High platelet reactivity – the challenge of prolonged anticoagulation therapy after ACS

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Summary
Despite dual antiplatelet therapy (DAPT), one-year event rates after acute coronary syndrome (ACS) vary from 9–12%. The development of novel oral anticoagulants (NOAC) without a need for monitoring has initiated renewed interest for prolonged adjunctive anticoagulation. Importantly, the cornerstone of treatment after ACS consists of long-term DAPT. In that context, the NOACs have only been tested as adjunctive therapy. Of all new agents, only rivaroxaban—in a substantially lower dose than used for atrial fibrillation—has been demonstrated to improve outcome, albeit at the cost of bleeding. In selected cases, adjunctive therapy with dose-adjusted vitamin-K antagonists (international normalized ratio [INR] 2.0–3.0) can be considered as well. These two strategies of prolonged anticoagulation can be considered in case of ‘high platelet reactivity’, i.e. in patients at high risk of recurrent thrombotic events despite DAPT. Both during admission and after discharge for ACS, the use of NOACs in doses indicated for atrial fibrillation is strictly contra-indicated in patients on DAPT. In case of post-discharge anticoagulation therapy for atrial fibrillation, patients should preferably receive vitamin-K antagonists (INR 2.0–3.0), with discontinuation of one antiplatelet agent as soon as clinically justifiable. Importantly, the impact of prolonged anticoagulation (low-dose rivaroxaban, vitamin-K antagonists) as adjunctive to DAPT after ACS has not been addressed with the most potent antiplatelet agents (prasugrel, ticagrelor) and merits further study. Despite the potential indication of prolonged oral anticoagulation as adjunctive treatment, it remains to be established whether anticoagulation therapy could also be an alternative for either aspirin or thienopyridine treatment in selected ACS patients on DAPT.

Keywords
Clinical trials, oral anticoagulants, coronary syndrome, direct antithrombin agents, coagulation inhibitors, heparins

Introduction
With new antiplatelet agents as adjunctive to long-term aspirin treatment, outcome after acute coronary syndromes (ACS) has improved over the years (1, 2). To date, for the majority of patients aspirin and clopidogrel form the standard regimen, but more potent agents such as ticagrelor and prasugrel have been introduced as more efficacious alternatives for clopidogrel, especially in case of coronary interventions (3-5).

Despite the use of long-term dual antiplatelet therapy (DAPT) after myocardial infarction (MI) (6, 7), there is still a considerable rate of death, MI and stroke of about 9-12% of patients at one year (2-4). Moreover, the strategy of revascularisation has changed over the years, in that the proportion of patients treated with a percutaneous coronary intervention (PCI) has increased. Stent thrombosis is an infrequent, but ominous complication, with mortality rates of up to 45% (8-10). These findings call for further optimisation of antithrombotic regimens, both during hospital admission, but also after discharge.

High platelet reactivity (HPR) has been proposed as an indicator for adverse cardiac events, which could guide the choice of a more aggressive antithrombotic approach. So far, this approach cannot be substantiated by randomised evidence on clinical end-points, and we feel that this strategy cannot be supported as regular clinical approach (11-13).

In daily clinical practice, we are frequently faced with patients who experience recurrent thrombotic events despite dual antiplatelet therapy. In particular, this is a group of patients that merits further attention with regard to a more aggressive antithrombotic regimen.

In the formation of arterial thrombosis there is a strong interaction between the clotting cascade and circulating platelets (14). In the acute phase of acute coronary syndromes, the impact of anticoagulation therapy has been extensively studied, and several new agents have been developed that have affected outcome (15-21). Research with long-term anticoagulation treatment has so far been primarily dominated by vitamin K antagonists (VKAs). With the introduction of newer agents without need for monitoring, anticoagulation after discharge has become a more feasible option.

Given the need for more refined antithrombotic strategies in patients with thrombotic events despite dual antiplatelet therapy, we will shortly summarise the pathophysiology of clot formation and the clinical evidence of (long-term) anticoagulation therapy. In the context of the available data, we will address both the risks and benefits of potential treatment options that can be considered in patients in whom DAPT has been proven clinically ineffective.
**Pathophysiological rationale**

The vast majority of ACS are caused by (sub)acute thrombosis in a coronary artery, resulting in a subtotal (non ST elevation acute coronary syndrome) or total (ST elevation acute coronary syndrome) occlusion. The precipitating pathophysiological event is often rupture of a plaque, with exposure of subendothelial matrix. In response, platelets adhere to the damaged vessel wall (adhesion) and secrete chemooattractive substances, involved in the process of platelet aggregation and the stimulation of the coagulation cascade.

Three key players in the process of coagulation are the tissue factor (TF)-factor (F)FIIa complex, FXa and FIIa (Figure 1). Thrombin (FIIa) promotes the formation of a fibrin-rich blood clot, but it is also a potent activator of platelet aggregation (22). This demonstrates that coagulation and platelet aggregation are interrelated processes in the formation of a (sub)total occlusion.

Angiographic studies have confirmed this hypothesis, suggesting that anticoagulation therapy affects the risk of (re)occlusion on both the short- and the long-term (23-26).

Therefore, several studies have been conducted based upon the rationale that anticoagulants such as (in)direct thrombin inhibitors (DTIs), or FXa inhibitors could improve clinical outcome in ACS.

**Anticoagulation therapy in ACS: clinical evidence**

**Indirect thrombin inhibition**

The first randomised studies on the impact of anticoagulation therapy demonstrated that unfractionated heparin (UFH) resulted in a ~30% risk reduction in MI in patients treated with aspirin for unstable angina (15). Subsequently, low-molecular-weight heparins (LMWH) were developed, which seem slightly more efficacious than UFH (16). They have a better bioavailability and more predictable effect, which obviates the need for monitoring.

For patients with ST-elevation myocardial infarction (STEMI) treated with fibrinolysis similar observations hold true (17), and it is suggested that reocclusion rates are lower with the use of LMWH (27). The ease of longer administration (subcutaneous) and its more stable effect may both account for these observations.

After primary PCI the evidence for the routine use of heparin after the procedure is not very well established. It is often stated that thrombin inhibition can be discontinued after the procedure, with a few exceptions (28). Still, routine periprocedural use of fondaparinux seemed less efficacious than UFH in the setting of primary PCI, indirect evidence that routine anti-thrombin therapy seems indicated (19).

**Direct thrombin inhibition**

Whereas UFH and LMWH both act on FIIa and FXa, DTIs only act on FIIa, and are also able to inhibit clot-bound thrombin (22). In patients with non ST elevation ACS, bivalirudin results in lower bleeding complications when compared to the combination of UFH/LMWH with glycoprotein (GPIIb/IIIa) receptor blockers. This was observed without significant difference in efficacy. However, in the subgroup of patients without pretreatment with a thienopyridine bivalirudin seemed less efficacious, indirect evidence that this new drug may have a less intense antithrombotic effect (20).

In patients treated with fibrinolytic therapy, bivalirudin resulted in a significant reduction in the combined endpoint of mortality and reinfarction at 30-days when compared to UFH (29). For patients undergoing primary PCI again bleeding complications were markedly lower with the use of direct thrombin inhibition, mortality was lower and the composite of ischaemic events was similar to the control arm of indirect thrombin inhibition with/without use of a GPIIb/IIIa receptor blocker (21).

![Figure 1: The coagulation cascade and the pharmacological interventions.](image-url)
FXa-inhibition

Based on the hypothesis that interference in the earlier stages of coagulation, i.e. “higher in the coagulation cascade” (Figure 1), would require less potent drugs with potentially less bleeding complications FXa inhibitors have been developed. Fondaparinux is a synthetic pentasaccharide that selectively binds antithrombin and inhibits FXa.

In non-ST elevation ACS it has improved 30-day outcome compared to enoxaparin, and the achieved clinical benefit was primarily realized through a reduction in mortality. Notably, at hospital discharge (i.e. at the end of treatment), there was no difference in efficacy between fondaparinux and enoxaparin. The reduction in 30-day mortality was associated with a lower bleeding rate on fondaparinux as compared to enoxaparin (18). These observations demonstrate that the choice of in-hospital anticoagulation, can affect outcome after discharge.

The fact that guiding cathether thrombosis was more often observed with this agent indirectly underscores its modest antithrombotic efficacy (18, 19), and shows that outcome improved despite this reduced antithrombotic potency. Based on these cath-lab observations, intravenous administration of an indirect or DTI is the preferred agent of choice in case of early PCI for non STEMI, and for similar reasons, FXa-inhibitors should not be given as anticoagulant shortly before/during primary PCI.

As adjunctive agent to fibrinolysis, the efficacy and safety of fondaparinux has unequivocally been demonstrated with use of streptokinase. In case of fibrin-specific agents, which require adjunctive thrombin inhibition, no randomised controlled evidence is available with FXa-inhibitors.

Oral anti-FXa inhibitors have been the topic of interest for many years, providing the opportunity of a feasible form of extended anticoagulation after discharge. Ximelagatran was the first drug that showed the potential of such a strategy, but due to an unacceptable incidence of liver toxicity this drug has not undergone further development. Notably, in this study patients used aspirin monotherapy (30). Recently, new oral FXa-inhibitors have been developed, and tested successfully in the field of atrial fibrillation (AF): rivaroxaban and apixaban (31, 32).

Of these agents, rivaroxaban is the only agent that has also been proven efficacious in ACS in a phase III trial (33, 34). In contrast to the study with ximelagatran, the vast majority of patients was on DAPT in the trials with the new agents (33-35). It should be appreciated that the dose administered was markedly lower than the dose tested in AF (5 or 10 mg per day vs 20 mg per day), and that the risk of bleeding was markedly increased (33). Yet, these data show again that new adjunctive anticoagulation therapies have been developed that are efficacious in ACS (Table 1).

Vitamin K antagonists

In contrast to all abovementioned agents which exert their action through inhibition of activated coagulation factors, the oral VKAs interfere with the production of FII, FVII, FIX and FX. For optimal efficacy in patients with a prothrombotic state (pulmonary embolism, venous thrombosis, ACS), VKAs should be initiated in combination with another form of anticoagulation therapy to counteract the potential procoagulant effect early after initiation. The adjunctive form of anticoagulation can be discontinued when two subsequent INRs are in the target range (22).

Importantly, VKAs have been proven to be efficacious in ACS as monotherapy, with outcomes similar to those achieved on patients managed with aspirin. Most of the clinical experience and randomised trials on the impact of prolonged anticoagulation therapy after discharge as adjunct to aspirin is with VKAs. There are robust data to demonstrate that the long-term combination of anticoagulation therapy and antiplatelet therapy results in better clinical outcome than aspirin alone, be it the cost of more bleeding (Table 1) (22, 36). This especially holds true for patients after non ST ACS and STEMI patients not undergoing primary PCI.

Now that primary PCI has become the preferred reperfusion strategy, and management of non ST ACS has become more aggressive, DAPT has become the standard. Notably, even in the more modern era of revascularisation with stenting, a strategy of aspirin and oral anticoagulation has been proven more efficacious than aspirin alone (37). Yet, only indirect comparisons between aspirin and clopidogrel versus aspirin and VKAs are available (38). Treatment with VKAs is cumbersome, and the effect of therapy largely depends on an infrastructure to guarantee dose-adjusted, frequently monitored and individually tailored therapy. It should be appreciated that during the first eight weeks after initiation of anticoagulation therapy, patients are less often in the therapeutic range than during long-term follow-up (39). In this context, inter-

Table 1: Efficacious strategies of prolonged OAC treatment after ACS.

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients at risk</th>
<th>Treatment</th>
<th>Control</th>
<th>Efficacy endpoint*</th>
<th>Safety endpoint**</th>
<th>NNT</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treatment</td>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andreotti (36)</td>
<td>7836</td>
<td>VKA (INR 2–3) + ASA</td>
<td>ASA</td>
<td>9.4%</td>
<td>12.3%</td>
<td>2.6%</td>
<td>1.1%</td>
</tr>
<tr>
<td>ATLAS-ACS-2 (34)</td>
<td>15,526</td>
<td>Riva 2.5 bid + DAPT</td>
<td>DAPT</td>
<td>9.1%</td>
<td>10.7%</td>
<td>1.8%</td>
<td>0.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Riva 5.0 bid + DAPT</td>
<td>DAPT</td>
<td>8.8%</td>
<td>10.7%</td>
<td>2.4%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

*Death, non-fatal myocardial infarction and/or stroke. **Major bleeding. †Numbers needed to treat and to harm were calculated based upon the duration of follow-up of the different studies. ACS, acute coronary syndrome; ASA, acetylsalicylic acid; bid, twice daily; DAPT, dual antiplatelet therapy; INR, international normalised ratio; NNT, number needed to treat; NNH, number needed to harm; OAC, oral anticoagulation; riva, rivaroxaban; VKA, vitamin-K antagonist.
vention studies with aspirin and ticlopidine showed better outcome than an antithrombotic regimen of aspirin with long-term anticoagulation therapy (40).

These aspects have largely contributed to the preference of DAPT after ACS. Despite the proven efficacy, it should be appreciated that bleeding on dual antiplatelet therapy has also been related to mortality (41).

Anticoagulation therapy and bleeding: the flip side

With the appreciation that bleeding is related to short- and long-term mortality (18, 41) intensifying antithrombotic therapy may not necessarily result in better clinical outcome.

Even more complicating, the clinical factors that predict ischaemic events are also associated with an increased risk of bleeding (42, 43). Therefore, the choice of adjunctive anticoagulation therapy to improve the net clinical benefit in patients with events while on DAPT forms a clinical challenge.

Both patient factors (age, sex, prior history of bleeding, renal function, etc) (44), concomitant medication and the choice of reperfusion strategy affect the options for adjunctive anticoagulation.

Renal function

In patients with poor creatinin clearance, UFH is the drug of choice. Although labour-intensive, UFH has the advantage that it can be discontinued and that protamine can be administered to counteract its effects. Fondaparinux has been tested in patients with a creatinin of up to 265 µmol and is a rather safe alternative, but no antidote exists (6, 7).

Concomitant medication

When GPIIb/IIIa blockers are administered, UFH dosing should be adjusted to reduce bleeding complications. In case of fibrinolysis, enoxaparin should be reduced to once daily dosing in case of a creatinine clearance < 30 ml/minute (min) (6, 7). Dosing of the newer agents like fondaparinux and bivalirudin is irrespective of patient characteristics and concomitant medication, which is likely to result in less administration errors. In case of non ST ACS or STEMI without reperfusion therapy, anticoagulation with fondaparinux is an attractive option given its excellent safety, and the reduced mortality compared to enoxaparin demonstrated in OASIS-5 (18, 19).

Bivalirudin monotherapy resulted in similar ischaemic events but lower bleeding rates in non ST ACS when compared to the combination of indirect thrombin inhibition and GPIIb/IIIa inhibition (ACUITY) (20).

Reperfusion therapy

In patients treated with fibrinolysis for STEMI, bivalirudin reduces ischaemic events, but increases bleeding as compared to UFH (29).

Yet, in the setting of primary PCI bivalirudin is associated with lower bleeding rates and similar ischaemic events as compared to UFH with the use of GPIIb/IIIa receptor blockers (21). Fondaparinux can be used with non-fibrin specific fibrinolysis, but is not recommended as pretreatment in the setting of a primary PCI.

These are only a series of examples of clinical decision making that affect efficacy and safety of the chosen antithrombotic regimen. As to the mechanism how bleeding results in worse outcome, various explanations have been proposed, varying from discontinuation of antithrombotic medication and subsequent events to the adverse impact of administration of blood transfusions and the statement that bleeding is merely a marker of a vulnerable patient (44).

Options for prolonged oral anticoagulation therapy in ACS

With the appreciation of the robust data on long-term adjunctive oral anticoagulation in patients using aspirin, and the recent ATLAS-2 trial (34, 36), it is clear that the mechanism behind recurrent events after discharge is not merely a process of platelet activity (Table 1). This is underscored by the fact that coagulation activity is increased up to six months after the index event, which is correlated with the risk of recurrent events (22).

Despite these correlations, evidence for causality is not present: there is no randomised evidence that a strategy of intensified antithrombotic therapy in patients with high platelet/coagulation activity improves outcome (11, 13, 45). To date, selection of patients at high risk for recurrent events, in whom antithrombotic should be optimised, should primarily be based on clinical risk models (46). Irrespective of these models, few clinicians will disagree that patients who experience a thrombotic event despite DAPT form a group of patients in whom antithrombotic therapy should be optimised.

During admission for ACS, recurrent events tend to cluster after cessation of anticoagulation therapy, often referred to as ‘rebound phenomenon’ (47). In addition, about half of recurrent events occur after discharge, despite (dual) antiplatelet therapy (25).

Prolonged anticoagulation with VKAs

Despite the disadvantages with regard to the rather complicated logistics to achieve dose-adjusted, frequently monitored, individually tailored anticoagulation, the risk-benefit ratio of this strategy merits appreciation. At the cost of one major bleeding, three MIs can be prevented in patients on aspirin monotherapy (Table 1) (36). These data compare fairly well with adjunctive therapy with clopidogrel in aspirin users, although direct comparisons are lacking (48). Importantly, randomised trials on the impact of triple therapy (aspirin, clopidogrel, VKA) are lacking as well.

Yet, the observed risk-benefit ratio suggests that there might be room for improvement in case a thienopyridine is added to aspirin and a VKA, provided that dose-adjusted (INR 2.0-3.0) adjunctive

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Prolonged anticoagulation with NOACs

Various new agents have been tested in phase II trials (Table 2) (30, 35, 50-52). Despite the successful data in AF studies, no phase III trials in ACS were initiated with oral thrombin inhibitors (dabigatran, ximelagatran). Of all NOACs, rivaroxaban is the only agent that has been proven effective in a phase III trial (34). Importantly, in this study almost all patients (93%) used dual antiplatelet therapy, and the risk-benefit ratio of this strategy should be interpreted in this context.

Dosing of the oral FXa-inhibitor seems crucial, and it should be realised that the doses used for AF are associated with unacceptable bleeding rates and a lack of efficacy in the setting of ACS (33, 50, 51). In the case of rivaroxaban, 2.5 mg twice daily seems the strategy with the best trade-off (Table 1), which has recently been confirmed in the subgroup of STEMI patients on DAPT (53). In contrast to the evidence with oral VKAs, the data on rivaroxaban reflects only one trial, with little information on how patients were managed with regard to revascularisations (PCI, coronary artery bypass grafting [CABG]), bleeding and peri-operative care for non-cardiac indications.

Optimising antiplatelet therapy

For both strategies of adjunctive oral anticoagulation it should be stressed that the available data reflect patients on aspirin monotherapy or dual antiplatelet therapy with clopidogrel. Information with the more potent agents such as prasugrel and ticagrelor is not available. We are of the opinion that in patients presenting with ACS while on dual therapy with aspirin and clopidogrel, optimisation of antiplatelet therapy (prasugrel, ticagrelor) forms the cornerstone of treatment in case a coronary intervention is performed (3-5). Prasugrel deserves attention with regard to the risk of intracranial haemorrhage and should be avoided in patients with a prior stroke and those > 75 years and < 60 kg (7). If the clinician decides to treat a STEMI patient with fibrinolysis we strongly advise against addition of these new antiplatelet agents during fibrinolysis.

How to initiate oral anticoagulation therapy

In patients with a high thrombotic risk on DAPT, without an established indication for oral anticoagulation therapy, VKAs can be considered as adjunctive therapy. When VKAs are initiated in a prothrombotic milieu (pulmonary embolism, deep venous thrombosis, MI) concomitant anticoagulation is initially required (22) to counteract the potential procoagulant effect of VKAs after the first few doses. This procoagulant effect can be minimised with use of a less aggressive dosing scheme. For example, in case of coumadin, initiation of oral anticoagulation with a three-day schedule of 4-4-2 mg (or 4-2-2) is to be preferred over 6-4-2 mg (Figure 2).

Given the fact that nowadays most patients are on DAPT, extra attention is required with regard to the prevention of bleeding complications. Traditionally, UFH infusion or LWMH twice daily in therapeutic dose are the agents of choice. However, fondaparinux seems a very interesting alternative, not only given the lower bleeding rate and superior efficacy as compared to these agents (18, 19). In contrast to most other anticoagulants, prolonged administration has been extensively studied (8 days/up to discharge). In addition, its dosing is irrespective of patient characteristics, and administration is only once daily.

Another strategy to reduce bleeding complications could be a dose-adjusted strategy of enoxaparin until the target INR has been reached twice. For example, patients with a creatinin clearance < 30 ml/min could be treated with once daily doses (1 mg/kg) and patients > 75 years with twice daily a reduced dose (0.75 mg/kg). It should be noted that this strategy is not evidence based, and has only been tested in case of fibrinolysis (7).

However, in lack of sufficient studies addressing the issue of DAPT with adjunctive anticoagulation, choices can only be made to the best of the physician’s knowledge. Prevention of bleeding and improving efficacy will more and more become a matter of individualised antithrombotic therapy, using adjusted doses or dosing intervals, based upon characteristics of the particular patient and without firm evidence from clinical trials.

With regard to the initiation of rivaroxaban, little information is available as to the initiation in the early phase after ACS. It seems rational to start these agents about 3-4 days after admission, at the time that the anticoagulants that were initiated in the acute phase have been discontinued. In ATLAS-2 rivaroxaban was started at a median of 4.7 days after the index event (34).

AF and ACS

The most challenging group of patients is formed by those with a strict indication for oral anticoagulation therapy. Although the introduction of NOACs seems a major step forward in the treatment of AF, these agents are insufficiently tested in the acute setting of ACS, or in case of urgent or primary PCI. Moreover, data on how to manage patients in the setting of an elective PCI are scarce as well. We therefore recommend that in patients with AF who develop ACS these new agents are discontinued during hospital admission. As mentioned before, the doses used in the prevention of systemic embolism are high, and have been proven unsafe in combination with dual antiplatelet therapy for ACS (33, 35, 50, 51).

Importantly, the anticoagulant regimens used for ACS (UFH, LWMH, fondaparinux) are also effective in the treatment of deep venous thrombosis. Therefore, VKAs and the new oral anticoagulants can be safely discontinued when patients are admitted for ACS.

With regard to the safest strategy to recontinue oral anticoagulation while on DAPT, fondaparinux followed by a VKA seems the
Table 2: Clinical trials on prolonged treatment with novel oral anticoagulants after an ACS.

<table>
<thead>
<tr>
<th>Drug/Trial*</th>
<th>Year</th>
<th>N</th>
<th>Antiplatelet therapy</th>
<th>Intended treatment duration</th>
<th>Investigated dose</th>
<th>Major bleeding</th>
<th>Efficacy</th>
<th>Definition</th>
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<tr>
<td><strong>Phase 2</strong></td>
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<td></td>
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<tr>
<td>Ximelagatran ESTEEM (30)</td>
<td>2003</td>
<td>1,883</td>
<td>ASA</td>
<td>6 months</td>
<td>24 mg bid</td>
<td>0.9%</td>
<td>2.0%</td>
<td>16.0%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>36 mg bid</td>
<td>1.3%</td>
<td>3.3%</td>
<td>24.5%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48 mg bid</td>
<td>3.2%</td>
<td>5.4%</td>
<td>50.1%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60 mg bid</td>
<td>3.2%</td>
<td>5.0%</td>
<td>50.2%</td>
</tr>
<tr>
<td>Apixaban APPRAISE (50)</td>
<td>2009</td>
<td>1,715</td>
<td>DAPT</td>
<td>6 months</td>
<td>2.5 mg bid</td>
<td>0.8%</td>
<td>1.6%</td>
<td>8.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 mg qd</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.9%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 mg bid**</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.9%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20 mg qd**</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Rivaroxaban ATLAS-ACS TIMI 46 (51)</td>
<td>2009</td>
<td>761</td>
<td>ASA</td>
<td>6 months</td>
<td>5 mg/day</td>
<td>0.0%</td>
<td>0.0%</td>
<td>13.4%</td>
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<td></td>
<td></td>
<td>10 mg/day</td>
<td>0.0%</td>
<td>0.0%</td>
<td>13.4%</td>
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<td></td>
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<td>20 mg/day</td>
<td>0.0%</td>
<td>0.0%</td>
<td>13.4%</td>
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<tr>
<td></td>
<td></td>
<td>2,730</td>
<td>DAPT</td>
<td>6 months</td>
<td>5 mg/day</td>
<td>0.1%</td>
<td>0.7%</td>
<td>5.0%</td>
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<td></td>
<td></td>
<td>10 mg/day</td>
<td>0.1%</td>
<td>0.7%</td>
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<td>15 mg/day</td>
<td>0.1%</td>
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<td></td>
<td></td>
<td>20 mg/day</td>
<td>0.1%</td>
<td>0.7%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Dabigatran REDEm (35)</td>
<td>2011</td>
<td>1,861</td>
<td>DAPT</td>
<td>6 months</td>
<td>50 mg bid</td>
<td>0.5%</td>
<td>0.8%</td>
<td>3.8%</td>
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<td></td>
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<td></td>
<td>75 mg bid</td>
<td>0.5%</td>
<td>0.8%</td>
<td>3.8%</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>110 mg bid</td>
<td>0.5%</td>
<td>0.8%</td>
<td>3.8%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>150 mg bid</td>
<td>0.3%</td>
<td>0.3%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Darexaban RUBY-1 (52)</td>
<td>2011</td>
<td>1,279</td>
<td>DAPT</td>
<td>6 months</td>
<td>10 mg/day</td>
<td>0.3%</td>
<td>0.6%</td>
<td>4.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30 mg/day</td>
<td>0.3%</td>
<td>0.6%</td>
<td>4.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60 mg/day</td>
<td>0.3%</td>
<td>0.6%</td>
<td>4.4%</td>
</tr>
<tr>
<td><strong>Phase 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban APPRAISE-2 (33)</td>
<td>2011</td>
<td>7,392</td>
<td>DAPT</td>
<td>Average 1.25 yrs</td>
<td>5 mg bid</td>
<td>1.1%</td>
<td>2.7%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Rivaroxaban ATLAS-ACS-2 TIMI 51 (35)</td>
<td>2012</td>
<td>15,526</td>
<td>DAPT</td>
<td>31 months</td>
<td>2.5 mg bid</td>
<td>0.6%</td>
<td>1.8%</td>
<td>10.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 mg bid</td>
<td>2.4%</td>
<td>1.8%</td>
<td>10.7%</td>
</tr>
</tbody>
</table>

*We performed a PubMed search using the search terms: “Acute Coronary Syndrome/Drug Therapy”; “Myocardial Infarction/Drug Therapy”; “Ximelagatran”; “Dabigatran”; “Rivaroxaban”; “Apixaban”; “Darexaban”; “Factor Xa”; “Factor Ila”; and used the filter “Clinical Trial”. We identified 34 articles of which the above mentioned studies were the only trials comparing a novel oral anticoagulant with placebo in the setting of prolonged secondary prevention after ACS/myocardial infarction. **Treatment arms of apixaban 10 mg bid and 20 mg qd were added during the trial and were discontinued prematurely due to excessive bleeding. N, number of patients; APT, antiplatelet therapy; NOAC, novel oral anticoagulant; ACS, acute coronary syndrome; ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; ISTH, International Society on Thrombosis and Haemostasis; TIMI, thrombolysis in myocardial infarction; CV, cardiovascular; MI, myocardial infarction; yrs, years; qd, quaque die (once daily); bid, bis in die (twice daily); rec, recurrent; revasc, revascularisation.

preferred strategy. As stated, post-discharge DAPT in combination with NOACs in a dose to prevent systemic embolism should be avoided at any time. The impact of DAPT with low-dose rivaroxaban as antithrombotic strategy to prevent systemic embolism in patients with AF is uncertain.

Triple therapy after ACS (aspirin, thienopyridine, VKA) is associated with considerable bleeding rates, but the evidence is limited to observational data (54-56). The first randomised trial on the adjunctive use of VKAs in patients with DAPT showed a markedly increased bleeding risk when compared to patients on VKAs and clopidogrel (49). Importantly, this trial was not powered for efficacy endpoints, and included only a minority of patients with ACS (57). All patients had an established indication for oral anticoagulation.

Given the increased risk of bleeding on triple therapy, the guidelines recommend to discontinue aspirin as soon as possible,
dependent on the type of stent placed after intervention (58). If, for specific reasons, a NOAC for the prevention of systemic embolism is the agent of choice, this should not be combined with DAPT, given the unacceptable bleeding risks demonstrated in the various phase II trials (▶Table 2). It should be appreciated that little information is available with regard to the efficacy and safety of combined treatment with a NOAC and a single antiplatelet agent after ACS. In patients with AF, we therefore recommend prolonged anticoagulation with VKAs in the first year after ACS. Then, based upon the patient’s clinical condition and the evidence available at that time, a renewed evaluation can be made.

Conclusions and implications

The collective data on prolonged adjunctive anticoagulation suggest that interference with the coagulation system can improve outcome after ACS. The development of NOACs without a need for monitoring has initiated a renewed interest for this strategy. Importantly, the cornerstone of antithrombotic treatment after ACS consists of optimal long-term DAPT.

To date, the NOACs have only been tested as adjunctive therapy. Of all the new agents, only rivaroxaban – in a substantially lower dose than used for AF – has been proven to improve outcome after ACS, albeit with an increased risk of bleeding. In selected cases, adjunctive therapy with dose-adjusted VKAs can be considered as well. These two strategies of prolonged anticoagulation can be considered in patients with ‘HPR’, i.e. patients at high risk of recurrent thrombotic events despite DAPT (▶Figure 2).

During admission for ACS, the higher doses of novel oral anticoagulants as indicated for AF should be avoided, given the unacceptably high bleeding rates. After discharge, patients on DAPT with AF should receive VKAs (INR 2.0-3.0). After careful evaluation of the expected risks and benefits, one of the two antiplatelet agents should be discontinued as soon as clinically justifiable. Whereas monitoring and dose-adjustment have previously been considered drawbacks of oral VKA therapy to treat large groups of patients, it may be of value in selected patients who need careful monitoring of the risks and benefits of a rather aggressive antithrombotic regimen. Moreover, an antidote is available and clinical experience has been obtained in many thousands of patients, also in case of CABG, PCI and peri-procedural management of non-cardiac surgery and intervention.

In case of post-discharge use of a NOAC for AF, DAPT is strictly contra-indicated in patients after ACS.

Notably, the accumulating evidence suggesting a role for prolonged adjunctive anticoagulation after ACS (low-dose rivaroxaban, VKAs) should be interpreted in the context that this strategy has not been addressed with the most potent antiplatelet agents (prasugrel, ticagrelor) and merits further study.

Despite the potential indication of prolonged oral anticoagulation as adjunctive treatment, it remains to be established whether anticoagulation therapy could serve as an alternative for either aspirin or thienopyridine treatment in selected cases and how the

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**Figure 2: Potential options for prolonged adjunctive OAC.** The initial antithrombotic management after admission for acute coronary syndromes (ACS) depends on many factors, such as patient characteristics, concomitant medication and the choice of the revascularisation/reperfusion strategy. The cornerstone of antithrombotic treatment after ACS consists of long-term optimal dual antiplatelet therapy. In patients with a high thrombotic risk, or “high platelet activity”, prolonged anticoagulation therapy can be considered. As initial strategy for anticoagulation unfractionated heparin (UFH), bivalirudin, enoxaparin or fondaparinux can be started. Following the acute phase, potential options for prolonged OAC are vitamin K antagonists (VKA) and low-dose rivaroxaban. Both bivalirudin and UFH are less attractive agents for long-term in-hospital treatment. Given the potential procoagulant effect of VKAs when initiated in patients in a prothrombotic state, concomitant anticoagulation therapy should be given until two subsequent INRs are within therapeutic range (22). No overlapping treatment is required for rivaroxaban (34). Note that the dose of rivaroxaban is considerably lower (5 mg per day) than for the indication atrial fibrillation (15-20 mg per day). New oral anticoagulants with a dosing scheme as in atrial fibrillation should not be combined with dual antiplatelet therapy. If VKAs are chosen, the expected benefit should be carefully weighed against the potential risk. In this context, dual antiplatelet therapy with a reduced target INR (2.0-2.5) can be considered, as alternative to a target INR of 2-3 (59). ACS, acute coronary syndrome; bid, twice daily; INR, international normalised ratio; OAC, oral anticoagulation; VKA = vitamin K antagonist.
risk-benefit ratio of this regimen compares to DAPT or triple therapy.

Conflicts of interest
J. Jaspers Focks and M.A. Brouwer have no conflicts of interest to declare. F. W. A. Verheugt has received educational and research grants from Bayer AG, Roche, Eli Lilly and Boehringer Ingelheim and has received honoraria for consultancies from Daichi Sankyo, Eli Lilly, Merck, The Medicines Company and Bayer AG.

References


