

**Is there a role for oral triple therapy in patients with acute coronary syndromes  
without atrial fibrillation?**

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## **ABSTRACT**

**BACKGROUND:** Acute coronary syndrome (ACS) patients, despite treatment with dual antiplatelet therapy (DAPT), have up to 10% risk of recurrent major adverse cardiac events (MACE) in the short term.

**METHODS:** Here we review studies using more potent antithrombotic agent combinations to reduce this risk, namely triple therapy (TT) with the addition of an oral anticoagulant, PAR-1 antagonist, or cilostazol to DAPT (mainly aspirin and clopidogrel), and discuss the limitations of trials to date.

**RESULTS:** Generally speaking, TT leads to an increase in bleeding. Vorapaxar showed a signal for reducing ischaemic events, but increased intracranial haemorrhage 3-fold in the subacute phase of ACS, although remains an option for secondary prevention beyond the immediate subacute phase, particularly if prasugrel or ticagrelor are not available. Non-vitamin K oral anticoagulants (NOACs) all increased bleeding, with only modest reduction in MACE noted with low dose rivaroxaban. Rivaroxaban can be considered combined with aspirin and clopidogrel in ACS patients at high ischaemic and low bleeding risk, without prior stroke/TIA. The combination of P2Y<sub>12</sub> inhibitor and NOAC, without aspirin, looks promising. DAPT may be replaced, not by TT, but by dual therapy comprising a NOAC with a P2Y<sub>12</sub> inhibitor.

**CONCLUSION:** More potent antithrombotic regimens increase bleeding and should only be considered on an individual basis, after careful risk stratification. Accurate risk stratification of ACS patients, for both ischaemic and bleeding risk, is essential to allow individualised treatment.

**Keywords:** acute coronary syndromes, apixaban, dabigatran, edoxaban, thrombosis, newer oral anticoagulants, rivaroxaban,

**List of abbreviations:**

ACS: acute coronary syndromes

CABG: coronary artery bypass graft

CI: confidence interval

CV: cardiovascular

DAPT: dual antiplatelet therapy

HR: hazard ratio

MACE: major adverse cardiac events

MI: myocardial infarction

NOAC: newer oral anticoagulant

OR: odds ratio

PCI: percutaneous coronary intervention

RR: risk ratio

TIMI: thrombolysis in myocardial infarction

VKA: vitamin K antagonists

## **INTRODUCTION**

Patients with ACS are treated with dual antiplatelet therapy (DAPT), namely the combination of aspirin with a P2Y<sub>12</sub> inhibitor, to reduce the risk of future thrombotic events. ACS most commonly results from rupture or fissure of a thin-cap fibrous atheroma within the coronary arterial tree. This results in exposure of plaque contents to flowing blood, which leads to platelet activation, and release of tissue factor leading to activation of coagulation(1-3). Activation of the coagulation pathway results in conversion of clotting factor X to Xa, which is a vital mediator in the formation of thrombin, the key modulator of the formation and stability of the platelet-rich plug (4) (figures 1 and 2).

The acute management of ACS therefore involves the use of antiplatelet agents and anticoagulants. This is an integral step to counteract the prothrombotic state that results from active platelet aggregation(5). Current medical treatment involves the use of aspirin and a P2Y<sub>12</sub> inhibitor(6), as well as anticoagulants, in particular low molecular weight heparin in the acute phase. As a general principle, the inhibition of multiple thrombotic pathways maximizes the antithrombotic effect in reducing future ischaemic events in ACS patients(5, 6).

### **Rationale for current pharmacotherapy for ACS**

Over the last two decades, increasingly potent antiplatelet agents have been introduced to reduce the risk of arterial thrombosis, especially in high-risk groups such as patients with ACS. Clopidogrel was added to aspirin after the results of the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial(7), which demonstrated that the addition of clopidogrel to aspirin in NSTEMI-ACS

significantly reduced the combined endpoint of CV death, MI and stroke (7, 8). More potent antiplatelet agents were introduced at least in part because of concerns that some 30% of patients taking clopidogrel exhibit high on-treatment platelet reactivity (HTPR)(9, 10). Subsequently, prasugrel was shown to be superior to clopidogrel in an ACS population undergoing PCI, with significant reduction in the risk of CV death, MI, stroke ( $p<0.001$ ) and stent thrombosis ( $p<0.001$ ), at a cost of significant increase in major bleeding ( $p=0.03$ )(11), but not superior in ACS patients who were not undergoing revascularization (12). Ticagrelor significantly reduced the occurrence of CV death, MI and stroke, compared to clopidogrel in ACS patients, with less stent thrombosis, but an overall increase in major bleeding(13).

Despite potent antiplatelet agents, some ~10% of ACS patients experience a recurrent major adverse cardiovascular events (MACE) over the subsequent 30 days(14-18).

This ongoing thrombotic risk led to the proposal for additional inhibition of thrombotic pathways. In the acute phase, GPIIb/IIIa inhibitors (GPI) or bivalirudin, a direct thrombin inhibitor, have been used with success to reduce ischaemic events(19). However, beyond the acute admission, acute thrombotic events continue to occur, particularly in the first 30 days, and so additional agents have been added to DAPT to try and minimise this risk.

## TRIPLE THERAPY COMBINATIONS IN ACS

### Warfarin

The addition of a vitamin K antagonist (VKA) to aspirin for the treatment of ACS resulted in a significant reduction in all ischaemic events (myocardial infarction, repeat revascularization, ischaemic stroke) with a three to four fold increase in major bleeding when compared to aspirin monotherapy(20, 21), but for this benefit to be realised required a very tight therapeutic window for warfarin (international normalized ratio 2-3) and the trials were conducted before DAPT became established as standard of care. Addition of warfarin to DAPT after ACS has only been assessed in small registries with results showing frequent bleeding events(22). In a nationwide Danish registry Sorensen and colleagues assessed 40,812 patients retrospectively after ACS who were treated with multiple different regimens including monotherapy with aspirin, clopidogrel, or warfarin; combination therapy with aspirin and clopidogrel, aspirin and warfarin and clopidogrel and warfarin; or triple therapy with all three agents. There was a three-fold increase in bleeding with the triple therapy compared to DAPT.

The WOEST (What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting) study compared the combination of warfarin and clopidogrel against triple therapy comprising of warfarin, aspirin and clopidogrel in patients undergoing PCI with an indication for anticoagulation(23). In this open label, randomised controlled trial, the main indication for anticoagulation was atrial fibrillation and a third of the patients had ACS. Triple therapy was associated with a significant increase in bleeding compared to warfarin and

clopidogrel (44.4 vs 19.4% HR 0.36;  $p < 0.0001$ ) and also increased the rate of bleeding and the need for blood transfusion. In addition, triple therapy increased the risk of the composite of all-cause death, myocardial infarction, stroke, target vessel revascularization and stent thrombosis, driven mainly by increase in all-cause mortality (6.3 vs 2.5%  $p = 0.0027$ ). The ESC/EACTS Guidelines on myocardial revascularization therefore recommend reserving triple therapy with warfarin and DAPT to a short period after PCI in those with an indication for oral anticoagulation(24).

### **Cilostazol**

Cilostazol is a selective phosphodiesterase III inhibitor that is shown to decrease platelet aggregation induced by collagen, 5'-adenosine diphosphate (ADP), epinephrine, and arachidonic acid. Unlike other antiplatelet agents, cilostazol not only inhibits platelet function but also improves endothelial cell function(25-27). Its additional benefit to current standard of care has been questioned with controversial results over the past decade(28, 29). A recent meta-analysis of 19 studies, comprising both randomised controlled trials and registries, compared aspirin and clopidogrel against triple therapy with cilostazol in 7464 patients with ACS undergoing PCI (30). Triple therapy was associated with a significant reduction in target vessel revascularization (RR 0.65, 95%;  $p < 0.00001$ ) but no difference in MACE or bleeding complications. In an updated meta-analysis of high risk ACS patients undergoing percutaneous revascularisation, triple therapy significantly reduced MACE, driven mainly by a reduction in all-cause mortality (OR 0.62,  $p < 0.001$ ) without an increase in bleeding compared to DAPT(31). Most of the studies included in both meta-

analyses were conducted in East Asia, where there the frequency of the *CYP2C19* loss-of-function allele carriers is >60% and the rate of HTPR on clopidogrel exceeds 50%, thus biasing the results against DAPT with clopidogrel. Cilostazol has not been combined with or compared against DAPT with prasugrel or ticagrelor. Cilostazol is not currently recommended by the European Society of Cardiology (ESC) or American College of Cardiology (ACC) nor is licensed for the treatment of ACS(24, 32, 33).

### **Thrombin receptor antagonists**

Thrombin, being the most potent platelet activator and integral for fibrin formation, is the key mediator of arterial thrombotic events. The cellular effects of thrombin are mainly mediated via the protease-activated receptors (PAR), primarily PAR-1 and PAR-4, on the platelet surface (figure 1)(34). The rationale of inhibiting these pathways resulted in the development of two novel PAR-1 inhibitors, vorapaxar and atopaxar, as a way of preventing arterial thrombosis. Vorapaxar was assessed in two large phase III randomised controlled trials TRACER(35) and TRA-2P(36).

In TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in ACS) 12,944 patients presenting with NSTEMI were randomised to receive vorapaxar or placebo in addition to aspirin and clopidogrel (Table 1). Treatment of the index event included PCI (57.7%), CABG (10.1%) and medical therapy (32.2%). The addition of vorapaxar failed to reduce the composite of CV death, MI, stroke, recurrent ischemia requiring rehospitalisation and urgent revascularization. Bleeding rates were significantly higher in the vorapaxar group compared to placebo (7.2 vs 5.2%;  $p<0.001$ ) with a threefold increase in intracranial haemorrhage (1.1 vs 0.2%;



$p < 0.001$ ). As a result of this, the trial was terminated prematurely, although it is noteworthy that the secondary ischaemic endpoint of CV death, MI and stroke was significantly lower in the vorapaxar group compared to placebo (14.7% vs 16.7%, HR 0.89, 95% CI 0.81-0.98;  $p = 0.002$ )(35). In a subsequent post hoc analysis, using multivariate risk stratification, vorapaxar showed a net clinical benefit of +2.8% in high ischaemic risk patients with low risk of bleeding(37).

In the TRA-2P (Thrombin Receptor Antagonist in Secondary Prevention of atherothrombotic ischemic events) study, 26449 patients with prior MI, stroke or peripheral vascular disease (Table 1) were randomised to receive vorapaxar or placebo in addition to standard of care, which consisted of aspirin and clopidogrel for the MI population (62%). Vorapaxar reduced the composite of CV death, MI or stroke (9.3 vs 10.5%;  $p < 0.001$ ), driven by lower rate of MI (5.2 vs 6.1%;  $p < 0.001$ ), but increased bleeding (4.2 vs 2.5% HR 1.66 95% CI 1.43-1.93;  $p = 0.001$ ) as well as intracranial haemorrhage (1% vs 0.5%;  $p < 0.001$ ) leading to premature termination of the study for the stroke patients(36). In a subgroup analysis of the MI patients, vorapaxar significantly reduced the primary efficacy endpoint ( $p < 0.001$ ), particularly in high risk patients, with significant increase in bleeding ( $p < 0.001$ )(38, 39).

Following these positive results vorapaxar was approved for secondary prevention in high risk, stable patients with a history of MI and no previous stroke, in addition to aspirin or DAPT(40). It has not been approved as treatment of ACS.

Atopaxar, another PAR-1 inhibitor, was evaluated in the phase II Lesson from Antagonizing the Cellular Effect of Thrombin-Acute Coronary Syndrome (LANCELOT-ACS) and Japanese-LANCELOT trials, exploring the safety and tolerability of different doses of atopaxar compared to placebo in addition to DAPT in ACS(41, 42). LANCELOT-ACS randomised 603 NSTEMI patients to receive 50mg,

100mg or 200mg of atropaxar versus placebo in addition to aspirin and clopidogrel or ticlopidine. Bleeding and the composite of CV death, MI, stroke or recurrent ischaemia, were similar in the atropaxar and placebo groups(41). Similar results were observed in the smaller Japanese-LANCELOT study, but with a dose-dependent transient increase in liver enzymes(41, 42) and dose-dependent QT<sub>c</sub> prolongation. As a result of these concerns, further trials with atropaxar were suspended.

### **Non-vitamin K oral anticoagulants**

The introduction of newer non-vitamin K oral anticoagulants (NOACs) without the need for laboratory monitoring, few drug interactions and fixed daily dose regimens rekindled the idea of anticoagulation in high risk patients with ACS(43).

The first randomised phase II control trial that evaluated a NOAC in patients with ACS was the ESTEEM trial(44). In this study, 1833 patients with recent ACS (>60%STEMI) were randomised to aspirin 160 mg or the combination of aspirin and ximelagatran, the first oral direct thrombin inhibitor, for 6 months. Importantly, this trial was done without concomitant use of an ADP receptor antagonist. Addition of ximelagatran was significantly superior to aspirin monotherapy for the combined primary endpoint of all-cause death, non-fatal MI and recurrent revascularization (HR 0.76;  $p=0.036$ ) and the secondary outcome of all-cause death, non-fatal MI and ischaemic stroke with an absolute risk reduction of 3.7% ( $p=0.0105$ ). However, bleeding rates were numerically non-significantly higher on combination treatment, and furthermore, ximelagatran had a toxic liver profile and was never approved for clinical use.

Four oral factor Xa inhibitors, apixaban, rivaroxaban, darexaban, letaxaban, and the oral direct thrombin inhibitor, dabigatran, have been evaluated in phase II and phase III trials in patients with ACS. NOACs were used either in addition to aspirin monotherapy or in combination with DAPT after ACS(45-53).

ATLAS ACS-TIMI 46(45) was a double blind, dose exploratory, phase II randomised controlled trial, to assess the efficacy and safety of different doses of rivaroxaban, in addition to DAPT or aspirin monotherapy in 3941 patients with recent ACS. Patients were initially randomised to receive 5mg, 10mg, 15mg or 20mg of rivaroxaban once or twice-daily doses or placebo. Patients were then randomised further to either receive aspirin monotherapy or the combination of aspirin and clopidogrel.

Rivaroxaban, at all doses, failed to reduce the primary efficacy endpoint of the composite of all cause death, MI, stroke and severe recurrent ischemia requiring revascularization ( $p=0.10$ ). Interestingly, rivaroxaban significant reduced the secondary end point of all cause death, stroke and MI, compared to placebo although the study was not powered to assess this. Clinically significant bleeding was increased in a dose-dependent manner in all triple therapy groups compared to DAPT ( $p<0.0001$ ).

Based on the above results, ATLAS ACS-TIMI 51, a phase III double blind, randomised controlled study was conducted to assess the safety and efficacy of the two lower doses of rivaroxaban (2.5mg bid and 5mg bid), against placebo, in addition to DAPT in 15,526 patients with ACS(46). The combined rivaroxaban dose significantly reduced the primary efficacy endpoint of cardiovascular death, MI and stroke compared to placebo (HR 0.84;  $p =0.002$ ) at 1 year. In the analysis of the two doses of rivaroxaban, each dose reduced significantly the primary efficacy endpoint

(Table 1), however the 5mg dose did not reduce the risk of CV death (HR 0.94;  $p=0.63$ ) compared to the 2.5mg dose ( $p=0.009$ ). Rivaroxaban combined doses reduced significantly the secondary end point, consisting of all cause death, MI, stroke compared to placebo (HR 0.84;  $p=0.006$ ). As expected, rivaroxaban combined doses significantly increased the rate of the primary safety endpoint, consisting of major bleeding (TIMI major bleeding not related to CABG) compared to placebo (HR 3.96;  $p<0.001$ )(46). This was numerically lower for the 2.5mg dose however remained significant for both doses of rivaroxaban (Table 1). All bleeding events were significantly higher in the combined rivaroxaban doses compared to placebo with the exception of fatal bleeding. In a subgroup analysis of the STEMI-ACS population, rivaroxaban was found to reduce the primary efficacy end point compared to placebo (HR 0.81;  $p=0.019$ ), a benefit that emerged as early as thirty days after the index event ( $p=0.042$ )(53). Interestingly, the low dose of rivaroxaban was the only one to significant reduce CV death when compared to placebo ( $p=0.006$ ), whereas both doses significantly increased the rates of major bleeding (2.2% vs 0.6%,  $p<0.001$ ) and intracranial haemorrhage (0.6% vs 0.1%,  $p=0.015$ ) but not fatal bleeding (0.2% vs 0.1%,  $p=0.51$ )(53). In an additional subgroup analysis, combined doses of rivaroxaban significantly reduced all stent thrombosis compared to placebo (1.9% vs 1.5%;  $p=0.017$ ) and the reduction was greater with the 2.5mg dose(54).

Based on these results, the 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC) state that rivaroxaban 2.5 mg twice daily, while not recommended in patients treated with ticagrelor or prasugrel, might be considered in combination with aspirin and clopidogrel if ticagrelor and prasugrel are not available for NSTEMI patients who have high ischaemic and low bleeding risks, with a class IIb recommendation with level of evidence B(32). It is contraindicated in patients with a prior history of ischaemic stroke/TIA and its use is cautioned in patients >75 years of age or <60 kg bodyweight.

The Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) study was a phase II double blind, dose exploratory trial, to evaluate the safety and efficacy of apixaban, in addition to single or dual antiplatelet therapy versus placebo in 1715 patients with ACS(47). Patients with a recent ACS were randomised to receive 2.5mg, 10mg, 10mg, 20mg twice or once daily respectively or placebo. All patients received aspirin and the use of clopidogrel was left up to the treating physician resulting in overall 76% DAPT use, with predominantly clopidogrel. Apixaban, in a dose-dependent manner, significantly increased the rate of major or clinically relevant non-major bleeding compared to placebo (apixaban 2.5mg b.i.d HR 1.78, 95% CI 0.91-3.48;  $p=0.09$ , apixaban 10mg o.d HR 2.45, 95% CI 1.31-4.61;  $p=0.005$ )(47). With the two lower doses of apixaban, a trend was seen towards reduction in the combination of CV death, MI, severe recurrent ischemia or ischaemic

stroke compared to placebo (apixaban 2.5mg b.i.d HR 0.73;  $p=0.21$ , apixaban 10mg o.d. HR 0.61;  $p=0.07$ )(47).

Following these results, APPRAISE-2 study, a double blind, phase III randomised controlled trial, comparing the combination of DAPT with apixaban 5mg b.i.d versus placebo was undertaken in 10,800 patients with a recent ACS(48). The primary efficacy endpoint of the composite of CV death, MI and ischaemic stroke was no different between patients on apixaban and those on placebo (HR 0.95;  $p=0.51$ ) and furthermore, the study had to be terminated early at a mean follow up of eight months, due to a significant increase in major bleeding in the apixaban arm (HR 2.59,;  $p=0.001$ )(48). Further analysis showed a significant increase in all bleeding outcomes with apixaban versus placebo, including fatal bleeding.

The APPRAISE-J trial was a double blind, phase II randomised controlled trial, to assess the safety and efficacy of apixaban 2.5mg b.i.d, or 5mg b.i.d or placebo in addition to DAPT in Japanese patients with ACS(51). This study was able to only recruit 151 patients before it was terminated early due to the results of the APPRAISE-2 trial(48, 51).

Darexaban, a factor Xa inhibitor, was examined in the RUBY-1 trial(50). RUBY-1 was a double-blind dose-escalating phase II randomised controlled trial, to assess efficacy and safety of different doses and regimens of darexaban versus placebo in addition to DAPT, in 1279 patients with recent ACS(50). Patients were randomised to receive 10mg o.d, 30mg o.d, 60mg o.d, 5mg b.id, 15mg b.i.d, 30mg b.i.d of darexaban or placebo, in addition to DAPT with aspirin and clopidogrel. Darexaban significantly increased the rates of major bleeding compared to placebo in a dose-dependent fashion (HR 2.275;  $p=0.022$ )(50). The study was not powered to assess efficacy

outcomes, however there was no significant difference between darexaban and placebo(50).

AXIOM was a double blind, phase II dose exploratory trial, to assess the safety and efficacy of letaxaban compared to placebo in combination with DAPT, in 2753 patients with ACS(52). There was no difference in major bleeding between letaxaban and placebo, but when evaluated for a composite of TIMI major and minor bleeding outcome, letaxaban showed a significant dose-dependent increase in bleeding compared to placebo (2.1 vs 0.9%,  $p=0.025$ ). Although not powered to assess efficacy endpoints, there were no observed differences between letaxaban and placebo for the composite of CV death, nonfatal MI, stroke or MI hospitalization(52).

Among the first clinically available NOACs was dabigatran, a direct thrombin inhibitor, in contrast to other NOACs, that target factor Xa. The efficacy and safety of dabigatran in ACS was evaluated in the RE-DEEM study(49). This double blind, phase II, randomised controlled trial, examined 1861 patients with recent ACS to assess the combination of different doses of dabigatran against placebo, in addition to DAPT. Patients were randomised to receive 50mg b.i.d, 75mg b.i.d, 110 mg b.i.d and 150mg b.i.d of dabigatran or placebo for six months. Dabigatran significantly increased major bleeding compared to placebo in a dose-dependent manner ( $p<0.001$ ). Additionally, patients older than 75 years and female had a higher incidence of bleeding with the 110mg and 150mg doses(49). The most prevalent source of bleeding was gastrointestinal (3%) with no intracranial bleeding observed. The two higher doses of dabigatran, 110mg b.id and 150mg b.i.d, were associated with a numerical reduction in the composite end point of CV death, non-fatal MI and

non-haemorrhagic stroke when compared to placebo, however this was of not statistically significant(49).

A meta-analysis of 7 published randomised, placebo-controlled phase II and III studies of NOACs (apixaban, dabigatran, darexaban, rivaroxaban, and ximelagatran) in addition to single (aspirin) or dual (aspirin and clopidogrel) antiplatelet therapy in ACS concluded that the addition of NOAC to DAPT reduced the rate of MACE (all-cause mortality, myocardial infarction and stroke) by 13% (HR 0.85;  $p=0.85$ ) at the expense of significantly increased major bleeding (HR 2.34;  $p<0.001$ )(55).

## **Discussion**

In an effort to reduce recurrent ischaemic events in patients with ACS, investigators have explored the use of triple therapy, using an oral anticoagulant, PAR1 antagonist or cilostazol in addition to DAPT comprising predominantly of aspirin and clopidogrel. As a broad generalisation, in patients with a recent ACS, triple therapy leads to a significant increase in bleeding, and this is unacceptably high with vorapaxar and with warfarin. There appears to be a definite signal for all triple therapy combinations to reduce MACE compared to DAPT. The risk:benefit ratio in ACS patients seems to be acceptable to justify the use of rivaroxaban and possibly dabigatran in triple therapy combinations in high risk patients(45-52).

However, some important points about need consideration when comparing the results of studies to date and drawing conclusions, which are outlined here.

### Assessing bleeding risk



The increased risk of bleeding is a universal theme in the studies where NOAC has been added to DAPT. A recent network meta-analysis showed that compared to aspirin monotherapy, major bleeding was increased up to 2-fold with DAPT, and 2–6-fold with triple therapy(56). We feel some of this could have been mitigated against. The source of bleeding was most commonly gastrointestinal in the APPRAISE and RE-DEEM studies with an incidence up to 5%(47-49, 57) yet the use of gastroprotection with a proton pump inhibitor was not common, and used in less than a quarter of patients in APPRAISE-2 (48). Identifying patients at high risk of bleeding is challenging, especially when there is no universally accepted scoring system in the setting of ACS. Patients in the ATLAS ACS-TIMI 46 and ATLAS ACS-TIMI 51 were younger and main exclusion criteria consisted of previous gastrointestinal bleed in the year preceding randomisation, any intracranial bleed and absolute haemoglobin < 10 g/dl(45, 46). In contrast to this, the population in the APPRAISE-2 study did not have these limitations in the exclusion criteria and patients were included with a haemoglobin >9 g/dl(48).

Given the increased risk of intracranial haemorrhage in patients with prior stroke treated with vorapaxar, perhaps this is another group where caution should be exercised in future trials of triple therapy.

There are several bleeding risk score calculators available to predict the risk of bleeding that could have been used in the trials to identify patients at risk of bleeding. These include the HASBLED score, extensively validated with OAC, albeit predominantly in patients with AF and scores assessing bleeding with antiplatelet agents such as DAPT score (Dual Antiplatelet Therapy)(58) and the PARIS score (Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients)(59) which use a variety of clinical and angiographic factors in order to predict the risk of

ischaemic events and bleeding. The PRECISE-DAPT (Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy)(60) is a relatively new five clinical point score that can be used to predict bleeding events in patients receiving DAPT. Overall, CRUSADE(61) and ACUITY(62) scores have reasonable predictive value for major bleeding in ACS patients undergoing coronary angiography, with the CRUSADE score considered the most discriminatory. However, in patients medically treated or on oral anticoagulants, the predictive value of these scores is not established.

### Definition of bleeding

Also pertinent is that different studies reported here have used different definitions of bleeding, with a lack of uniformity among the trials, making relative comparisons of bleeding risk with different agents impossible. Bleeding events, classified as in the studied by the GUSTO(63), ISTH(64), TIMI(65) or CURE(8) bleeding risk scores have included laboratory parameters, such as decrease in haemoglobin, and clinical events, including the need for transfusion or surgery, cardiac tamponade, haematomas, and various degrees of bleeding. Each definition incorporates a different combination of these elements and then ranks orders these combinations into severity categories, which vary widely between definitions. To standardise the reporting of bleeding events between studies, the Bleeding Academic Research Consortium was convened and published guidelines that should now be used, but were not available at the time of some of these publications(66).

## Dosing

A further consideration is that the dose of apixaban in all the ACS studies was based on the previously effective full anticoagulation dose used for atrial fibrillation in the ARISTOTLE trial(67). On the other hand, the rivaroxaban dose employed in the ATLAS studies was only one-quarter to one-half the anticoagulant treatment dose used in the ROCKET-AF trial(68). Although a reduced bleeding rate would be expected with a lower dose of anticoagulation, in both the ATLAS ACS-TIMI 51 and APPRAISE-2 trials the increase in the rate of bleeding was still significant(46, 48). Moreover, the observed benefit in MACE reduction was noted with the lower effective dose in ATLAS ACS-TIMI 51 and not with the higher dose in both ATLAS ACS-TIMI 51 and APPRAISE-2, a finding that is not easy to understand(46, 48).

## Heterogeneous patient group

The studies have been focused on ACS patients, but no real attempt has been made to focus on those patients with ACS who are at highest risk of recurrent events.

Patients included in all studies had a recent ACS and one or more additional risk factor, apart from ATLAS ACS-TIMI 46 and ATLAS ACS-TIMI 51(45, 46). In ATLAS ACS-TIMI 46 patients were included with no risk factors for future MACE and in the ATLAS ACS-TIMI 51 subjects were required to have a history of either diabetes mellitus or a prior MI.

Another interesting observation is that patients in the APPRAISE-2(48) trial were at higher risk of recurrent events, with a higher proportion of female patients (32.2%), and almost half the population were diabetic. However, less than half the population

underwent PCI for their index event, which appears relatively low and suggests, perhaps, that insufficient revascularisation may have contributed to recurrent events, that may have masked the potential benefit of triple therapy(6, 32, 69).

#### Identifying and targeting high risk patients

Several risk stratification scores have been suggested to assess the risk of recurrent ischaemic events in patients with ACS. These include the GRACE score (Global Registry of Acute Cardiac Events), the PURSUIT score (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) the TIMI score (Thrombolysis in Myocardial Infarction) consisting of a variation of clinical and angiographic risk factors.

#### Choice of P2Y<sub>12</sub> inhibitor

The choice of P2Y<sub>12</sub> inhibitor in the DAPT and triple therapy arms of the study may be relevant. Most ACS studies included patients that received a combination of aspirin and clopidogrel(45-52). Contemporary evidence-based medicine recommends more potent P2Y<sub>12</sub> inhibitors ticagrelor or prasugrel in ACS, rather than clopidogrel, due to their superiority in reducing the risk of further MACE(32) (11) (13). It therefore suggests that the combination of triple therapy with DAPT and a NOAC should be compared to a control arm that comprised DAPT with ticagrelor or prasugrel, and not clopidogrel. A very recent systematic review and network meta-analysis of 47 randomised controlled trials of nearly 200,000 participants with ACS

showed that compared to aspirin monotherapy, only the combination of aspirin with ticagrelor was reduced cardiovascular mortality (OR 0.80, 95% CI 0.68–0.93), whilst the combination of aspirin, clopidogrel, and very low dose rivaroxaban reduced all-cause mortality (OR 0.67, 95% CI 0.49–0.90)(56). There is intuitive fear that the combination of a NOAC with DAPT that includes these more potent P2Y<sub>12</sub> inhibitors will likely increase bleeding compared to clopidogrel, but this is by no means guaranteed. Although prasugrel reduced MACE compared to clopidogrel in ACS patients in the TRITON-TIMI 38 at a cost of increased bleeding(11) , ticagrelor reduced MACE compared to clopidogrel without significant increase in bleeding(13). Comparisons of triple therapy including ticagrelor versus clopidogrel have not shown a difference in bleeding(70) and the results of the GEMINI-ACS-1 study are also encouraging (*vide infra*).

### Clinical efficacy endpoints

There has also been heterogeneity in the primary efficacy outcomes (Table 1) with some studies including only ischaemic strokes and others all strokes, some including all-cause mortality and others only CV death, and some others including the need for revascularisation.

### **Conclusions**

In patients with a recent ACS where DAPT is the current standard of care, the use

instead of triple therapy, with addition of an oral anticoagulant, PAR1 antagonist or cilostazol, has been investigated with the aim of reducing future ischaemic events. Triple therapy leads to a significant increase in bleeding, and this is unacceptably high with vorapaxar and with warfarin. Low dose rivaroxaban 2.5 mg twice daily can be considered in combination with aspirin and clopidogrel for ACS patients who have high ischaemic and low bleeding risk. There is a clear signal that triple therapy can, at times, reduce ischaemic events, but the excessive bleeding seems to exceed the potential benefit. There is an absolute necessity for accurate risk stratification of these patients, both in terms of risk of future ischaemic events as well as bleeding, to allow targeted, individualised treatment.

### **Future directions**

Future trials should focus on identifying patients at high risk of recurrent adverse ischaemic events, who may gain most from more potent antithrombotic agent combinations.

In addition to GRACE and TIMI risk scores in ACS patients, several angiographic markers of recurrent thrombosis, such as stent diameter and length of stented segment or stent under-expansion, as well as completeness of revascularisation, could be incorporated into risk assessment.

Platelet function tests may have a role in identifying patients at high risk of future ischaemic events. Multiple large observational studies have described the association between HTPR while on clopidogrel and increased rates of nonfatal MI, definite/probable stent thrombosis, and CV mortality(71, 72). In the ADAPT-DES

(Assessment of Dual AntiPlatelet Therapy With Drug Eluting Stents) study of 8,582 patients undergoing PCI with DAPT, 51.7% presented with ACS. HTPR was an independent predictor of stent thrombosis (HR 2.49,  $p = 0.001$ ) and MI (HR 1.42, 95% CI 1.09-1.86;  $p=0.01$ ) at 1 year, but not a predictor of mortality(73). Although there is very limited data to support the concept that alterations of therapy based on platelet function measurements improve clinical outcome, this should not deter from using platelet function tests to identify patients at high risk of ischaemic events that may benefit from more aggressive pharmacotherapy.

Since bleeding remains a concern with more potent combinations of agents, accurate bleeding risk stratification and perhaps mandated prophylactic use of proton-pump inhibitors should be seriously considered.

Another newer antiXa inhibitor, edoxaban is currently being evaluated in a phase II trial, together with aspirin and clopidogrel, in patients with ACS(74).

The recently published GEMINI-ACS study was a phase II randomised controlled trial, of 3037 patients with ACS assessing the effect of the newer P2Y<sub>12</sub> inhibitors in addition to aspirin or NOAC(75). Patients were randomised to receive aspirin or low dose 2.5mg b.i.d rivaroxaban in addition to clopidogrel or ticagrelor. There was no significant difference between rivaroxaban and aspirin with respect to the primary endpoint of clinically significant (non-CABG related) bleeding (HR 1.09;  $p=0.548$ ). Moreover, amongst patients receiving ticagrelor, there was no significant difference in bleeding whether combined with aspirin or rivaroxaban, and no difference when compared to the clopidogrel arm. Of note, the bleeding rates were non-significantly higher for the ticagrelor group, and would need to be addressed in a larger study in order to assess the safety of the combination treatment with rivaroxaban and ticagrelor. Nevertheless, the combination of P2Y<sub>12</sub> inhibitor and NOAC seems

promising. The concept of DAPT may be replaced, not by triple therapy, but by dual therapy comprising an OAC with a P2Y<sub>12</sub> inhibitor.

The challenge is not only to find the right combination, but also to get it to the right patient.

### **CONFLICT OF INTEREST**

The authors confirm that there are no conflicts of interest pertaining to this manuscript.



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**Table 1 Study characteristics**

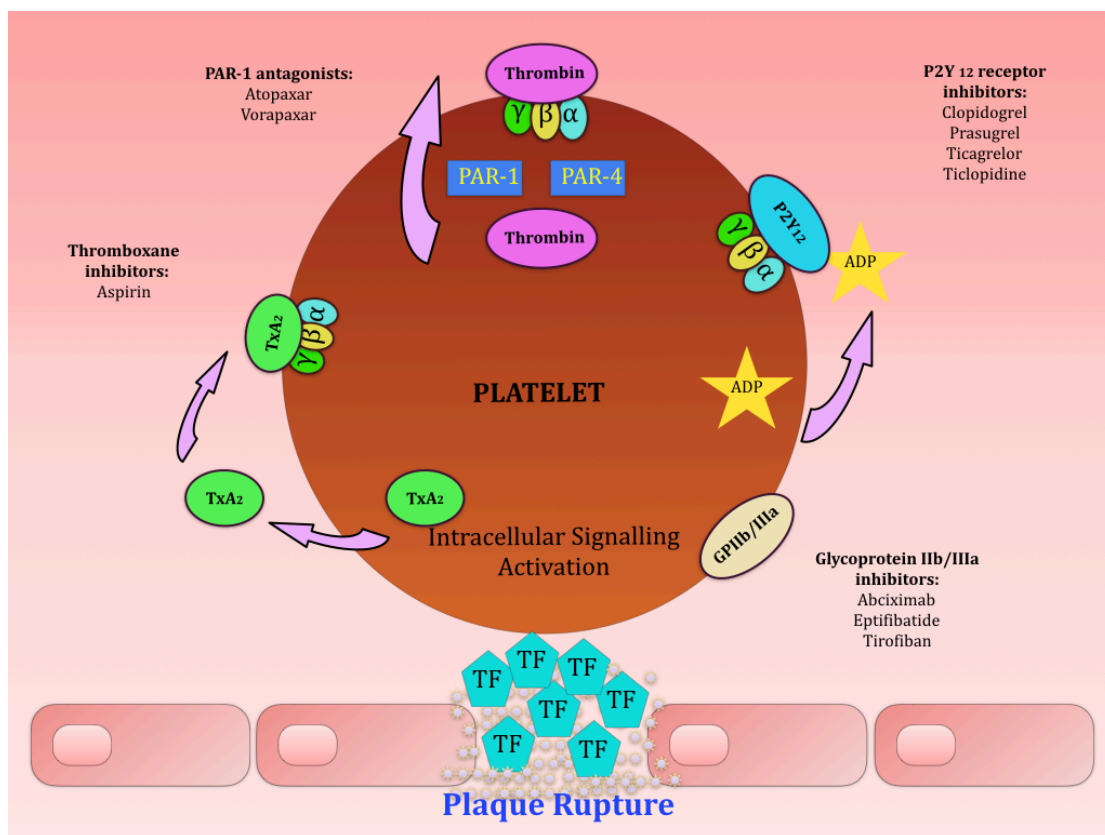
<b>Study</b>	<b>Type</b>	<b>Patients (n)</b>	<b>Clinical presentation (%)</b>	<b>STEMI</b>	<b>Non STEMI</b>	<b>Unstable angina</b>	<b>PCI for index admission (%)</b>	<b>Antithrombotic use</b>
<b>TRA-2P(36)</b>	Double blind placebo-controlled phase III	26449		0	0	0	0	Vorapaxar
<b>TRACER(35)</b>	Double blind placebo-controlled phase III	12944		0	100	0	57	Vorapaxar
<b>APPRAISE-2(48)</b>	Double blind placebo-controlled phase III	7392		40	42	18	44	Apixaban
<b>ATLAS ACS2-TIMI51 (46)</b>	Double blind placebo-controlled phase III	15526		50	26	24	60	Rivaroxaban

DAPT use, (%)	P2Y <sub>12</sub> inhibitor use	Duration of treatment, (months)	Dose, (mg)	Primary safety endpoint	Safety outcome, HR (95% CI); <i>p</i> value
62	Clopidogrel	12	2.5mg o.d or placebo	TIMI clinically significant bleeding and moderate or severe bleeding GUSTO	2.5mg o.d: 1.66 (1.43-1.93) <i>p</i> <0.001
92	Clopidogrel	12	2.5mg o.d or placebo	TIMI clinically significant bleeding and moderate or severe bleeding GUSTO	2.5mg o.d: 1.35 (1.16-1.58) <i>p</i> <0.001
81	Clopidogrel	8	5mg b.i.d or placebo	TIMI major bleeding not related to CABG	5mg b.i.d: 2.59 (1.40-4.46) <i>p</i> =0.001
93	Clopidogrel	13	2.5mg b.i.d, 5mg b.i.d or placebo	TIMI major bleeding not related to CABG	2.5mg b.i.d: 3.46 (2.08-5.77) <i>p</i> <0.001
					5mg b.i.d: 4.47 (2.71-7.36) <i>p</i> <0.001

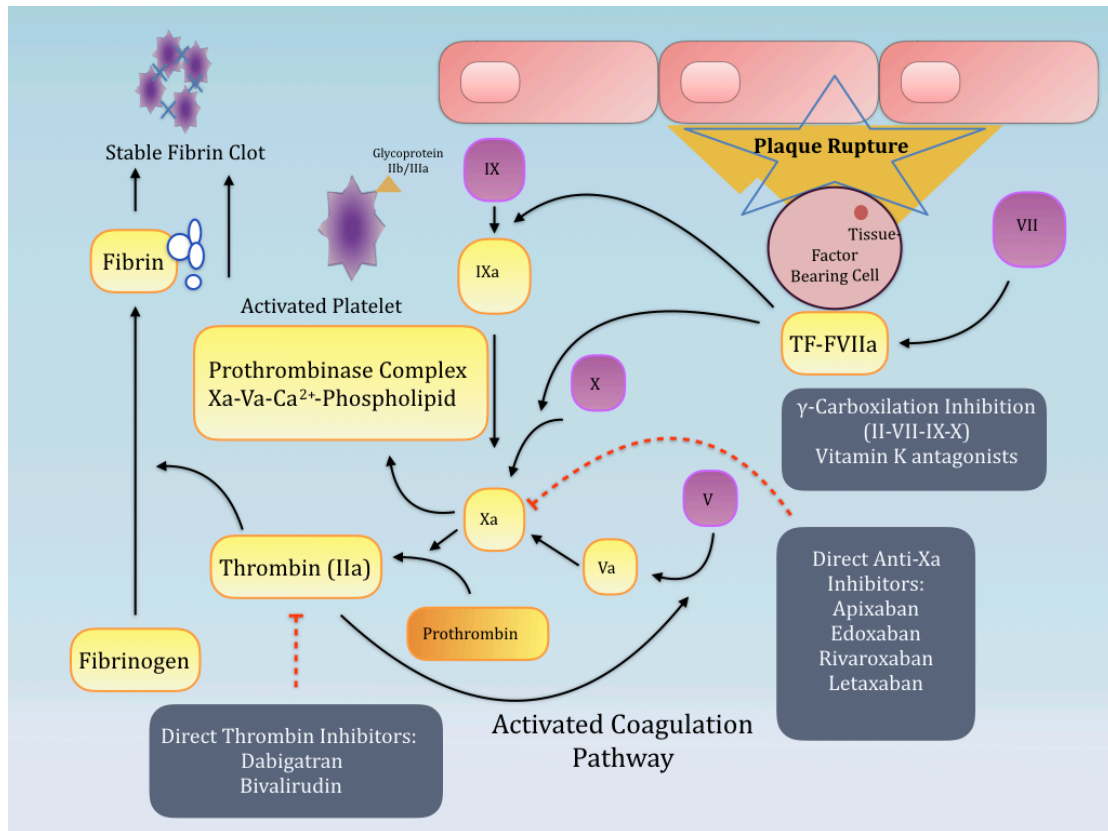


Primary efficacy endpoint	Efficacy outcome, HR (95% CI); p value
CV death, MI or stroke	2.5mg o.d: 0.87 (0.80-0.94) p<0.001
CV death, MI, stroke, recurrent ischemia with rehospitalization or urgent revascularization	2.5mg o.d: 0.92 (0.85-1.01) p=0.07
CV death, MI or ischaemic stroke	5mg b.i.d: 0.95 (0.80-1.11) p=0.510
CV death, MI, stroke	2.5mg b.i.d: 0.84 (0.72-0.97) p=0.007
	5mg b.i.d: 0.85 (0.73-0.98) p=0.03

STEMI: ST-elevation myocardial infarction, NSTEMI: non ST-elevation myocardial infarction, PCI: percutaneous coronary intervention, DAPT: dual antiplatelet therapy, TIMI: Thrombolysis In Myocardial Infarction, CABG: coronary artery bypass graft, GUSTO: Global Use of Strategies To Open Occluded Arteries, HR: hazard ratio, CI: confidence interval, CV: cardiovascular, MI: myocardial infarction, b.i.d: twice daily, o.d: once daily



**Figure 1:** Platelet activation and aggregation in response to endothelial injury following plaque rupture in acute coronary syndrome  
GP: glycoprotein, TxA2: thromboxane, TF: tissue factor, PAR: protease activated receptor



**Figure 2:** Activated coagulation pathway and common sites of anticoagulant action  
 TF: transfer factor, GP: glycoprotein