Anti-thrombotic drugs constitute the cornerstone of therapy in the management of acute coronary syndromes (ACS) and for patients undergoing percutaneous coronary intervention. Anti-thrombotic therapy during percutaneous coronary intervention for ACS has evolved substantially over the past 15 years. In the original 1996 ACC/AHA guidelines for the management of acute myocardial infarction (MI), only one antiplatelet agent (aspirin) and one anticoagulant (unfractionated heparin) were recommended as class I therapies. Much has since changed and the contemporary therapeutic armoury for the treatment of ACS reflects the pharmacological advances that have taken place. Recent developments in the medical management of ACS have been based around developing drugs with more predictable efficacy and at known drug targets. However there has also been considerable development of novel agents. New pharmacotherapies for ACS reflect efforts to improve efficacy and minimize complications by increasing target specificity and reducing inter-individual variation in therapeutic response.

**KEYWORDS:** acute coronary syndrome • anticoagulant • antiplatelet • antithrombotic • myocardial infarction • NSTEMI • PCI • STEMI

**Antiplatelet therapy**

Platelet activation and aggregation is a key step in the development of thrombus over a ruptured coronary plaque. The current pharmacological agents used to target platelet activation and aggregation fall into three different mechanisms: cyclo-oxygenase inhibition with aspirin, glycoprotein IIb/IIIa inhibition and P2Y12 receptor antagonism. However, newer therapeutic agents, such as vorapaxar and atorvapaxar, have been developed to modify novel targets (Figure 1). Table 1 shows the standard doses for the drugs covered in this paper.

Cyclo-oxygenase inhibitors, namely, aspirin, inhibit the production of thromboxane A₂. Thromboxane A₂ is normally produced by activated platelets and stimulates further platelet activation and aggregation. Aspirin irreversibly inhibits cyclo-oxygenase, thereby preventing platelets synthesizing new COX and subsequent thromboxane A₂. Aspirin’s effect on platelet inhibition and aggregation are both predictable and reliable and monitoring is typically only performed to assess compliance; this contrasts with other antiplatelet agents such as clopidogrel, which have a more variable dose–response relationship.

The evidence for aspirin efficacy in ST-elevation myocardial infarction (STEMI) comes from the second international study of infarct survival trial, which demonstrated a 23% reduction in vascular mortality in patients presenting with acute MI (AMI) (p < 0.00001) [1], a benefit maintained alongside thrombolysis with streptokinase. Aspirin also reduced nonfatal recurrent MI and stroke with no significant excess major bleeding. The evidence for aspirin use in non-ST-segment elevation acute coronary syndromes (NSTEMI) is from older trials, often where neither ECG criteria nor cardiac enzyme elevation were required for trial enrolment. However, in these trials a benefit from aspirin alone (relative risk [RR]: 0.30; p = 0.072) [2] and in addition to heparin (absolute risk reduction: 3%; p = 0.01) [3] was demonstrated. In summary, aspirin has been shown to reduce mortality in STEMI and unselected NSTEMI-ACS patients as both monotherapy and in addition to heparin. Its predictable antiplatelet effects mean ex vivo monitoring is rarely necessary.
P2Y12 inhibitors include the second-generation thienopyridine drug clopidogrel, third-generation prasugrel and the cyclo-pentyltriazolopyrimidine ticagrelor, which have now replaced the first-generation drug ticlopidine. Cangrelor is an intravenous first-generation drug ticlopidine. Cangrelor is an intravenous P2Y12 inhibitor currently in clinical testing. Recently, preclinical data have led to the hypothesis that these agents may contribute an additional pleiotropic effect, reducing the burden of MI in ACS patients through a mechanism akin to ischemic pre- and postconditioning.

Clopidogrel and prasugrel are pro-drug thienopyridines that bind irreversibly to the P2Y12 receptor, preventing ADP-mediated platelet activation and aggregation. Ticagrelor is thought to bind allosterically to the same receptor, and unlike clopidogrel and prasugrel, is not a pro-drug. Thienopyridines have significantly improved clinical results after implantation of coronary stents and ACS. Initially, trials in the late 1990s of ticlopidine, in addition to aspirin, had shown reduced cardiac events and stent thrombosis in those undergoing an invasive strategy compared with those treated with aspirin alone or aspirin and anticoagulation with warfarin. However, ticlopidine was limited by its potential severe gastrointestinal and hematological adverse effects, with neutropenia constituting a life-threatening complication. Clopidogrel in contrast did not exhibit these side effects and replaced ticlopidine in routine practice after the CLASSICS trial showed noninferiority for clopidogrel versus ticlopidine and an improved safety profile.

The CREDO trial went on to show prolonged treatment (1 year) with clopidogrel and aspirin versus aspirin alone reduced the composite of death, MI or stroke (relative risk reduction: 26.9%; 95% CI: 3.9–44%; p = 0.02) and there was a trend of further benefits to those treated earlier (6 h or more pre-PCI) with clopidogrel (relative risk reduction: 38.6%; p = 0.051). Clopidogrel was also shown to offer benefit in STEMI patients not undergoing an invasive strategy in the COMMIT trial.

In the large landmark CURE study, clopidogrel (300 mg loading dose and 75 mg daily) for 9–12 months in combination with aspirin was tested against aspirin alone in patients with non ST-elevation acute coronary syndromes, irrespective of the initial treatment strategy (medically or invasively). The composite of CV death, MI and stroke was reduced versus aspirin alone (RR: 0.80; 95% CI: 0.72–0.90; p < 0.001). This was driven by a reduction in MI (RR: 0.77; 95% CI: 0.67–0.89) and cardiovascular mortality was similar between groups (RR: 0.93; 95% CI: 0.79–1.08). Major bleeding was increased in the clopidogrel arm (RR: 1.38; 95% CI: 1.13–1.67; p = 0.001), though the increase in life-threatening bleeding was not significant and fatal bleeding was similar between the groups. Subsequently, the CURRENT-OASIS trial indicated a loading clopidogrel dose of 600 mg conferred additional benefits above 300 mg in patients undergoing an early invasive strategy. However, the higher dose did not appear beneficial for patients treated medically, and was associated with an increased rate of major bleeding. Based on these studies, clopidogrel in addition to aspirin has become the standard of care for both patients with ACS and those undergoing elective PCI.

Clopidogrel however has limitations, including a delayed onset of action and a variable clinical response due to interindiv-idual variation in metabolism. A pro-drug, clopidogrel’s antiplatelet activity is variable due to differences in both absorption and metabolism. Absorption is affected by polymorphisms in the ABCB1 gene, which encodes P-glycoprotein, an ATP-dependent eflux pump whose active substrates include clopidogrel. Clopidogrel metabolism is affected by polymorphisms in the cytochrome P450 3A4 (CRP3A4) and cytochrome P450 2C19 (CYP2C19), which act to activate clopidogrel through oxidation in the liver. Clopidogrel-treated patients with reduced functional variants of the CYP2C19 gene have lower levels of clopidogrel metabolites and diminished
platelet inhibition (Figure 2). Data have shown that patients with loss of function mutations in the CYP2C19 gene are at an increased risk of cardiovascular events following PCI [16]. It has been suggested that tailored antiplatelet regimens based on peri-procedural tests of platelet reactivity may improve outcomes [17]. Recently, the benefits of platelet reactivity testing ex vivo were tested in the ARCTIC trial, which assessed platelet reactivity using the VerifyNow P2Y12 and aspirin point-of-care assays in the catheterization laboratory both immediately pre-PCI and several weeks later in the outpatient clinic [18]. Those in the active arm who demonstrated residual high platelet activity (34.5% of those taking clopidogrel) received extra P2Y12 inhibition in the form of extra clopidogrel or prasugrel as well as being administered a glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitor intraprocedurally. The composite of death, MI, stent thrombosis, stroke and urgent revascularization were no different at 1 year however (hazard ratio (HR): 1.13; 95% CI: 0.98–1.29; p = 0.10), and no benefit was seen in the composite of stent thrombosis or urgent revascularization. Therefore, the benefit of routine platelet function testing remains unproven.

The limitations of clopidogrel have led to the development of potentially more effective agents. Some of these agents offer increased efficacy at proven targets involved in platelet activation (P2Y12 inhibitors prasugrel and ticagrelor) while other drugs modulate new targets, such as protease-activated receptor-1 (vorapaxar, atopaxar).

**Recent advancements of p2y12 inhibitors**

**Prasugrel**

**Background**

Prasugrel, like clopidogrel, is a thienopyridine prodrug whose active metabolite mediates its antiplatelet effect through irreversible inhibition of the P2Y12 receptor. Both drugs require transformation to their active metabolites in a two-step process. In the case of clopidogrel, both of these steps are reliant on the cytochrome P450 system, and polymorphisms in these pathways can result in a larger proportion of the drug to be shunted through an alternative inactive pathway, mediated by esterases. Prasugrel, however, is less sensitive to such polymorphisms, with the first step of activation mediated by these esterases. Prasugrel activation therefore delivers a more rapid and predictable therapeutic effect as neither ABCB1 nor CYP2C19 polymorphisms significantly affect its metabolism.

**Evidence**

The TRITON-TIMI 38 trial assessed prasugrel versus clopidogrel in STEMI and moderate-to-high risk NSTEMI patients undergoing an invasive treatment strategy [10]. Patients were treated with either 60 mg loading dose prasugrel followed by 10 mg daily or 300 mg clopidogrel followed by 75 mg daily. NSTEMI patients needed a TIMI risk score >3, and either ST-segment deviation not meeting STEMI criteria or elevated cardiac enzymes. A total of 3534 patients presenting with STEMI within 12 h of the onset of symptoms were randomized pre-PCI. Those treated with prasugrel demonstrated a significant reduction in the composite primary endpoint of CV death, MI and stroke (HR: 0.79; 95% CI: 0.65–0.97; p = 0.02). However, from subgroup analysis most of the benefit appeared to be in patients not treated by primary percutaneous coronary intervention (PPCI) as PCI-treated patients appeared to receive little benefit compared with clopidogrel [21].

NSTEMI patients were only randomized following coronary angiography if a lesion amenable to PCI was demonstrated (conservatively managed NSTEMI patients were excluded). Prasugrel or clopidogrel was predominantly administered during PCI or within 1 h after leaving the catheterization laboratory. The primary endpoint of a composite of CV death, MI and stroke was significantly reduced (HR: 0.82; 95% CI: 0.73–0.93; p = 0.002). However, most of this effect was due to a reduction in subsequent non-fatal MI (HR: 0.76; 95% CI: 0.67–0.85; p < 0.001) with no independent effect on cardiovascular death (HR: 0.89; 95% CI: 0.70–1.12; p = 0.31). The benefits from prasugrel were at the expense of an increase in major bleeding including fatal bleeding. Both the US FDA and EMA have provided warnings for patients with prior stroke or transient ischemic attack due to a greatly increased bleeding risk with prasugrel in this cohort [22]. Furthermore, subgroup analysis of patients aged above 75 and those weighing less than 60 kg has shown a greater risk of bleeding and reduced benefits from prasugrel among these patients [22]. These high-risk groups may make up a third of real-world high-risk ACS patients [23] and a lower maintenance dose of 5 mg has been recommended in such patients; however, there is no evidence for superiority over clopidogrel at this dose [24]. Interestingly, subgroup analysis of diabetic patients suggests that prasugrel may be associated with a greater clinical benefit without an elevated bleeding risk, [25], though reasons for this are not fully understood.

![Figure 2. The activation of clopidogrel is highly cytochrome-dependent, with polymorphisms in CYP2C19 (italicized) resulting in variable shunting through an esterase-dependent inactive pathway. Prasugrel activation is largely unaffected by such polymorphisms.](image-url)
It is important to note that these composite endpoints were largely powered by a reduction in non-fatal MI. However, the definition of MI (creatine kinase greater than two-times the upper limit of normal) has been criticized by some as being ‘liberal’, and may have resulted in overdiagnosis of events representing an ‘increase in cardiac ischemic biomarkers that is common during successful reperfusion’ [27]. Stent thrombosis was reduced in the prasugrel group, but this endpoint included ‘definite and probable’ stent thrombosis, and mortality was not reduced. Prasugrel therapy was associated with an increased risk of major (p = 0.003), life-threatening (p = 0.01) and fatal bleeding (p = 0.002). Furthermore, studies examining platelet reactivity after a loading dose of prasugrel or ticagrelor have shown STEMI patients to demonstrate higher platelet reactivity than those not suffering AMI [28]. Finally, as with the other antiplatelets, prasugrel, marketed as Effient®, costs significantly more than generic clopidogrel (£47.56 per 28-tap packet versus £1.71 at time of writing) [29].

The ACCOAST trial went on to assess the benefit of pretreatment with prasugrel in the setting of high-risk NSTEMI/UA versus the postangiography strategy used in TRITON-TIMI 38 [30]. It randomized 4033 NSTEMI patients to receive either pretreatment with 30 mg prasugrel or placebo before their scheduled angiography. When PCI was indicated, a further 30 mg prasugrel ‘top-up’ was administered to the
pretreatment group, while 60 mg was administered to the patients who had received placebo prior to angiography. The compound primary endpoint of CV death, MI, stroke, urgent revascularization or GP IIb/IIIa inhibitor bail-out was not reduced in the pretreatment group (HR: 1.02; 95% CI: 0.84–1.25; p = 0.81) but there was an increased risk of TIMI major bleeding (HR: 1.9; 95% CI: 1.19–3.02; p = 0.006).

Finally, the TRILOGY-ACS trial assessed prasugrel in patients with high risk treated conservatively. Follow-up was relatively long (median >14 months), reflecting the trial hypothesis that long-term treatment with prasugrel over clopidogrel might reduce future cardiovascular events [31]. However, the composite endpoint of CV death, MI and stroke was not significantly reduced. Furthermore, none of the prespecified efficacy endpoints were met. However, in contrast to TRITON-TIMI 38, bleeding was not increased. This may be partly due to the decreased dose (5 mg rather than 10 mg) used in patients above 75 years of age and body weight below 65 kg.

Summary
Prasugrel’s metabolism is more predictable than that of clopidogrel and with a faster speed of onset. Compared with clopidogrel, prasugrel therapy reduces non-fatal MI but not mortality in those undergoing PCI post-ACS; however, this is at the cost of increased bleeding. Evidence supports delaying the use of prasugrel in NSTE-ACS until a lesion amenable to clopidogrel might reduce future cardiovascular events [31]. However, the composite endpoint of CV death, MI and stroke was not significantly reduced. Furthermore, none of the prespecified efficacy endpoints were met. However, in contrast to TRITON-TIMI 38, bleeding was not increased. This may be partly due to the decreased dose (5 mg rather than 10 mg) used in patients above 75 years of age and body weight below 65 kg.

**Ticagrelor**

**Background**
The nucleoside analogue ticagrelor is an allosteric inhibitor of the P2Y12 receptor. This is in contrast to the thienopyridines that act at the ADP binding site. Unlike clopidogrel and prasugrel, ticagrelor is not a pro-drug and is rapidly reversible. It is not influenced by variations in CYP450. Its reversible binding coupled with the speed of offset is reflected in its twice-a-day dosing regimen. This may offer advantages in patients who may go on to receive surgery, but may lead to safety concerns in patients with compliance issues.

**Evidence**
The PLATO trial randomized 18,624 patients with STEMI or high-risk NSTE-ACS within 24 h of onset of symptoms [32]. Patients received either ticagrelor or clopidogrel. NSTE-ACS patients required ST-segment changes on electrocardiography, a positive biomarker of MI or one of several risk factors that included age >60 years, previous MI, peripheral vascular disease and renal disease.

The composite of death from vascular causes, MI or stroke was reduced across all subgroups receiving ticagrelor including those with STEMI and NSTE-ACS at 12 months (HR: 0.84; 95% CI: 0.77–0.92; p < 0.001). The secondary endpoints of all-cause mortality, MI and death from vascular causes were also reduced in the ticagrelor arm. Major bleeding overall as defined by PLATO criteria was not increased in patients receiving ticagrelor (11.6 vs 11.2%; p = 0.43), though there was an increased rate of non-CABG-related major bleeding and fatal intracranial bleeding. The benefit of ticagrelor was consistent among patients with renal dysfunction (GFR <60 ml/min) [33].

**Summary**
Ticagrelor offers a more rapid onset of antiplatelet effects compared with clopidogrel and reduced mortality in STEMI and high-risk NSTE-ACS patients at the expense of an increase in major but not fatal bleeding.

**Intravenous P2Y12 inhibitors**

**Cangrelor**

**Background**
Cangrelor, like ticagrelor, is an allosteric inhibitor of the P2Y12 receptor with a half-life of 3–5 min. It is administered as an intravenous infusion and normal platelet function is restored within 1 h of cessation. At present, cangrelor is unlicensed in both Europe and the USA.

**Evidence**
The CHAMPION-PLATFORM trial randomized 5362 clopidogrel-naive NSTE-ACS patients to either cangrelor or placebo at the time of PCI, followed by 600 mg of clopidogrel [34]. The trial initially included patients with stable angina, but a protocol amendment went on to limit the trial to NSTE-ACS patients. The composite of death, MI or ischemia-driven revascularization was not significantly different between the two arms, and the trial was stopped early after it was judged unlikely that the trial would demonstrate superiority for cangrelor. However, the rates of stent thrombosis were reduced in the cangrelor arm at 48 h (OR: 0.31; 95% CI: 0.11–0.85; p = 0.02).

The CHAMPION-PCI trial randomized 8877 patients with STEMI, NSTE-ACS or stable angina [35]. Patients were randomized to either cangrelor or 600 mg oral clopidogrel prior to PCI. As in the CHAMPION-PLATFORM trial, patients with stable angina were later rendered ineligible for randomization. Cangrelor infusion was commenced 30 min before PCI and continued for 2 h afterwards. The composite of death, MI or ischemia-driven revascularization did not demonstrate superiority for cangrelor versus clopidogrel.

The CHAMPION-PHOENIX trial randomized 11,145 patients undergoing PCI for STEMI, NSTE-ACS or stable angina [36]. Patients were randomized to either cangrelor or 300 mg or 600 mg oral clopidogrel. The composite endpoint of death, MI, ischemia-driven revascularization or stent thrombosis within 48 h of randomization was significantly reduced for cangrelor (OR: 0.78; 95% CI: 0.66–0.93;
p = 0.005). Stent thrombosis was significantly reduced (OR: 0.62; 95% CI: 0.43–0.90; p = 0.01). However, there have been some concerns about the methodology of the trial [37]. These include the 300 mg loading dose of clopidogrel given to some of the patients in the control arm (rather than the 600 mg dose shown to be superior in the setting of PCI). Furthermore, over a third of the patients in the control arm received their first dose of clopidogrel during or after PCI. Finally, there is little evidence comparing cangrelor with prasugrel or ticagrelor in the setting of STEMI and NSTE-ACS.

Summary

Intravenous cangrelor offers rapid onset and offset of antiplatelet therapy, though its role in STEMI and NSTE-ACS is unclear. Only the CHAMPION-PHOENIX trial has demonstrated superiority above clopidogrel, and concerns exist regarding the timing and doses of clopidogrel in the control arm.

Other antiplatelet therapies in practice

**GP IIb/IIIa inhibitors**

The GP IIb/IIIa inhibitors include abciximab, tirofiban and eptifibatide (all intravenously administered agents) and target the final common pathway in platelet aggregation by preventing the GP IIb/IIIa integrin complex binding with fibrinogen and von Willebrand factor. Although they have a role in patients undergoing PCI for ACS, the popularity of these agents has declined with the development of effective oral antiplatelet drugs.

Evidence

The majority of trials supporting the use of GP IIb/IIIa inhibitors in STEMI and NSTE-ACS were conducted before the routine use of P2Y12 inhibitors. Recent studies have concentrated on their use in PPCI for STEMI looking at route of administration, timing and use in addition to dual antiplatelet therapy.

Intracoronary abciximab in STEMI

The recent INFUSE-AMI trial was a randomized 2 × 2 factorial single-blinded trial of STEMI patients with left anterior descending artery occlusion undergoing PPCI. Patients were randomized to a single 0.25 mg/kg intracoronary bolus of abciximab with bivalirudin compared with bivalirudin alone as well as manual aspiration thrombectomy versus PCI alone. All patients received dual antiplatelet therapy. There was a 2.3% reduction in the primary endpoint of 30-day infarct size assessed by cardiac magnetic resonance imaging with the use of intracoronary abciximab (15.1 vs 17.9%; p = 0.03). However, although infarct size at 30 days was reduced with intracoronary abciximab, early markers of microcirculatory reperfusion (Myocardial Blush Grade and ST-segment resolution) were not improved, results that are consistent with the comparable 30-day clinical event rates between the groups. Moreover, the magnitude of the absolute reduction in infarct size with intracoronary abciximab, while statistically significant, was modest (mean reduction 2.3% (95% CI: 0.2–4.4%) of total left ventricular mass, less than the 6% that was considered clinically relevant during planning of the study).

**Early administration in STEMI**

The recent MISTRAL study was a prospective, randomized, double-blinded study involving 256 patients with acute STEMI [38]. Patients were randomized to either 0.25 mg/kg abciximab in the ambulance (early) or in the catheterization laboratory (late). Both groups received aspirin and unfractionated heparin (UFH) in the ambulance. The primary endpoint of complete ST-segment resolution 60 min after PCI did not differ between group, though procedural embolization was significantly reduced in the early group (8.1 vs 21.1%; p = 0.008). The study findings were consistent with those of the FINESSE trial where 2452 patients with STEMI were treated with either reduced-dose reteplase with abciximab, abciximab alone or placebo, followed by expedited primary PCI. Placebo-treated patients received abciximab at the time of PCI. This trial found no effect from early abciximab administration on the 90-day composite outcome of all-cause mortality/rehospitalization for congestive heart failure, resuscitated ventricular fibrillation more than 48 h after randomization and cardiogenic shock [39].

These studies have provided further information about the use of abciximab in PPCI. Administration in the ambulance appears to have limited benefit, especially if transfer to the catheterization lab is efficiently achieved. Intracoronary abciximab use appears to modestly reduce infarct size but does not affect early outcomes. Finally, the data on these drugs must also be interpreted in view of the use of older dual antiplatelet agents in the studies (aspirin and clopidogrel).

**GP IIb/IIIa inhibitors in NSTE-ACS**

There is no evidence for a benefit from these agents outside of the setting of PCI. Furthermore, as with STEMI, the majority of studies were performed before the routine use of clopidogrel or other P2Y12 receptor antagonists. The ISAR-REACT 2 trial however randomized 2022 patients undergoing PCI for NSTE-ACS to either abciximab or placebo, in addition to 500 mg aspirin and 600 mg clopidogrel [40]. There was a significant reduction in the composite of death, MI or urgent target vessel revascularization at 30 days in patients treated with abciximab (RR: 0.75; 95% CI: 0.58–0.97; p = 0.03). This benefit was limited to patients with positive troponin levels (NSTE-ACS).

Summary

The role of GP IIb/IIIa inhibitors in PPCI alongside newer P2Y12 antagonists remains debatable. However, despite the lack of clear evidence they are still used by many operators when there is angiographic evidence of high thrombotic burden or low-flow states [41].
In the setting of NSTE-ACS, NSTEMI patients may benefit from the addition of abciximab to oral dual antiplatelet therapy, but deferred and selective treatment with these agents reduces bleeding and does not seem to compromise clinical outcomes. European guidelines state it is ‘reasonable’ to combine a GP IIb/IIIa inhibitor with dual oral antiplatelet therapy in NTE-ACS patients undergoing PCI who have a high peri-procedural complication risk with a low risk of bleeding [42]. American guidelines state both GP IIb/IIIa inhibitors and a P2Y12 receptor antagonist should be given in high-risk troponin-positive NTE-ACS patients prior to angiography [43].

Future antiplatelet drugs
PAR-1 antagonists
Vorapaxar and atopaxar are oral protease-activated-receptor 1 (PAR-1) antagonists, which are inhibitors of thrombin-mediated platelet activation. Preclinical studies have shown that selective blockade of this pathway results in a significant reduction in platelet reactivity in pro-thrombotic states, while largely preserving hemostatic function [44].

Vorapaxar
The TRACER trial randomized 12,944 patients to either vorapaxar or placebo in NSTEMI patients on top of standard therapy of dual antiplatelet therapy [45]. The trial was terminated early after median follow-up of 502 days due to concerns over increased rates of major bleeding, including intracerebral hemorrhage. There was no significant difference in the composite primary endpoint of cardiovascular mortality, MI, stroke, hospitalization for recurrent ischemia or urgent revascularization (HR: 0.92 for vorapaxar; 95% CI: 0.85–1.01; p = 0.07). The secondary endpoint of the composite of cardiovascular death, MI or stroke was significantly reduced for those on vorapaxar (HR: 0.89; 95% CI: 0.81–0.98; p = 0.02). However, rates of moderate and severe bleeding (HR: 1.35; 95% CI: 1.16–1.58; p < 0.001) and intracranial hemorrhage were significantly increased (HR: 3.39; 95% CI: 1.78–6.45; p < 0.001).

TRA 2P-TIMI 50 trial went on to assess whether vorapaxar may have a net clinical benefit in the setting of secondary prevention [46]. It randomized 26,449 patients with a history of previous MI (two-thirds of patients), ischemic stroke or peripheral arterial disease to either 2.5 mg daily vorapaxar or placebo. During the trial, enrollment to patients with a history of stroke was closed due to a significantly increased rate of intracranial hemorrhage in these patients. By median 30 months follow-up, the composite of CV death, MI or stroke was significantly reduced (HR: 0.87; 95% CI: 0.80–0.94; p < 0.001) among patients taking vorapaxar, though moderate or severe bleeding was increased (HR: 1.66; 95% CI: 1.43–1.93; p < 0.001), including intracranial hemorrhage. Furthermore, patients with a body weight below 60 kg showed an increased rate of adverse events. In light of these two trials, vorapaxar’s manufacturers are not seeking approval for the drug in the setting of ACS. However, a recent US FDA review has endorsed the drug for secondary prevention in prior MI patients with no history of stroke where risk of bleeding is low [47]. Vorapaxar remains unlicensed in Europe.

Atopaxar
The Phase II trial LANCELOT-ACS trial randomized 603 patients within 72 h of onset of high-risk NSTE-ACS to one of three doses of atopaxar or a matching placebo [48]. In total, 43% of patients underwent PCI, 96% received aspirin and 82% clopidogrel or ticlopidine. The incidence of CV death, MI, stroke or recurrent ischemia was similar between both arms (8.03% for atopaxar vs 7.75% for placebo; p = 0.93). There was no clear dose-dependent trend. The incidence of CURE major bleeding was nonsignificantly increased in patients receiving atopaxar (1.8 vs 0%; p = 0.12). The authors note that atopaxar treatment was associated with a significant reduction of ischemia on continuous ECG monitoring at 48 h (RR: 0.67; p = 0.02), though the significance of this is unclear, and larger Phase III trials are required to test the safety and efficacy of the drug.

Summary
Currently, there are no data to support the use of new PAR-1 antagonists in the acute treatment of ACS. It appears that with the development of improved P2Y12 antagonists there may be little benefit in the acute administration of PAR-1 antagonists. However, there may be a role as additive agents for these drugs in the secondary presentation of ischemic events in post-MI patients.

Acute anticoagulation
While platelet activation is an essential step in coronary atherothrombosis, the hallmark of thrombosis is the conversion of soluble fibrinogen into insoluble strands of fibrin (Figure 3). This step requires the activation of prothrombin into thrombin. Inhibition of thrombin generation, activation or both is therefore a logical target in the treatment of ACS, especially since patients may continue to suffer thrombotic events during the weeks and months after an ACS. Also, 17% of patients surviving an ACS event still experience recurrent events without secondary prophylaxis, and even with the newer antithrombotics there remains an 10% risk of recurrence over 12 months [49]. The high rates of recurrence highlight the need for more effective secondary prevention strategies. UFH and low molecular weight heparins (LMWH) have both been traditionally used in the acute management of ACS (STEMI and NSTEMI), though newer agents have been developed and tested extensively in clinical trials.

UFH is a naturally occurring glycosaminoglycan produced by basophils and mast cells. It consists of a highly heterogeneous mixture of molecules that contain a pentasaccharide sequence conferring the ability to reversibly bind with antithrombin III, increasing antithrombin III’s inhibition of factor Xa. It is given intravenously due to its poor subcutaneous absorption, and its therapeutic effect is unpredictable due to the variety of
molecules present. Its anticoagulant effect therefore requires close monitoring. UFH still remains widely used during PCI for ACS due to its reversibility; the anticoagulant effect disappears within hours and can be reversed rapidly with protamine.

Although UFH is still used extensively during PCI, alternative therapies are now typically used prior to PCI and in medically managed patients. Newer agents such as fondaparinux and, more recently, bivalirudin have all been shown to be of benefit in the management of ACS in certain settings. The mechanisms, evidence and role of these classical and newer agents in ACS are discussed in more detail alongside the novel oral anticoagulants (NOAC). Their mechanism of action is shown in Table 2.

LMWHs have predictable anti-Xa and antithrombin activity. They are almost completely absorbed when administered subcutaneously and demonstrate less protein binding. The result is a more predictable anticoagulation effect, though dosing alterations are required in patients with renal dysfunction. While activity can be measured through factor Xa assays, this is typically not performed in clinical practice. The risk of heparin-induced thrombocytopenia appears significantly lower in patients treated with LMWH [50]. However, unlike UFH, protamine does not fully reverse the effects of LMWH. In STEMI, enoxaparin is an alternative to UFH in the catheterization laboratory setting. A recent meta-analysis of 23 trials including 30,966 patients examined the safety and efficacy of enoxaparin versus UFH during PCI [51]. Patients were a mixture of those undergoing PPCI for STEMI (33.1%), secondary PCI following thrombolysis for STEMI (28.2%) and patients undergoing scheduled PCI, which included NSTEMI (38.7%). Enoxaparin was associated with a significant reduction in death (RR: 0.66; 95% CI: 0.57–0.76; p < 0.001), the composite of death and MI (RR: 0.68; 95% CI: 0.57–0.81; p < 0.001) and the complications of MI (RR: 0.75; 95% CI: 0.60–0.85; p < 0.001) while also reducing major bleeding (RR: 0.80; 95% CI: 0.68–0.85; p = 0.009). The reduction in both mortality (RR: 0.52; 95% CI: 0.42–0.64; p < 0.001) and major bleeding (RR: 0.72; 95% CI: 0.56–0.93; p = 0.01) remained significant on subgroup analysis of those patients undergoing PPCI for STEMI.

In NSTEMI, short-term enoxaparin use has been shown to improve outcomes [52] and is a more practical alternative to UFH, reducing recurrent MI beyond that seen on UFH therapy. Also, LMWH does not require regular monitoring. However, many operators performing PCI for STEMI or NSTEMI prefer still to use UFH due to their experience with this rapidly acting and reversible agent.
**Factor Xa inhibitors**

**Background**
The synthetic pentasaccharide fondaparinux is the only clinically available indirect selective factor Xa inhibitor. Its antithrombin binding domain is similar to that of the heparins. This domain confers avid but reversible antithrombin binding leading to increase antithrombin-mediated factor Xa inhibition. Its bioavailability is 100% when given subcutaneously. As with LMWH, it is renally cleared and is not licensed in patients with a creatinine clearance <20 ml/min.

**Evidence**
The OASIS-6 trial randomized 12,092 patients with STEMI to either fondaparinux or standard therapy (UFH or no anticoagulation) [53]. A total of 3768 patients (31.1%) were treated with primary PCI. Across all patients, fondaparinux significantly reduced the primary endpoint of the composite of death or reinfarction at 30 days (HR: 0.86; 95% CI: 0.77–0.86; p = 0.008), with a significant reduction in mortality alone, regardless of whether UFH was employed. However, subgroup analysis of those undergoing primary PCI and treated with fondaparinux demonstrated no reduction in the composite of death or reinfarction at 30 days (HR: 1.20; 95% CI: 0.91–1.57; p = 0.19) and a higher risk of catheter thrombosis (0 vs 22 patients, p < 0.001). Fondaparinux is therefore not recommended in this setting.

In the setting of elective or urgent PCI for STEMI, NSTE-ACS and stable angina, the ASPIRE study demonstrated that fondaparinux does not offer benefits over UFH in the catheterization laboratory due to increased abrupt vessel closure and unexpected angiographic thrombus [54]. In the setting of NSTE-ACS, however, OASIS-5 showed it to be noninferior to enoxaparin with similar composite outcomes of death, MI or refractory ischemia at 9 days [55]. However, this trial did demonstrate a significantly reduced rate of major bleeding 2.2% compared with 4.1% with enoxaparin (HR: 0.52; 95% CI: 0.44–0.61; p < 0.001), which translated to a statistically significant reduction of mortality at 6 months (11.3 vs 12.5%; HR: 0.89; 95% CI: 0.82–0.97; p = 0.007).

Following the catheter-related thrombosis findings of both OASIS 5 and 6, this prompted the OASIS investigators and guideline committees to recommend the use of UFH as adjunctive therapy at the time of PCI for patients with NSTE-ACS who were treated with fondaparinux and undergoing PCI, although the range of dosing recommended differed between the European Society of Cardiology guidelines (50–100 u/kg) and American College of Cardiology-American Heart Association guidelines (50–60 u/kg irrespective of GP IIb/IIIa inhibitor use). This uncertainty arises from the fact that dosing strategies are largely based on retrospective analysis of limited data.

The Fondaparinux trial with UFH during revascularization in acute coronary syndromes (FUTURA/OASIS-8) trial evaluated the safety of two dose regimens of adjunctive intravenous UFH during PCI in high-risk patients with NSTE-ACS who were initially treated with subcutaneous fondaparinux and referred for early angiography. The trial found that catheter-related thrombosis was rare (0.1%) when using the standard guideline-based dose of UFH in patients pretreated with fondaparinux. Based on a comparison with the fondaparinux group of the OASIS-5 PCI population, the addition of either dose of UFH to fondaparinux does not increase the rate of major bleeding. Reducing bleeding is important because several studies have suggested that moderate reductions in bleeding may lead to a reduction in longer-term ischemic events, particularly mortality [56].

Finally, heparin-induced thrombocytopenia is caused by platelet factor 4 (PF4)-heparin complexes. Its frequency is reduced by a factor of about 10 with LMWH as compared with UFH. The risk of heparin-induced thrombocytopenia is believed to be even lower with fondaparinux, and a causal association between fondaparinux and heparin-induced thrombocytopenia has not yet been described [57].

**Summary**
While not a replacement for UFH in the catheterization laboratory setting, fondaparinux is a safer alternative to LMWH when used as short-term antithrombotic treatment in NSTE-ACS. It should not be used in STEMI patients undergoing primary PCI.

**Direct thrombin inhibitors**

**Background**
Bivalirudin is the only direct thrombin inhibitor used clinically in STEMI and NSTE-ACS. It binds directly to thrombin, inhibiting both conversion of fibrinogen to fibrin and thrombin-mediated platelet aggregation. It can be monitored, as with heparin, via the activated partial thromboplastin time and activated clotting time, though it has a much more predictable anticoagulation effect as it is a single renally cleared molecule with no plasma protein binding.

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**Table 2. The mechanisms of action of anticoagulants used in the setting of acute coronary syndromes.**

<table>
<thead>
<tr>
<th>Indirect</th>
<th>Indirect thrombin inhibitors</th>
<th>Unfractionated heparin</th>
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</thead>
<tbody>
<tr>
<td>Indirect factor Xa inhibitors</td>
<td>Low-molecular-weight heparins</td>
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<tr>
<td>Direct</td>
<td>Direct thrombin inhibitors</td>
<td>Bivalirudin</td>
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<tr>
<td>Direct factor Xa inhibitors</td>
<td>Dabigatran</td>
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<td></td>
<td>Ximelagatran (withdrawn due to excessive liver dysfunction prior to license)</td>
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<td></td>
<td>Apixaban</td>
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<td>Rivaroxaban</td>
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<td></td>
<td>Edoxaban (in clinical trial development)</td>
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Evidence
The HORIZONS-AMI trial randomized 3602 patients with STEMI who were undergoing primary PCI to either treatment with bivalirudin alone or GP IIb/IIIa antagonist with UFH. Treatment with bivalirudin was associated with an improvement in 30-day adverse clinical events (RR: 0.76; 95% CI: 0.63–0.92; p = 0.005) and all-cause mortality (RR: 0.66; 95% CI: 0.44–1.00; p = 0.047). This is at least partially attributable to lower rates of major bleeding (RR: 0.6; 95% CI: 0.46–0.77; p < 0.001). While stent thrombosis at 24 h was higher in the bivalirudin arm, by 30 days there was no significant difference.

The recent EUROMAX trial went on to assess pretreatment in the ambulance setting with bivalirudin [58]. A total of 2,218 patients with STEMI planned for PCI were randomized to either bivalirudin or UFH with or without a GP IIb/IIIa inhibitor (used in 69%). Bivalirudin infusion was continued for at least 4 h after PCI. The composite of death or major bleeding was significantly reduced in the bivalirudin arm (5.1 vs 8.5%; RR: 0.60; 95% CI: 0.43–0.82; p = 0.001), a result almost entirely powered by a reduction in major bleeding (2.6 vs 6.0%, p < 0.001). However, there was an increase in the risk of acute stent thrombosis (2.6 vs 6.0%; RR: 0.43; 95% CI: 1.37–27.24; p = 0.007). There was no significant difference in the rates of death or reinfarction. Almost 50% of patients received either ticagrelor or prasugrel and again almost 50% underwent radial access for PCI. These patients were underrepresented in HORIZONS-AMI, and the low use of the radial approach in the earlier study was suggested to favor the efficacy of bivalirudin due to access site bleeding related to the femoral approach.

The recently presented HEAT study assessed the performance of bivalirudin versus UFH in the setting of PCI at a single high-volume center [59]. This pragmatic trial randomized 1829 STEMI patients planned for PCI to either UFH or bivalirudin with a primary composite endpoint of mortality, cerebrovascular accident, reinfarction and additional unplanned target lesion revascularization at 28 days. They found that UFH was associated with a significantly lower rate of MAC compared with bivalirudin (5.7 vs 8.7%), with no difference in bleeding rates seen [60].

The ACUITY trial assessed bivalirudin specifically in NSTEACS, either alone or with a GP IIb/IIIa inhibitor, versus standard therapy (UFH or LMWH with a GP IIb/IIIa inhibitor) [61]. The arm receiving both bivalirudin and a GP IIb/IIIa inhibitor demonstrated similar outcomes to standard therapy for both ischemia outcomes and major bleeding. However, bivalirudin alone showed better 30-day outcomes than standard therapy due to similar composite ischemia outcomes (7.8 vs 7.3%; RR: 1.08; 95% CI: 0.93–1.24; p = 0.32) but significantly reduced rates of major bleeding (3.0 vs 5.7%; RR: 0.53; 95% CI: 0.43–0.65; p = 0.001). The only subgroup to which this benefit did not extend was patients not pretreated with clopidogrel, where an increase in ischemic events was noted. This suggested that GP IIb/IIIa inhibitors may be beneficial in patients who might have suboptimal antiplatelet therapy with clopidogrel.

Finally, the ISAR-REACT 4 trial randomized 1721 NSTEMI patients to either bivalirudin or abximab plus UFH [62]. It was expected that bivalirudin may be inferior in high-risk patients where the ISAR-REACT 2 trial had demonstrated a benefit from additive abximab. The composite of death, large recurrent MI, urgent target-vessel revascularization or major bleeding within 30 days was not significantly different between groups, but those in the abximab/UFH arm suffered significantly higher major bleeding rates (RR: 1.84; 95% CI: 1.10–3.07; p = 0.02).

Summary
The recent HEAT-PPCI has raised questions about the efficacy of bivalirudin in the setting of PPCI for STEMI. However, in NSTE-ACS patients receiving dual antiplatelet therapy and undergoing an invasive strategy, therapy with bivalirudin alone offers similar efficacy to UFH/LMWH with a GP IIb/IIIa inhibitor but with an improved safety profile. In patients undergoing PPCI, bivalirudin reduces bleeding risk but appears to be associated with an excess early rate of stent thrombosis.

Finally, it is important to note that the agents discussed to date are all used in the acute period for short durations and not continued beyond this. The need for parenteral administration limits the use of these agents outside the hospital setting and following discharge. However, results of trials investigating the benefits of warfarin in addition to aspirin following ACS indicate that long-term anticoagulation may reduce the risk of future ischemic events [63]. Strategies that avoid the limitations of warfarin therapy (variable dose–response relationship, narrow therapeutic window, need for frequent monitoring and a high propensity to bleeding when used in conjunction with antiplatelet therapy) may offer new treatment strategies in patients with ACS. The NOAC have therefore been evaluated in this setting.

The novel oral anticoagulants
The NOAC are increasingly being prescribed in the setting of atrial fibrillation and deep vein thrombosis treatment and prevention. However, they may also be of use in the setting of ACS, and numerous trials have been performed to assess their efficacy and safety. The oral direct thrombin inhibitors dabigatran and ximelagatran and the factor Xa inhibitors apixaban, ruxarxaban and darexaban have all undergone double-blinded placebo-controlled trials to assess the effect of treatment on recurrent major adverse cardiac events following acute coronary syndromes.

A recent meta-analysis [64] included seven Phase II and III trials of these agents with follow-up times ranging from 6 to 13 months [65–71]. 13.4% of patients received single antiplatelet therapy (aspirin only) while the remaining majority received dual antiplatelet therapy (aspirin and clopidogrel). In patients receiving aspirin only, additional treatment with a new oral anticoagulant reduced major adverse cardiac events by 30%, with no apparent superiority for any individual agent amongst ximelagatran, apixaban and ruxarxaban. However, there was a 79% increase in clinically significant bleeding events. It was
estimated adding a NOAC to 1000 patients on a single antiplatelet therapy for 6 months prevents 44 MACE events but causes 70 clinically significant bleeding events. For patients on dual antiplatelet therapy (aspirin and clopidogrel), the reduction in MACE was more modest (13%), with no apparent difference between apixaban, rivaroxaban, dabigatran and darexaban. The rate of significant bleeding however was even higher, with an increase of 134%. It was estimated adding a NOAC to 1000 patients on a dual antiplatelet therapy for 6 months prevents only 5 MACE events while causing 42 clinically significant bleeding events. No trials have assessed NOACs in patients treated with the more potent P2Y12 receptor antagonists prasugrel and ticagrelor, which theoretically may result in a further increased risk of bleeding.

Summary
Due to the higher rates of bleeding when NOACs are added to antiplatelet therapy, their use in the management of ACS is not routinely advised.

Expert commentary & five-year view
Significant progress has been made in the treatment of patients with ACS with multiple choices of antithrombotic drugs now available. Over recent years, there has been an interest in finding replacements for both clopidogrel, due to its variability regarding in vitro efficacy, and also the conventional antithrombotic drugs that require laboratory monitoring and parental administration. ACS patients still suffer significant rates of recurrent events and bleeding complications. Today the attention is focused on the development of new drugs that bind directly to specific molecules with high specificity and have both predictable pharmacokinetics (drug absorption, distribution, metabolism and excretion) as well as pharmacodynamics (drug efficacy at the molecular level). However, the ideal antithrombotic drug still needs to be discovered and the interventional cardiologist must still consider the balance between thrombosis and bleeding on an individual patient level.

Current best practice: STEMI with PCI
Current guidelines (ESC 2012) recommend the use of prasugrel or ticagrelor as the antiplatelet of choice in PCI (in addition to aspirin) for STEMI unless contraindicated or unavailable, at which point clopidogrel should be used [41]. However, in the case of prasugrel we feel the benefit in STEMI patients treated by PPCI is less clear. In addition, prasugrel pretreatment is associated with an increased risk of non-CABG-related major bleeding, both in the overall ACS population and STEMI subgroups (HR: 8.19) as a whole. Prasugrel may be considered in the diabetic subgroup, but it is the authors’ opinion that ticagrelor may be preferable over prasugrel in treating this overall group of patients.

In the catheterization laboratory, additional anticoagulation is required. Intravenous UFH is still the default strategy for many cardiologists although the LMWH enoxaparin is an effective alternative. Until an effective intravenous rapidly acting P2Y12 therapy becomes available, there may still be a need for additional antithrombotic therapy to cover the period before the newer antiplatelet drugs reach their full therapeutic effect.

Bivalirudin is an effective anticoagulant for use in patients undergoing PCI for STEMI in view of its improved safety and potentially lower mortality. However, bailout GP IIb/IIIa inhibitors may still be employed to reduce acute thrombotic complications in high-risk patients. The recent findings of the EUROMAX trial (discussed above) highlight the balance between safety and efficacy of antithrombotic agents. Some evidence suggests that bivalirudin reduces hemorrhagic complications even when used either in combination with newer platelet inhibitors or when using radial artery access. However, this reduction in bleeding is offset by the apparent reduction in efficacy and higher rate of stent thrombosis. The rate of early stent thrombosis with bivalirudin was increased in the EUROMAX study to the same extent as seen in HORIZONS-AMI, despite the use of newer antithrombotics and longer and earlier infusions. The magnitude of bleeding benefit (3.4 major bleeds prevented per 100 patients) might be argued to outweigh the thrombotic harm (0.9 stent thrombosis). However, the consequences of stent thrombosis may appear greater than those of a major bleed with 70% of patients with a stent thrombosis suffering a reinfarction and all requiring emergency repeat revascularization. Furthermore, the recently reported HEAT trial supported the continued use of UFH compared with bivalirudin in the setting of PPCI [60]. We therefore would recommend the use of aspirin, ticagrelor and UFH in PPCI for STEMI. GPIIb/IIIa inhibitors may also be used to cover the early risk of thrombosis (1st 6–12 h) in patients, with longer infusions recommended in high thrombus burden/no or slow reflow or thrombotic complications. Currently, the use of oral anticoagulants as triple therapy in this patient group is not advised as the evidence has revealed high rates of bleeding with this combination of therapies.

Current best practice: NSTE-ACS
Ticagrelor and prasugrel have superseded clopidogrel as the antiplatelets of choice in the ESC guidelines in patients with NSTE-ACS [42]. This recommendation is based on the results from the TRITON-TIMI 38 and PLATO studies, demonstrating the superiority of prasugrel and of ticagrelor over clopidogrel. Both of these trials included patients with ST-elevation and were not pure NSTE-ACS studies. Trials have demonstrated it is probably safe to delay prasugrel treatment until a lesion amenable to PCI is demonstrated on angiography, and that there is no incremental benefit from early treatment and there may be a risk of harm due to increased bleeding. Ticagrelor use (unlike prasugrel) is associated with reduced mortality in these patients, and in the PLATO trial pre-angiography treatment was standard.

The addition of a third agent, typically a GP IIb/IIIa inhibitor, is controversial; the use of these agents will likely depend on angiographic appearance and the anticoagulant employed – evidence
serves that GP IIb/IIIa inhibitors offer little benefit alongside bivalirudin when patients have received dual antiplatelet therapy. In patients treated with dual antiplatelet therapy, bivalirudin appears to offer improved outcomes compared with NSTE-ACS patients treated with UFH or LMWH, with or without a GP IIb/IIIa inhibitor. Outside of the catheterization laboratory, fondaparinux appears to offer improved outcomes secondary to reduced rates of bleeding compared with enoxaparin, but it is not a safe substitute for UFH during angiography.

Newer agents are characterized by more predictable pharmacokinetics, reduced interindividual response variability and activity at the site of coronary occlusion. Recently approved agents (bivalirudin, fondaparinux, prasugrel, ticagrelor) have improved outcomes in clinical trials by more effectively balancing the antiischemic benefits and bleeding risks during ACS. Identifying the timing and setting of antiplatelet and anticoagulant initiation, and the subgroups in which one agent provides a comparably favorable risk–benefit profile remains an area of active investigation.

**Five-year review**

The novel P2Y12 inhibitors, prasugrel and ticagrelor, offer some advantages in their predictable metabolism and quicker onset. However, in many cases an intravenous P2Y12 inhibitor, such as cangrelor, could offer large advantages in patients where quick offset is favorable (those progressing to cardiopulmonary bypass) or gut absorption is undependable. While at present it is unlikely that cangrelor will replace oral P2Y12 inhibitors, the need for a safe P2Y12 inhibitor that has an immediate onset of action, combined with a short half-life, will drive further research in this area.

New agents (e.g., vorapaxar) are in development despite somewhat disappointing initial results, but different combinations of drugs may result in improved outcomes. It is also important to note that it is currently unclear how these new agents compare with the older ‘standard’ agents such as aspirin.

Indeed, it is unclear whether aspirin will remain part of the standard ACS cocktail. Physicians have numerous antiplatelet and anticoagulant agents at their disposal. Trials until now have consistently shown that addition of a third agent to aspirin and a P2Y12 inhibitor reduces cardiovascular events, but at the expense of bleeding. It may be that the optimum combination, at least in some patients, would require the addition of a newer antithrombotic at the expense of omitting an antiplatelet agent such as aspirin. Indeed, the importance of patient selection is seen in the trial of vorapaxar in patients with coronary artery disease; during the trial, enrollment criteria were changed as it was noted patients with previous stroke were particularly at risk of adverse events [46]. Currently, meta-analysis of the NOAC in ACS yields somewhat unconvincing data for their routine use; cardiovascular events were indeed reduced, but the safety profiles are questionable. Indeed, in January 2013 the FDA reiterated once more it will not approve the use of rivaroxaban for patients with ACS based off current trial data [72]. However, it may be that it is aspirin that steps back to allow these powerful new therapies to be used safely.

**Financial & competing interests disclosure**

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**Key issues**

- Patients suffering from acute coronary syndromes are in a prothrombotic state and benefit from both antiplatelets and anticoagulants, regardless of whether they progress to percutaneous coronary intervention.
- The novel antiplatelet agents, prasugrel and ticagrelor, have been shown to offer more predictable antiplatelet activity and this has translated to improved outcomes in trials to date. Intravenous P2Y12 inhibitors such as cangrelor are on the horizon and may fill a role as a bridging strategy in patients awaiting surgery.
- The use of glycoprotein IIb/IIIa inhibitors is declining as more potent oral antiplatelets are available and evidence shows bivalirudin alone may yield better outcomes due to decreased bleeding rates.
- The protease-activated-receptor 1 blockers vorapaxar and atopaxar are new drugs, though the benefits when added to standard dual oral antiplatelet therapy appear modest at best.
- Anticoagulation remains largely an acute practice. Newer agents such as bivalirudin focus on safer and more predictable anticoagulation and improved endpoints in trials are largely secondary to improved safety profiles rather than efficacy. However, a recent trial questions the efficacy of bivalirudin in the setting of PCI for ST-elevation myocardial infarction.
- Longer-term anticoagulation with new oral anticoagulants does indeed improve cardiovascular endpoints, but at the expense of large increases in bleeding.
- Future medical management of acute coronary syndromes will likely focus on individualized care, where bleeding rates can be better estimated and a combination of drugs tailored to the patients; the ‘standard’ therapy including aspirin may become increasingly ubiquitous.
Recent advances in anti-thrombotic treatment for ACS

References


