New oral anticoagulant agents after ACS

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Abstract

Despite tremendous progress in the management of patients with an acute coronary syndrome (ACS), morbidity and mortality remains high even in stable patients after discharge. The benefit of adding vitamin K antagonists (VKA) on top of antiplatelet therapy to prevent recurrent ischaemic events after an ACS has been successfully studied in the past. Because of their need for frequent monitoring and drug and food interactions, however, systematic long-term use of VKA has not been recommended in this setting. The new oral anticoagulants offer several advantages compared to VKA, including a faster onset and offset of action and the absence of frequent monitoring. In this review, we evaluate the current evidence and practical consequences of using the oral direct thrombin inhibitor dabigatran or the oral anti factor Xa inhibitors apixaban, rivaroxaban, and darexaban in stable ACS patients.

Keywords

Acute coronary syndrome, anticoagulation, antiplatelet

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Introduction

Long-term evidence-based therapies to reduce the risk of recurrent events after an acute coronary syndrome (ACS) now include statins, angiotensin-converting enzyme inhibitors, beta-blockers, and antiplatelet agents. Several landmark studies have established the benefit and safety of a P2Y₁₂ receptor blocker such as clopidogrel, prasugrel, or ticagrelor on top of low-dose aspirin.^{1–3} Despite tremendous progress in the management of patients with an ACS, however, morbidity and mortality remains unacceptably high. In the GRACE registry, mortality was almost 20% during 5-year follow up, vs. 9% myocardial infarction, 7% stroke, and 17% subsequent revascularizations.⁴ Rehospitalizations are even more common, on average 1.6 times per patient, and 9% of patients require even more than five readmissions during the same period.⁴ In addition, most deaths occur after discharge. Even taking into account that clinical trials usually recruit patients with a somewhat lower overall risk, about one out of six patients experiences an ischaemic event in contemporary ACS trials during the first year after their index event.^{1,2} Hence, it makes sense to consider and evaluate additional long-term therapies, including novel anti-inflammatory or lipid-modifying drugs, but also old and new antiplatelet and anticoagulant

agents in ACS patients. In this review, we evaluate the current evidence and practical consequences of the oral direct thrombin (Factor II) inhibitor (DTI) dabigatran and the oral anti-factor Xa (FXa) inhibitors apixaban, rivaroxaban, and darexaban in ACS.

What came before: warfarin after ACS

Adding anticoagulants to antiplatelet therapy after an ACS is not a new concept, but has been studied quite extensively in the past. From a pathophysiological point of view, this is an attractive approach: although platelet activation and adhesion is essential for atherothrombosis, it is thrombin that remains the pivotal factor leading to thrombus formation.⁵ In addition, the coagulation system remains considerably activated during months if not longer after an ACS.⁶ Traditional oral anticoagulants such as warfarin reduce the

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Figure 1. Event rates with vitamin K antagonists or aspirin in acute coronary syndrome patients.⁷

synthesis of the four vitamin K-dependent procoagulants factors II, VII, IX, and X. A meta-analysis of ten trials including 5938 patients assessed the risk vs. benefit of intensive warfarin plus aspirin vs. aspirin alone after an ACS (Figure 1).⁷ Warfarin in combination with aspirin was associated with a significantly lower risk of myocardial infarction (risk ratio, RR, 0.56, 95% CI 0.46–0.69), ischaemic stroke (RR 0.46, 95% CI 0.27–0.77), and revascularization (RR 0.80, 95% CI 0.67–0.95); there was no difference in mortality rates. There was an increased risk of major bleeding (RR 2.48, 95% CI 1.67–3.68), with an overall absolute annual risk of 1.5%. Unsurprisingly, the lowest risk/benefit ratio was observed in patients at high ischaemic risk and low bleeding risk.

A few studies dating from the pre-thienopyridine era also examined whether low-to-moderate-intensity anticoagulation could reduce the risk of bleeding while maintaining a protective effect on recurrent ischaemic events. In the open-label ASPECT-2 study, high-intensity oral anticoagulation with warfarin (international normalized ratio, INR, 3.0–4.0) or medium-intensity anticoagulation with aspirin (INR 2.0–2.5) vs. aspirin alone was tested in 999 patients with ACS.⁸ Both strategies reduced the primary combined endpoint of death, myocardial infarction, and stroke compared to aspirin alone. Combination therapy was associated with a non-significant 2-fold increase in major bleeding and a significant 3-fold increase in minor bleeding. In the WARIS-II study, 3630 patients with ST-segment elevation myocardial infarction (STEMI) were randomized to high-intensity oral anticoagulation with warfarin (INR 2.8–4.2) or medium-intensity anticoagulation (INR 2.0–2.5) with aspirin (75 mg), or aspirin alone (160 mg).⁹ Warfarin alone or in combination with low-dose aspirin appeared to be superior to aspirin in reducing the composite endpoint of death, re-infarction, and stroke. Unfortunately, major bleeding rate was more than 3-fold higher in both warfarin groups. Other studies evaluating a lower intensity

of anticoagulation failed to show a significant benefit for warfarin or warfarin plus aspirin vs. aspirin in monotherapy.^{10,11} In addition, a significant reduction of ischaemic events was only seen in countries with high rates of compliance to oral anticoagulation in the OASIS-2 trial.¹² Taken together, high-intensity oral anticoagulation or moderate-intensity oral anticoagulation plus aspirin seem to be effective in reducing ischaemic complications after acute coronary syndromes, but are associated with an increased risk of bleeding, while low-intensity anticoagulation does not appear to be beneficial.

A new era of oral anticoagulants

The oral vitamin K antagonist (VKA) warfarin is far from an ideal drug. The anticoagulant response to warfarin is inconsistent and unpredictable and varies over time, and maintaining optimal anticoagulation can be challenging, especially in elderly persons. In an individual patient, the level of anticoagulation is influenced by genetic factors, comorbidities, diet, concomitant medication, age, and compliance. Also, several drug-related characteristics limit its practical use, including its slow onset and offset of action and multiple drug and food interactions. Due to its narrow therapeutic window, warfarin also requires frequent anticoagulant monitoring and dose adjustments to avoid both thrombotic risk due to a low INR and bleeding risk due to a high INR. As a consequence, new anticoagulant agents targeting different levels of the coagulation cascade have been developed to overcome some of warfarin's drawbacks. Especially oral DTI and oral FXa inhibitors have promised to become safer and easier alternatives to VKAs, and have been extensively evaluated in the setting of prophylaxis and treatment of venous thrombosis and for stroke prevention in atrial fibrillation (AF).

Oral direct thrombin inhibitors

Ximelagatran. Ximelagatran was the first oral DTI available. It was evaluated in 1900 patients with a recent non-ST-segment elevation ACS (NSTEMI-ACS) or STEMI in the ESTEEM (Efficacy and Safety of the oral direct thrombin inhibitor ximelagatran in patients with recent myocardial damage) trial.¹³ Ximelagatran was associated with a 24% reduction in the composite primary endpoint of death, myocardial infarction, and recurrent ischaemia (hazard ratio, HR, 0.76, 95% CI 0.59–0.98, $p=0.036$). In a post-hoc analysis, the 'thrombotic' endpoint of death, myocardial infarction, and stroke also was reduced by 34% (HR 0.66, 95% CI 0.48–0.90) with ximelagatran. Unfortunately, ximelagatran was not further developed because of severe liver toxicity.

Dabigatran. Dabigatran is a new and safer oral DTI, with a serum half-life of 12–17 hours. About 80% is renally

excreted and it does not require regular INR monitoring. In the RE-LY trial, dabigatran 110 mg b.i.d. was shown to be non-inferior to warfarin for the prevention of stroke in patients with AF, while reducing the risk of major bleeding.¹⁴ Patients receiving 150 mg dabigatran b.i.d. even had a significantly lower risk of stroke or systemic embolism compared to warfarin and a similar risk of major bleeding.¹⁴ With the higher dose, there was an increased risk of myocardial infarction (RR 1.38, 95% CI 1.00–1.91) but a lower risk of ischaemic strokes as well as cardiovascular and all-cause death (RR 0.85, 95% CI 0.72–0.99; RR 0.88, 95% CI 0.77–1.0). Fatal intracerebral bleedings were significantly reduced with both dosages of dabigatran (60–70% RR reduction).

Dabigatran in addition to dual antiplatelet therapy was subsequently evaluated in patients with a recent (<14 days) NSTEMI-ACS or STEMI in the RE-DEEM study.¹⁵ Patients were required to have at least one additional risk factor for new cardiovascular complications, such as age ≥ 65 years, diabetes, previous myocardial infarction in addition to the index event, congestive heart failure (ejection fraction <40%), moderate chronic kidney disease, or not undergoing revascularization for the index event. A total of 1861 patients were randomized to placebo or 50, 75, 110, or 150 mg dabigatran b.i.d., at a mean of 7.5 days after their initial event. The proportion of patients on dual antiplatelet therapy remained very high throughout the 6-month follow up (84%). Although the overall incidence of major bleeding events was relatively low, there was a dose-dependent increase in the risk of major or clinically relevant minor bleeding events: HR 1.7 (95% CI 0.7–4.5) for 50 mg b.i.d., HR 2.2 (95% CI 0.9–5.3) for 75 mg b.i.d., HR 3.9 (95% CI 1.7–8.9) for 110 mg b.i.d., and HR 4.3 (95% CI 1.9–9.8) for 150 mg b.i.d. The increased risk of bleeding associated with dabigatran was consistent across most of the subgroups. Event rates were higher in female and elderly (>75 years) patients in the 110 and 150 mg b.i.d. dose groups; no intracranial haemorrhages were observed. In addition, ischaemic events were infrequent overall and numerically lower with the two highest doses compared to the 50 mg dose arm. Taken together, dabigatran on top of dual antiplatelet therapy in high-risk ACS patients increases the risk of significant bleeding 2–4-fold, while its effect on preventing ischaemic events remains unclear. To date, a large phase III trial to evaluate outcome with dabigatran in this setting has not been planned.

Oral FXa inhibitors

To date, three oral FXa inhibitors (apixaban, rivaroxaban, and darenxaban) have been evaluated in patients with a recent ACS; a fourth one, edoxaban, has not yet been used in this setting. As with dabigatran, the appeal of these new anticoagulants is in their ease of use, including no need for frequent monitoring, more consistent and predictable

anticoagulation, and fewer food or drug interactions. The safety and benefit of apixaban and rivaroxaban have been extensively evaluated in stroke prevention in AF and prophylaxis and treatment of venous thromboembolism. Apixaban at a dose of 5 mg b.i.d. was shown to be superior to warfarin in the prevention of stroke and systemic embolism in the ARISTOTLE trial and was associated with less bleeding and lower mortality.¹⁶ Rivaroxaban, on the other hand, was found to be non-inferior to warfarin in preventing stroke, and resulted in fewer intracranial and fatal bleedings (rivaroxaban was superior to VKA in an ‘on-treatment’ analysis).¹⁷

Apixaban. A range of doses of apixaban was compared to placebo in patients with a recent ACS in the APPRAISE trial.¹⁸ Patients having at least one additional risk factor for recurring events (including age ≥ 65 years, elevated cardiac markers, heart failure, diabetes, or prior infarction) could be enrolled, when they were clinically stable, within 7 days of STE- or NSTEMI-ACS. As apixaban’s half-life is about 12 hours, both once-daily and twice-daily doses were tested: 2.5 mg b.i.d., 10 mg q.d., and 10 mg b.i.d. vs. 20 mg q.d. The primary endpoint was major or clinically relevant non-major bleeding complications during a 6-month follow-up period. Nearly all patients received aspirin and over 75% received dual antiplatelet therapy. The two low doses were associated with an increase in major or clinically relevant bleeding (5.7 and 7.9%, respectively, vs. 3.0% for placebo). As expected, bleeding complications were even more frequent with the two higher doses. In all groups, the addition of clopidogrel even further increased the risk of bleeding. Although not powered for ischaemic events, the incidence of cardiovascular death, MI, recurrent ischaemia, or stroke tended to be lower across all doses, and this effect appeared to be more pronounced in patients not taking clopidogrel. Interestingly, the overall net clinical benefit (i.e. reduction in ischaemic events minus bleeding) seen with 2.5 mg b.i.d. (–0.3%) and 10 mg q.d. (–1.6%) was largely driven by a net benefit in higher-risk non-revascularized patients not taking clopidogrel. Conversely, the bleeding risk was higher and the benefit smaller in patients on dual antiplatelet therapy.

In APPRAISE-2, 5 mg b.i.d. was subsequently tested in high-risk ACS patients, a dose not evaluated in the preceding dose-finding study.¹⁹ Patients needed to be clinically stable and were randomized after a median of 6 days after their index event and about 2 days after discontinuation of parenteral antithrombotic therapies. The primary endpoint was the composite of cardiovascular death, myocardial infarction, or stroke. In part because medical management only was one of the enrichment criteria for inclusion, over 50% of the total population was not revascularized after the index event.

The trial was terminated prematurely after enrolling 7392 of the planned 10,800 patients because of an increase

Figure 2. Event rates with factor Xa or placebo in ATLAS-2 and APPRAISE-2.^{19,28}

* $p < 0.05$.

in major bleeding complications, with no counterbalancing benefit in ischaemic events (Figure 2). The primary endpoint was not significantly different between patients taking apixaban or placebo (7.5% vs. 7.9%, $p = 0.51$), as were all secondary efficacy outcomes including stent thrombosis. In addition, no benefit was observed in patients taking only aspirin; the lack of benefit was also consistent across all subgroups. In contrast, major bleeding complications were more than twice as frequent with apixaban than with placebo (HR 2.59, 95% CI 1.50–4.46). There were also more fatal bleeding events and intracranial haemorrhages with apixaban. The increased risk of bleeding was not only irrespective of antiplatelet regimen or revascularization, but also consistent among all other key subgroups.

Rivaroxaban. In the phase II ATLAS trial, clinically stable STE- or NSTEMI-ACS patients were randomized to rivaroxaban or placebo.²⁰ Rivaroxaban was given in doses ranging from 5 to 20 mg, either given in a single dose or the same dose given twice daily. Aspirin doses of 75–100 mg were recommended, and enrolment was stratified according to thienopyridine use as to local practice recommendations. The primary endpoint was clinically significant bleeding (major or minor thrombolysis in myocardial infarction or requiring medical attention). Although the overall major bleeding rates were low, there was a dose-dependent increase in clinically significant bleeding complications in patients only taking aspirin as well in those on dual antiplatelet therapy. Hazard ratios for the primary bleeding endpoint ranged from 2.2 (95% CI 1.2–3.9) with 5 mg to 5.1 (95% CI 3.4–7.4) with 20 mg. The increased risk of

bleeding was consistent among various key subgroups and irrespective of once-daily vs. twice-daily dosing. Bleeding was also more frequent in medically managed patients. Although the overall event rate was low, rivaroxaban was associated with lower risk of death, myocardial infarction, or stroke (HR 0.69, 95% CI 0.50–0.96), irrespective of once-daily or twice-daily dosing or thienopyridine use. Net clinical benefit, on the other hand, was significantly better in aspirin-only patients (HR 0.57, 95% CI 0.35–0.94 vs. placebo) but not in patients on dual antiplatelet therapy (HR 1.17, 95% CI 0.78–1.75) when combining all rivaroxaban doses. There was a trend towards net clinical benefit for the two lowest doses (2.5 and 5 mg b.i.d.); however, resulting in these doses taken forward in the large phase III ATLAS-2 trial.²¹

In ATLAS-2, 15,526 ACS patients were randomized to placebo or twice-daily doses of either 2.5 or 5 mg rivaroxaban. Clinically stable patients could be enrolled within 7 days after admission for a STE- or NSTEMI-ACS; randomization was stratified according to planned thienopyridine use. Patients needed to be >55 years of age, unless they either had diabetes or a previous myocardial infarction before the index event. Patients with a gastrointestinal bleeding within 12 months or a previous intracranial haemorrhage could not be randomized, as well as patients with a previous stroke or transient ischaemic attack requiring dual antiplatelet therapy. Median time from admission to randomization was 4.7 (95% CI 3.2–6.0) days. Thienopyridine use was planned in 93% of patients, and the mean duration of thienopyridine treatment was 13.3 months. The primary efficacy endpoint was cardiovascular death, myocardial infarction or stroke.

Rivaroxaban significantly reduced the risk of death, myocardial infarction, or stroke by 16% (HR 0.84, 95% CI 0.74–0.96), implicating one event prevented per 56 patients treated over a period of 2 years (Figure 2). In addition, cardiovascular death (including those related to haemorrhage) was also significantly lower with rivaroxaban (HR 0.80, 95% CI 0.65–0.99, $p=0.04$), as was stent thrombosis (HR 0.69, 95% CI 0.51–0.93) and myocardial infarction (HR 0.85, 95% CI 0.72–1.00, $p=0.047$). When assessed separately, both doses significantly reduced the primary efficacy endpoint, but only the 2.5 mg b.i.d. dose significantly reduced the risk of cardiovascular and all-cause death (HR 0.66, 95% CI 0.51–0.86, and HR 0.68, 95% CI 0.53–0.87, respectively). Conversely, myocardial infarction but not death was significantly lower with the 5 mg b.i.d. dose vs. placebo. Major non-coronary artery bypass graft-related bleeding complications, although infrequent, were almost 4 times more frequent with rivaroxaban (HR 3.96, 95% CI 2.46–6.38), irrespective of dose and consistent across key subgroups. No difference in fatal bleeding was observed (0.3% vs. 0.2% for placebo, $p=0.66$). Rates of fatal bleeding, minor bleeding complications or bleeding requiring medical attention were all significantly higher with the 5 mg b.i.d. dose compared to the very low dose.

Darexaban. The safety of a third oral FXa inhibitor, darexaban, was evaluated in the dose-ranging RUBY-1 study.²² Stable patients with a recent STEMI or NSTEMI-ACS with high-risk features ($n=1279$) and on dual antiplatelet therapy were randomized to placebo or one of six regimens of darexaban ranging from 10 to 60 mg daily, given as a single or b.i.d. dose. The primary endpoint was major and clinically relevant non-major bleeding during 6 months of follow up. There was a dose-dependent increase of bleeding, ranging from 5.6% in the 10 mg q.d. group to 11.3% in the 30 mg b.i.d. group, compared to 3.1% with placebo, but there were no fatal or intracranial haemorrhages. Pooling together all dose arms of darexaban, there was no decrease of the combined efficacy endpoint of all-cause death, myocardial infarction, stroke, and recurrent ischaemia. In contrast, the rates of ischaemic events were even numerically higher in the 30 and 60 mg doses, as well the risk of stent thrombosis in the combined darexaban group (1.1% vs. 0.4% for placebo). To date, an outcome (phase III) trial has not yet been started.

Theories and practical consequences

Taken at face value, the message distilled from these trials appears to be relatively straightforward: a low dose of rivaroxaban but not a high dose of apixaban on top of dual antiplatelet after an ACS improves outcome, at the price of an increased bleeding risk. Adding dabigatran or darexaban to dual antiplatelet therapy after an ACS also increases bleeding complications, but clinical outcome data are

lacking. Nevertheless, there are more shades of grey as to these results, and their practical implications of in these trials deserve a closer look.

Since APPRAISE-2 and ATLAS-2 enrolled patients with somewhat different risk profile and used different dosing strategies, it is difficult (and speculative) to try to compare both drugs directly. It might well be that the ‘secret’ of rivaroxaban lies in the very low dose used in ATLAS-2: 2.5 mg b.i.d., much lower than the 20 mg q.d. dose used in the AF trial ROCKET-AF. In contrast, the same high dose of apixaban shown to be beneficial in monotherapy in the AF trial ARISTOTLE was used in APPRAISE-2 on top of dual antiplatelet therapy. Experience with parenteral anticoagulants in the acute setting has indeed taught that (very) low doses can be effective while minimizing bleeding risk.^{23,24} On the other hand, fixed-dose warfarin or low-intensity anticoagulation has not been shown to improve outcome in randomized studies before, as discussed previously. In addition, baseline risk was higher in APPRAISE-2 than in ATLAS; the finding that rivaroxaban’s benefit was consistent across all subgroups (except prior stroke), including elderly or patients with chronic kidney disease, suggest that this did not play a major role in the difference between outcome in both studies. On aggregate, (very) low doses of oral anticoagulants appear to be more effective than high doses when added to dual antiplatelet, while maintaining an acceptable bleeding risk.

The reduction in cardiovascular and all-cause mortality on top of dual antiplatelet therapy with low-dose rivaroxaban observed in ATLAS-2 is intriguingly unexpected. The beneficial effect of rivaroxaban on stent thrombosis as well as myocardial infarction for both doses in aggregate suggests that this is probably not a chance finding. On the other hand, there was no effect on myocardial infarction with the very low dose, nor was there a difference in death with a higher dose of rivaroxaban. This raises questions about the potential mechanisms of the mortality benefit observed with rivaroxaban. In part, this might be due to the higher bleeding risk with high-dose rivaroxaban, leading to premature discontinuation of antiplatelet therapy.

Dabigatran and the three FXa inhibitors tested all increase the risk of bleeding in patients already on dual antiplatelet therapy. This confirms previous experience with so-called triple therapy, irrespective of the indication.^{25,26} Rivaroxaban, at the very low dose that was shown to improve outcome, was associated with a 3.5-fold increase in major bleeding and an almost 3-fold increase in intracranial haemorrhage, while fatal bleeding was not increased. This implies that low-dose rivaroxaban appears to be particularly attractive for ACS patients with a relatively low bleeding risk. However, there was no significant interaction for treatment effect as to bleeding risk for all subgroups including those known to be at increased risk for bleeding such as the elderly or those with depressed renal function. A thorough risk–benefit assessment will be necessary in

daily practice, given the high proportion of elderly patients with significant comorbidities among those presenting with ACS. Although prior stroke was an exclusion criterion in ATLAS-2, the few patients with a prior stroke who did end up being randomized per protocol violation appeared to be harmed by adding rivaroxaban to their medical therapy. Taken together with the bleeding risk observed with the other agents, it seems to be unwise to consider long-term anticoagulation on top of dual antiplatelet therapy in patients with a prior stroke or transient ischaemic attack.

In both APPRAISE-2 and ATLAS-2, FXa inhibitors were tested on top of aspirin plus clopidogrel for most patients. It remains to be seen whether rivaroxaban's efficacy/safety profile can be maintained when added to the new P2Y₁₂ blockers prasugrel and ticagrelor as well. Both agents, although evaluated in different settings, have been shown to improve outcome after ACS compared to clopidogrel while increasing the risk of bleeding complications.^{1,2} The bleeding risk might become unacceptably high when combining rivaroxaban with either two, while its protective effect remains in question. In addition, adding rivaroxaban to ticagrelor or prasugrel might prove to be prohibitively costly. Although the price setting remains to be determined, adding rivaroxaban to generic clopidogrel might be an interesting alternative for ACS patients at about the same cost or only marginally higher cost than dual antiplatelet therapy with one of newer P2Y₁₂ inhibitors. Vice versa, low-dose rivaroxaban might be particularly appealing for ACS patients not taking clopidogrel. However, aspirin monotherapy was planned up front only for very few patients in ATLAS-2, so no firm conclusions can be drawn.

Except for dabigatran, the new anticoagulants discussed here have been successfully compared to warfarin for preventing stroke in AF. AF is fairly common in ACS patients, and is associated with a poorer outcome.²⁷ Per protocol, patients requiring oral anticoagulation, including those with AF, however, were excluded from the ACS trials. Yet, it is appealing to speculate about the optimal antithrombotic strategy for these patients. It is clear that apixaban at a dose that prevents stroke in AF does increase the risk of bleeding when added to dual antiplatelet therapy and does not additionally protect against recurrent coronary events. Likewise, dabigatran increases bleeding risk after ACS even at doses below those shown to reduce the risk of stroke in AF. On the other hand, low-dose rivaroxaban decreases the risk of recurrent ischaemic events and increases bleeding risk, but at a dose not evaluated in AF. This conundrum clearly shows that dedicated trials with these new agents in ACS patients with AF need to be considered.

Finally, in the setting of ACS, the new FXa blocking agents and DTIs have only been evaluated in clinically stable patients, after completing invasive procedures and cessation of parenteral therapies. It remains to be determined whether an earlier initiation is as safe and might prevent early events as well.

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