 1) a thienopyridine (DAPT was the intended therapy for 93% of the study population) [43]. Both doses were associated with a significant reduction in the risk of the composite endpoint of death from CV causes, MI or stroke (*Figure 3*). For the 2.5 mg dose of rivaroxaban, the reduction in risk of the composite primary endpoint was 16% compared with placebo (HR 0.84; 95% CI 0.72–0.97; $P = 0.02$), with a 34% reduction in the risk of death from CV causes alone (HR 0.66; 95% CI 0.51–0.86; $P = 0.002$) and a 32% reduction in the risk of death from all causes (HR 0.68; 0.53–0.87; $P = 0.002$) (*Table 1*). For the 5 mg twice-daily dose, the reduction in risk of the composite primary endpoint was 15% compared with placebo (HR 0.85; 95% CI 0.73–0.98; $P = 0.03$), with a more modest and not statistically significant risk reduction of 6% for CV mortality (HR 0.94; 95% CI 0.75–1.20; $P = 0.63$). The reduction in the risk of the primary endpoint was consistent across all patient

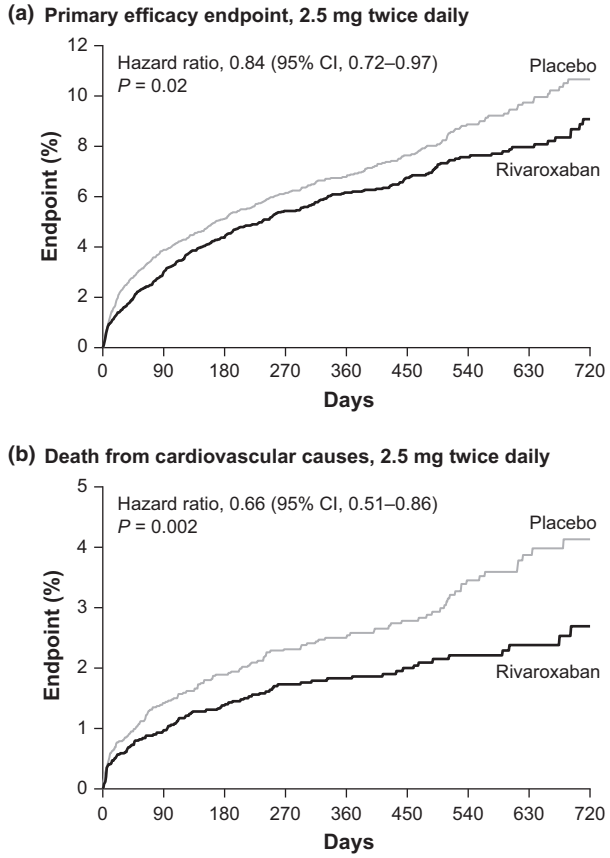

Figure 3 The probability of (a) CV death, MI, stroke, or (b) death from CV causes during follow-up in patients treated with rivaroxaban 2.5 mg bid or placebo after an ACS event [43]. ACS, acute coronary syndrome; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.

subgroups analysed except for those with a history of prior stroke. Furthermore, a statistically significant reduction in the risk of stent thrombosis was observed with rivaroxaban 2.5 mg twice daily compared with placebo in patients with a pre-existing stent or who had a stent placed for their index event (HR 0.61; 95% CI 0.39–0.94; $P = 0.023$) [45]. However, the reduction did not reach statistical significance for the 5 mg twice-daily dose ($P = 0.089$) [45].

An iterative landmark analysis showed that mortality outcomes of patients who experienced major bleeding and survived for at least a further 30 days were similar to outcomes for propensity-matched controls [46]. Although the overall rate of major bleeding events in ATLAS ACS 2 TIMI 51 was higher with rivaroxaban than with placebo (2.1% vs. 0.6%, respectively; $P < 0.001$), fatal bleeding events were rare and occurred at a similar rate with both rivaroxaban and placebo (0.3% vs. 0.2%, respectively; $P = 0.66$) [43]. This finding mirrored the noted increase in intracranial haemorrhage events but not in fatal intracranial haemorrhage events associated with rivaroxaban (*Table I*). The safety analysis favoured the 2.5 mg twice-daily dose with a lower rate of clinically significant bleeding (1.8% compared with 2.4% with 5 mg twice daily) [43].

The 2.5 mg twice-daily dose was subsequently selected for regulatory submission based in part on a more detailed comparison of the balance between efficacy and safety for the 5 and 2.5 mg doses [47]. Although both doses reduced the rate of CV events in patients with ACS receiving antiplatelet therapy, the 2.5 mg dose was associated with lower incidence of mortality and fewer bleeding complications. In a net clinical benefit analysis (to evaluate fatal or irreversible events prevented or caused) for the rivaroxaban 2.5 mg dose, presented at the American Heart Association Scientific Sessions in 2012, it was found that 87 patients would need to be treated for 1 year to prevent one fatal or irreversible ischaemic event, compared with 984 patients to cause one fatal or irreversible harmful event [48].

Acute coronary syndrome is an umbrella term that covers both MI (with or without ST-elevation) and UA. To make a differential diagnosis between MI and UA, the cardiac biomarker level must be determined, with elevated levels supporting a diagnosis of MI. Cardiac troponin is a biomarker currently recommended in clinical guidelines to distinguish between MI and UA [1], although others, such as CK-MB, are also used. A retrospective analysis of data from the ATLAS ACS 2 TIMI 51 trial in patients with elevated cardiac biomarkers (and without prior stroke or transient ischaemic attack) revealed a greater efficacy benefit for rivaroxaban 2.5 mg twice daily in this subgroup compared with the overall study population [27]. For the composite primary endpoint of CV death, MI or stroke, the absolute risk reduction was 1.3% for rivaroxaban versus placebo in the overall population (HR 0.84; $P = 0.02$) compared with 1.7% in the subgroup of patients with elevated biomarkers (HR 0.80; $P = 0.007$) (*Table II*). A similar pattern – for a numerically increased risk – was observed for CV death ($P < 0.001$).

Based on the results of these two studies, in May 2013, the European Commission approved the use of rivaroxaban 2.5 mg twice daily in patients with

Table I ATLAS ACS 2 TIMI 51 trial – efficacy and safety outcomes[a] [43].

Endpoint, *n* (%)[b]	Rivaroxaban 2.5 mg bid	Rivaroxaban 5 mg bid	Placebo	Rivaroxaban 2.5 mg bid vs. Placebo		Rivaroxaban 5 mg bid vs. Placebo	
				HR (95% CI)[c]	*P*-value[d]	HR (95% CI)[c]	*P*-value[d]
Efficacy outcomes[e]	*N* = 5114	*N* = 5115	*N* = 5113				
Primary endpoint[f]	313 (9.1)	313 (8.8)	376 (10.7)	0.84 (0.72–0.97)	*P* = 0.02	0.85 (0.73–0.98)	*P* = 0.03
Death from CV causes	94 (2.7)	132 (4.0)	143 (4.1)	0.66 (0.51–0.86)	*P* = 0.002	0.94 (0.75–1.20)	*P* = 0.63
MI	205 (6.1)	179 (4.9)	229 (6.6)	0.90 (0.75–1.09)	*P* = 0.27	0.79 (0.65–0.97)	*P* = 0.02
Stroke							
Any	46 (1.4)	54 (1.7)	41 (1.2)	1.13 (0.74–1.73)	*P* = 0.56	1.34 (0.90–2.02)	*P* = 0.15
Ischaemic	30 (1.0)	35 (0.9)	34 (1.0)	0.89 (0.55–1.45)	*P* = 0.64	1.05 (0.65–1.68)	*P* = 0.84
All-cause death	103 (2.9)	142 (4.4)	153 (4.5)	0.68 (0.53–0.87)	*P* = 0.002	0.95 (0.76–1.19)	*P* = 0.66
Stent thrombosis	47 (2.2)	51 (2.3)	72 (2.9)	0.65 (0.45–0.94)	*P* = 0.02	0.73 (0.51–1.04)	*P* = 0.08
Safety outcomes[e]	*N* = 5115	*N* = 5110	*N* = 5125				
TIMI major bleeding not related to CABG	65 (1.8)	82 (2.4)	19 (0.6)	3.46 (2.08–5.77)	*P* < 0.001	4.47 (2.71–7.36)	*P* < 0.001
TIMI minor bleeding	32 (0.9)	49 (1.6)	20 (0.5)	1.62 (0.92–2.82)	*P* = 0.09	2.52 (1.50–4.24)	*P* < 0.001
Intracranial haemorrhage	14 (0.4)	18 (0.7)	5 (0.2)	2.83 (1.02–7.86)	*P* = 0.04	3.74 (1.39–10.07)	*P* = 0.005
Fatal bleeding	6 (0.1)	15 (0.4)	9 (0.2)	0.67 (0.24–1.89)	*P* = 0.45	1.72 (0.75–3.92)	*P* = 0.20

bid, twice-daily; CABG, coronary artery bypass graft; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

[a]Event rates are reported as Kaplan–Meier estimates through 24 months and so are not presented as numerical percentages.

[b]*n* (%): n is the number of subjects with event, % = hazard rate in the corresponding treatment group based on a stratified Cox proportional hazards model.

[c]HR (95% CI): Hazard ratios (95% confidence interval) as compared to placebo arm are based on the stratified (by standard of care with ASA or ASA + thienopyridine) Cox proportional hazards model.

[d]*P*-values (two-sided) as compared to placebo arm are based on the stratified (by standard of care with ASA or ASA + thienopyridine) log rank test.

[e]*n* = number of subjects at risk; for efficacy events the mITT (excluding three potentially noncompliant study sites) Analysis Set was used; for safety events the treatment-emergent Safety Analysis Set was used.

[f]Primary efficacy endpoint as adjudicated by the CEC: first occurrence of CV death, MI or stroke.

elevated biomarkers after ACS; specifically rivaroxaban 2.5 mg, co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers [27].

LESSONS FROM THE PAST

The past two decades have witnessed marked improvements in the care available for patients after an ACS event. The recognition that these patients face a significant and ongoing risk of recurrent and potentially life-threatening CV events has driven the search for suitable long-term treatments to reduce this risk. Antiplatelet therapy is the cornerstone of this long-term risk reduction strategy and, in recent years, oral anticoagulation therapy has shown a potential for additional efficacy benefits, particularly in patients with non-ST-elevation MI [1].

The safety and logistic limitations of 'triple therapy' regimens including VKAs continue to restrict their clinical utility as a long-term solution for patients after an ACS event [1,10], and a number of novel OACs have been evaluated as potential alternative candidates to overcome the limitations of warfarin. The greatest challenge has been and continues to be achieving an acceptable balance between the risk of bleeding (which is a challenge with all antithrombotic agents) and efficacy in terms of clinically relevant reductions in the risk of further CV events. In this regard, dose selection may be an important consideration for the novel OACs. In the phase III APPRAISE-2 study for apixaban, the dose selected for evaluation (5 mg twice daily) was the same as that trialled for stroke prevention in patients with atrial fibrillation [41]. By contrast, in the phase III ATLAS ACS 2 TIMI 51 study for rivaroxaban, the total daily doses administered were equivalent to one-quarter to one-half of the dose regimen trialled and approved for

Table II ATLAS ACS 2 TIMI 51 trial – incidence rates of efficacy and safety outcomes in all patients and in those with elevated cardiac biomarkers and without prior stroke/transient ischaemic attack [27].

		Incidence rate, %				
Endpoint	Population[a]	Rivaroxaban 2.5 mg bid[b]	Placebo[b]	ARR[e], %	HR (95% CI)[f]	*P*-value[g]
CV death, MI or stroke	Overall	6.1	7.4	1.3	0.84 (0.72–0.97)	$P = 0.020$*
	Elevated biomarkers (without prior stroke/TIA)	6.2	7.9	1.7	0.80 (0.68–0.94)	$P = 0.007$**
CV death	Overall	1.8	2.8	1.0	0.66 (0.51–0.86)	$P = 0.002$**
	Elevated biomarkers (without prior stroke/TIA)	1.7	3.1	1.4	0.55 (0.41–0.74)	$P < 0.001$**
Stroke (ischaemic or haemorrhagic)	Overall	0.9	0.8	0.1	1.13 (0.74–1.73)	$P = 0.562$
	Elevated biomarkers (without prior stroke/TIA)	0.9	0.7	0.2	1.23 (0.75–2.02)	$P = 0.403$
MI	Overall	4.0	4.5	0.5	0.90 (0.75–1.09)	$P = 0.270$
	Elevated biomarkers (without prior stroke/TIA)	4.3	4.9	0.6	0.88 (0.72–1.08)	$P = 0.215$
TIMI major bleeding not related to CABG[c]	Overall	1.3	0.4	0.9	3.46 (2.08–5.77)	$P < 0.001$
	Elevated biomarkers (without prior stroke/TIA)	1.3	0.4	0.9	3.44 (1.97–6.01)	$P < 0.001$
Stent thrombosis (in patients who underwent PCI)[d]	Overall	1.3	2.0	0.7	0.64 (0.43–0.95)	$P = 0.026$
	Elevated biomarkers (without prior stroke/TIA)	1.4	2.0	0.6	0.64 (0.42–0.96)	$P = 0.028$

bid, twice-daily; CABG, coronary artery bypass graft; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

*Statistically superior.

**Nominally significant.

[a]For efficacy events, the mITT (excluding three potentially noncompliant study sites) Analysis Set was used; for safety events, the treatment-emergent Safety Analysis Set was used. For stent thrombosis, the component of the mITT population who had undergone PCI (either history of stent or for the index event) was used.

[b]mITT populations: Rivaroxaban 2.5 mg bid: $N = 5114$ overall, $n = 4104$ elevated biomarkers; Placebo: $N = 5113$ overall, $n = 4160$ elevated biomarkers.

[c]Safety Analysis Set populations: Rivaroxaban 2.5 mg bid: $N = 5115$ overall, $n = 4096$ elevated biomarkers; Placebo: $N = 5125$ overall, $n = 4157$ elevated biomarkers.

[d]mITT population for PCI patients: Rivaroxaban 2.5 mg bid: $N = 3114$ overall, $n = 2757$ elevated biomarkers; Placebo: $N = 3096$ overall, $n = 2759$ elevated biomarkers.

[e]ARR = Absolute risk reduction (percentage points) vs. placebo (difference of incidence rates between placebo and rivaroxaban).

[f]HR (95% CI): Hazard ratios (95% confidence interval) as compared to placebo arm are based on the stratified (by standard of care with ASA or ASA + thienopyridine) Cox proportional hazards model.

[g]*P*-values (two-sided) as compared to placebo arm are based on the stratified (by standard of care with ASA or ASA + thienopyridine) log rank test.

stroke prevention in atrial fibrillation (20 mg once daily) [43]. However, other differences between the trials, such as the populations enrolled, may also have contributed to the different results obtained.

LOOKING TO THE FUTURE

The past decade has seen a significant amount of activity in evaluating oral anticoagulation strategies for secondary prevention after ACS. One outcome of this activity is the approval of the OAC rivaroxaban for use in the prevention of atherothrombotic events after an ACS in adult patients with elevated cardiac biomarkers [49]. But what can we expect to achieve in the future?

The achievement of an acceptable benefit–risk profile with rivaroxaban in this setting, and the subsequent approval of the therapy, gives us the opportunity to evaluate this approach on a larger scale. Data from postmarketing surveillance studies and registries, and growing clinical experience will be extremely valuable for assessing the utility of the dual-pathway approach using rivaroxaban in ACS and providing further refinement about how, in whom and when anticoagulant therapy should be implemented after an ACS event. As

reported, the benefit of OAC compared with placebo was greater in the subgroup of patients with elevated cardiac biomarkers and without prior stroke or transient ischaemic attack than in the overall population included in the phase III study of rivaroxaban, forming the basis for this agent's approved indication [27]. The introduction of the newer antiplatelet agents ticagrelor and prasugrel will necessitate further studies to determine the benefit–risk profile of dual-pathway strategies involving these newer agents.

These remaining questions notwithstanding, this is an exciting time in secondary prevention of ischaemic events after ACS. It is not only encouraging to look back to where we were a decade ago and to review the reduction in recurrence rates we have since achieved but also exciting to look forward to what further progress we may achieve for patients with ACS in the coming years.

SUMMARY

An ACS event is a medical emergency that requires rapid, potentially life-saving medical intervention. After an ACS event, patients face an increased and ongoing risk of further CV events and now routinely receive antiplatelet therapy to reduce this risk. Evidence suggests a period of elevated thrombin generation of at least 6 months after an ACS event, a phenomenon that is thought to contribute to this residual risk in patients receiving therapies targeted predominantly at platelets. Given that the addition of anticoagulant therapy to antiplatelet therapy has been shown to provide an additional risk reduction, research efforts are now focused on evaluating the efficacy of novel OACs in this setting. Although trials with the direct thrombin inhibitor dabigatran and the direct Factor Xa inhibitor apixaban were disappointing, more positive data have recently emerged for another oral, direct Factor Xa inhibitor, rivaroxaban. Despite the failure of the apixaban phase III trial to demonstrate a benefit in terms of ischaemic risk reduction, the efficacy trends in several of the trials described in this review provide evidence that inhibition of coagulation may yield benefits in ACS. The achievement of an acceptable benefit–risk profile with rivaroxaban in this setting provides vindication of the dual-pathway approach in ACS.

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ABBREVIATIONS LIST

ACS – acute coronary syndrome
ARR – absolute risk reduction
ASA – acetylsalicylic acid (aspirin)
bid – twice daily
CABG – coronary artery bypass graft
CEC – clinical events committee
CI – confidence interval
CV – cardiovascular
DAPT – dual antiplatelet therapy
HR – hazard ratio
MI – myocardial infarction
mITT – modified intent-to-treat
OAC – oral anticoagulant
OR – odds ratio
PCI – percutaneous coronary intervention
TIA – transient ischaemic attack
TIMI – Thrombosis in Myocardial Infarction
UA – unstable angina
VKA – vitamin K antagonist

CONFLICTS OF INTEREST

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