

REVIEW ARTICLE

Antiplatelet therapy in acute coronary syndrome

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Abstract

Antiplatelet therapy is an essential component in the treatment of acute coronary syndromes (ACS). ACS management has evolved significantly over recent years with new antiplatelet agents with distinct pharmacological properties that offer a faster onset of action and greater potency. Prospective randomized controlled trials have not only focused on reducing ischemic events, but also on complications. There is a tipping point with safety/efficacy, beyond which bleeding risk can outweigh any anti-ischemic benefit. This tipping point is not fixed and estimating its position for an individual patient remains a major challenge and is critically influenced by a multitude of factors including age and comorbidity. The European Society of Cardiology (ESC) guidelines provide important direction to the trainee and practicing cardiologist. This article outlines development in antiplatelet therapy focusing on mechanism of action, the evolution in the evidence-base, clinical indications, and clinical controversies.

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Introduction

Platelet activation at sites of vascular injury, such as a plaque fissure or rupture, triggers a cascade of events leading to platelet aggregation and thrombin generation that play a dominant role in atherothrombosis [1]. Thus, antithrombotic drugs that interfere with platelet aggregation (antiplatelets) and blood coagulation (anticoagulants) are the mainstay of acute coronary syndrome (ACS) therapy. The pursuit of an optimum antithrombotic strategy in ACS has been a principal goal in cardiovascular medicine since ISIS-2 demonstrated a large reduction in vascular mortality in ST-elevation myocardial (STEMI) patients treated with aspirin and streptokinase [2]. Subsequent advances in antithrombotic therapy have improved outcomes in patients with ACS and, in parallel, percutaneous coronary intervention (PCI). More recently, the balance of efficacy and safety has been brought into sharp focus with the recognition that bleeding events are an independent marker of a poor outcome following ACS [3].

Following the diagnosis of ACS, antiplatelet therapy is indicated to reduce acute ischemic complications,

recurrent atherothrombotic events, and to facilitate PCI. Several drug classes have an antiplatelet effect; each have a distinct mechanism of action and evidence base (Figure 1). This article will focus on antiplatelet therapy in ACS, with an emphasis on mechanism of action, evolution of the evidence-base, current indications, and clinical controversies.

Aspirin

Aspirin targets cyclo-oxygenase 1 (COX-1) inhibiting thromboxane A₂ (TXA₂) formation inducing a functional inhibition of platelet function [1]. TXA₂ is produced in response to platelet activation and induces platelet aggregation by mediating expression of the glycoprotein IIb/IIIa complex (GP IIb/IIIa) complex (Figure 1). Mature platelets cannot synthesize COX-1, so the duration of inhibition lasts for the approximate 8 to 9 day life span of a circulating platelet.

In the pre-PCI era, randomized control trials (RCTs) demonstrated a substantial reduction in the risk of death or myocardial infarction (MI) among patients with ACS

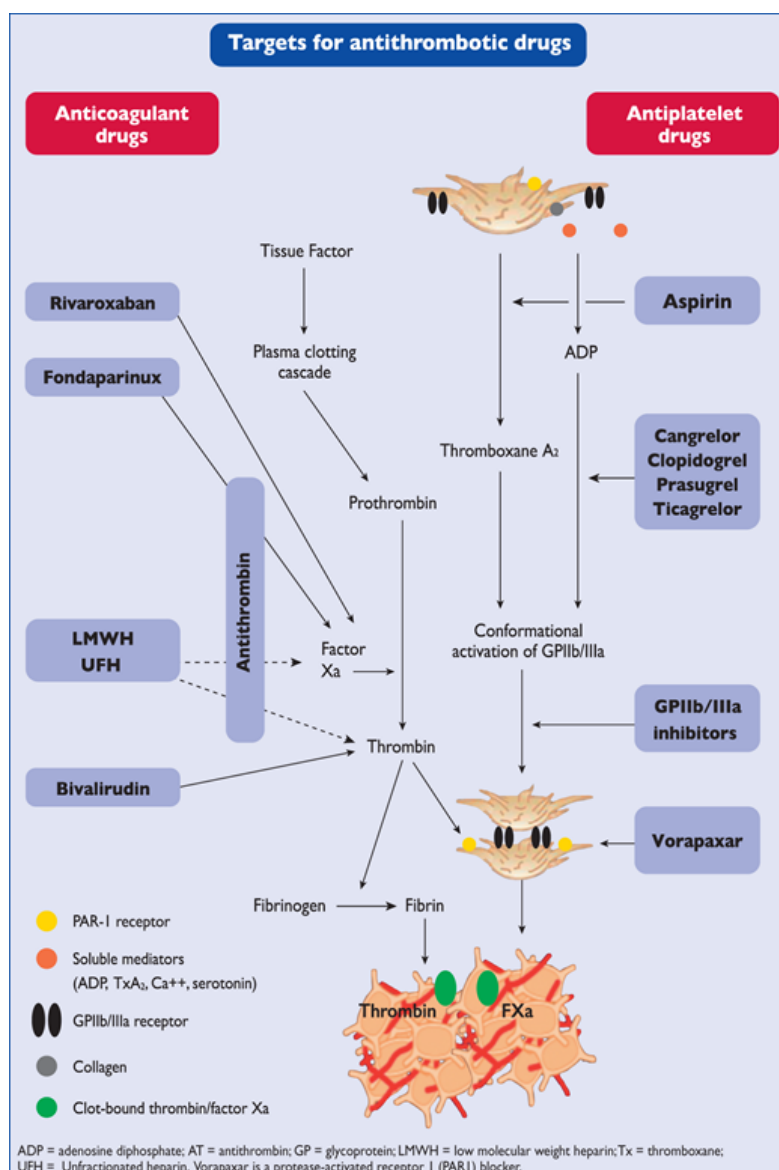


Figure 1. Antithrombotic and Antiplatelet drugs for Acute Coronary Syndromes. Figure depicts the targets available that can be used to inhibit coagulation and platelet aggregation. Reproduced with permission of The European Society of Cardiology. From M. Roffi 2015 ESC guidelines for the management of acute coronary syndrome presenting without persistent ST-segment elevation [7]. <http://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Acute-Coronary-Syndromes-ACS-in-patients-presenting-without-persistent-ST-segm>

who treated with aspirin over control. In ST elevation ACS (STE-ACS), aspirin reduced early vascular mortality as a lone agent, with an additive benefit when used alongside thrombolysis; this benefit was maintained at 10 years [2, 4]. Meta-analysis has shown aspirin to be effective across a range of clinical indications, including a 46% reduction in major vascular events in patients treated for unstable angina. The beneficial effects of aspirin are present at doses of 75 mg/day with no incremental benefit provided by higher doses [5, 6]. The inhibition of

TXA₂ dependent platelet function by aspirin leaves other platelet pathways largely unaffected, providing rationale for additional antiplatelet agents (Figure 1). Aspirin remains the foundation stone onto which further antiplatelet therapy is added (Figure 2). It is interesting to consider that there is no data on the efficacy of recently developed antiplatelet drugs other than in combination with aspirin, and that we remain unaware of the extent to which combinations with aspirin improve efficacy but increase risk.

ASPIRIN

- Aspirin is recommended for all patients at an initial oral loading dose of 300 mg and a maintenance dose of 75–100 mg/day long-term regardless of treatment strategy in both STE-ACS (**Class I, Level A**) and NSTEMI-ACS (**Class 1, Level A**)

P2Y₁₂ INHIBITORS

- A P2Y₁₂ inhibitor is recommended, in addition to aspirin, for 12 months in both STE-ACS (**Class 1 level A**) and NSTEMI-ACS (**Class 1 Level A**)
- Ticagrelor 180 mg loading dose followed by 90 mg twice daily is recommended for STE-ACS (**Class 1, Level B**) and NSTEMI-ACS patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy (**Class I, Level B**)
- Prasugrel 60 mg loading dose followed by 10 mg daily is recommended for STE-ACS (**Class 1, Level B**) and NSTEMI-ACS in patients who are proceeding to PCI (**Class 1, Level B**)
- Clopidogrel 300–600 mg loading dose followed by 75 mg daily dose is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation in both STE-ACS (**Class I, Level B**) and NSTEMI-ACS (**Class 1, Level B**).
- P2Y₁₂ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischaemic and bleeding risks of the patient in both STE-ACS (**Class IIb, Level A**) and NSTEMI-ACS (**Class IIb, Level A**)

GPIIb/IIIa INHIBITORS

- GPIIb/IIIa inhibitors during PCI should be considered for bailout situations or thrombotic complications in STE-ACS (**Class IIa, level C**) and NSTEMI-ACS (**Class IIa, level C**)

General Recommendations

- A proton pump inhibitor in combination with DAPT is recommended in patients at higher than average risk of gastrointestinal bleeds (**Class I, Level B**).

DAPT=Dual Antiplatelet Therapy, GPIIb/IIIa = Glycoprotein IIb/IIIa , NSTEMI-ACS = Non ST elevation acute coronary syndrome, STE-ACS = ST elevation acute coronary syndrome

Figure 2. Summary of European Society of Cardiology (ESC) guidelines for antiplatelet therapy in NSTEMI-ACS and STE-ACS [7, 43].

P2Y₁₂ Inhibitors**Dual antiplatelet therapy**

A second oral antiplatelet agent—an adenosine diphosphate (ADP) receptor antagonist—is indicated to reduce ischemic events following ACS [7, 8]. In the field of PCI, dual-antiplatelet therapy (DAPT), originally with aspirin and ticlopidine, is also mandated to allow coronary stent deployment [9]. Hematological side effects, and the availability of the better tolerated clopidogrel, have rendered ticlopidine obsolete. Over the past two decades, there has been an evolution toward more potent oral antiplatelet therapy [10, 11]. The newest oral P2Y₁₂ inhibitors,

ticagrelor and prasugrel, have a rapid onset of action and less variability in activity between individuals than clopidogrel (Table 1) [10, 12].

Clopidogrel

ADP binding to the P2Y₁₂ receptor plays an important role in platelet activation and aggregation, amplifying the initial response to vascular damage [1]. Clopidogrel is a thienopyridine which irreversibly blocks the P2Y₁₂ platelet receptor. The efficacy and safety of clopidogrel, combined with aspirin, in patients with NSTEMI-ACS was first established in the CURE trial ($n = 12\,562$) [13]. A 300 mg loading dose of clopidogrel, followed by 75 mg daily

Table 1. Comparison of the pharmacokinetics of different antiplatelet therapy.

Drug	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor	Tirofiban	Eptifibatide	Abciximab	Voraxapar
Prodrug	Yes	Yes	No	No	No	No	No	No
Route	Oral	Oral	Oral	Intravenous	Intravenous	Intravenous	Intravenous	Oral
Mechanism of Action	P2Y ₁₂ inhibition	P2Y ₁₂ inhibition	P2Y ₁₂ inhibition	P2Y ₁₂ inhibition	GP1Ib/IIla inhibition ³	GP1Ib/IIla inhibition ⁴	GP1Ib/IIla inhibition ⁵	PAR -1 inhibition
Onset of Action ²	2–6 h	30 mins	30 mins	2 mins	<15 mins	<15 mins	<10 mins	1–2 h
Duration of Action	3–10 days	7–10 days	3–5 days	1–2 h	4–8 h	4–8 h	24–48 h	2–3 weeks ¹
Withdrawal before surgery	5 days	7 days	5 days	1 h	8 h	8 h	>48 h ⁶	–
Loading Dose ⁷	300–600 mg	60 mg	180 mg	30 µg/kg	25 µg/kg	180 mcg/kg	0.25 mg/kg	–
Regular Dose ⁷	75 mg OD	10 mg OD	90 mg BD	4 µg/kg/min infusion	0.15 µg/kg/min infusion	2 µg/kg/min infusion	0.125 µg/kg/min infusion	2.5 mg OD

BD, Twice Daily; GP1Ib/IIla, Glycoprotein IIb/IIIa; OD, Once Daily; PAR 1, Protease Activated Receptor 1.

¹Dose dependent—2–3 weeks if taking 2.5 mg OD for 28 days.

²Absorption of oral drugs may be slower in acute STE-ACS.

³Non-peptide.

⁴Peptide.

⁵Monoclonal antibody mediated.

⁶Low level GP IIb/IIIa inhibition present for up to 15 days.

⁷Dose adjustment may be required in renal impairment.

maintenance for 9–12 months, reduced cardiovascular death, non-fatal MI, or stroke by 20% compared with aspirin monotherapy (9.3% vs. 11.4%; Relative Risk (RR) 0.80 (95% Confidence Interval (CI): 0.72–0.90), $P < 0.001$). A 1% absolute increase in major bleeding events was noted, but there was no significant increase in life threatening or fatal bleeds [13].

In the thrombolysis era, the addition of clopidogrel was associated with improvement in vessel patency and ischemic complications in STEMI patients [14]. In the current era of primary PCI (PPCI), a second antiplatelet agent is also mandated to facilitate safe coronary stent deployment. The CURRENT-OASIS 7 trial did not demonstrate a benefit of higher clopidogrel dosing overall, but there was a reduction in the primary end-point and stent thrombosis within the PCI sub-group [6]. For patients with a planned invasive strategy, or presenting for PPCI it is common practice to use a higher loading dose of clopidogrel (600 mg) in order to more rapidly achieve full antiplatelet effect.

Clopidogrel is a prodrug, requiring metabolism to its active form. Key genetic polymorphisms to cytochrome P450 (CYP) isoenzymes including CYP3A4 and CYP2C19 cause a wide variation in the effectiveness of clopidogrel between individuals. Clopidogrel non-response has been identified as a risk for recurrent atherothrombotic events and stent thrombosis. The antiplatelet effect of clopidogrel is slow in onset (over several hours), and due to the irreversible binding of clopidogrel to P2Y₁₂ receptors, slow in offset (over several days) [1, 7]. The slow offset can be clinically important when urgent coronary artery bypass surgery is required. In a post hoc analysis of

CURE, there was a trend for higher bleeding where surgery was performed within 5 days of clopidogrel discontinuation [15]. Despite these limitations, clopidogrel remains first line therapy in elective PCI, and is commonly used in ACS indications due to its lower cost, and where bleeding risk is high (e.g., in those requiring concomitant treatment with an anticoagulant) [16].

Prasugrel

In common with clopidogrel, prasugrel is a prodrug with a similar active metabolite. However, unlike clopidogrel metabolism of prasugrel to its active form is rapidly achieved through esterases, and then a single CYP450 step. Importantly, the isoenzyme CYP2C19, responsible for much of the interpatient variability with clopidogrel, is not required to convert prasugrel to its active form. Consequently, prasugrel produces a more predictable effect, and platelet inhibition is within 30 min [17–19].

Prasugrel was compared to clopidogrel in patients with NST-ACS and STE-ACS undergoing PCI in TRITON-TIMI 38 [11]. 13 608 patients were included and randomized to either clopidogrel (300 mg loading dose and 75 mg maintenance dose) or prasugrel (60 mg loading dose, 10 mg daily maintenance dose). Patients were commenced on the study drug following angiography, and up to 1-h post PCI. There was a significant reduction in recurrent cardiovascular events in the prasugrel treated group (9.3% vs. 11.2%; hazard ratio (HR) 0.82 [95% CI: 0.73–0.90] $P < 0.001$), driven by a reduction in non-fatal MI (7.1% vs. 9.2%; HR 0.76 (95% CI: 0.67–0.85)

$P < 0.001$). A significantly lower rate of stent thrombosis was also seen in the trial with prasugrel treatment (1.1% vs. 2.4%; HR 0.48 [95% CI: 0.36–0.64] $P < 0.001$). More bleeding was observed in the prasugrel arm (2.4% vs. 1.8%; HR 1.3 [95% CI: 1.03–1.67] $P = 0.03$), which included a small increase in fatal bleeding (0.4% vs. 0.1%; HR 4.19 [95% CI: 1.58–11.11] $P = 0.002$). Post hoc analysis identified that older patients (>75 years) and those with low body weight (<60 Kg), had no net clinical benefit with prasugrel owing to higher bleeding in these sub-groups. Patients with a previous TIA or CVA experienced net harm with prasugrel in whom the drug is contraindicated [11].

Ticagrelor

Ticagrelor is the first non-thienopyridine ADP blocker and reversibly inhibits the P2Y₁₂ platelet receptor. Unlike thienopyridines, ticagrelor does not require metabolic activation and therefore produces more rapid and consistent platelet inhibition than clopidogrel and more rapid reversal [20]. In addition to reversible inhibition of the P2Y₁₂ receptor, ticagrelor also inhibits adenosine reuptake in cells. This can cause additional complaints of dyspnoea (approximately a 5% excess) and bradycardia in addition to the more typical bleeding side effects [10].

The PLATO study compared ticagrelor (180 mg loading dose, followed by 90 mg twice daily) with clopidogrel (300–600 mg loading dose, followed by 75 mg daily) in 18 624 patients who presented with either STE-ACS or NSTEMI-ACS. Treatment was commenced before angiography and continued for 12 months; median duration of follow-up was 9 months. The trial cohort included patients that were managed with PCI (60%), coronary artery bypass graft (4.5%), and with medical therapy alone (35.5%) [10].

Ticagrelor was associated with a 16% reduction in the primary endpoint of vascular death, MI, or stroke compared with clopidogrel (10% vs. 12.3%; HR 0.83 [95% CI: 0.74–0.93] $P = 0.0013$). Across the whole cohort, all-cause mortality (4.5% vs. 5.9%; HR 0.76 [95% CI: 0.64–0.90] $P = 0.0020$) and definite or probable stent thrombosis (1.4% vs. 1.9%; HR 0.67 [95% CI: 0.50–0.90] $P = 0.0091$) was lower in the ticagrelor arm. The benefit with ticagrelor was noted in both STE-ACS and NSTEMI-ACS patients. The study reported no difference in major bleeding or blood transfusions, but there was higher non-CABG-related major bleeding observed in the ticagrelor group (4.8% vs. 3.8%; HR 1.28 [95% CI: 1.05–1.56] $P = 0.0139$).

Should Patients have Pre-Treatment with DAPT?

Given the pathophysiological mechanisms in ACS, it has been commonly understood that administration of P2Y₁₂

inhibitors as early as possible would provide the greatest benefit. Anticipated benefits of DAPT treatment before coronary angiography (“upstream” use) include a reduction in ischemic events, the potential to reduce PCI complications (e.g., acute stent thrombosis), and a reduced need for more potent GP IIb/IIIa inhibitors. As such, DAPT is often commenced as soon as ACS is clinically suspected. The practice of early institution of DAPT is derived from the CURE study. It should be noted that invasive management and subsequent PCI was undertaken in only 43.7% and 21.2% of CURE study patients, respectively [13]. Thus, pretreatment in the modern era has been questioned. [21] Indeed, there are no RCTs specifically supporting a pre-treatment strategy, and the TRITON-TIMI 38 study randomized patients following angiography [11]. Potential downsides of “upstream” DAPT include an increased risk of bleeding, especially if femoral access is employed. Additionally, there is a higher risk of CABG associated bleeding with DAPT if urgent surgery is required, or alternatively a longer hospital stay to allow P2Y₁₂ inhibitor washout.

Recently two double-blind, placebo-controlled RCTs have addressed the question of DAPT timing. In a NSTEMI-ACS cohort, the ACCOAST study compared prasugrel pretreatment (30 mg pre-angiography, followed by 30 mg post angiography), with 60 mg prasugrel loading post angiography and pre-PCI [22]. There was no difference in the primary end-point of cardiovascular death, stroke, MI, and urgent revascularization (10% vs. 9.8%; HR 1.02 [95% CI: 0.84–1.25], $P = 0.81$), although bleeding was nearly twice as high in the pretreatment arm (2.6% vs. 1.4%; HR 1.90 [95% CI: 1.19–3.02], $P = 0.006$). The median time from prasugrel loading to angiography was just over 4 h; access to invasive management was therefore rapid in the ACCOAST patient cohort.

The ACCOAST study led the recent European Society of Cardiology (ESC) guideline to recommend avoiding pretreatment with prasugrel in patients diagnosed with NSTEMI-ACS [7]. It should also be noted that prasugrel is not indicated for medically managed NSTEMI-ACS patients on the basis of the neutral results of the TRILOGY ACS trial [23]. Whether the results of ACCOAST reflect P2Y₁₂ inhibitors in general or prasugrel specifically remains a matter of debate [21, 24, 25]. In PLATO, as noted above, ticagrelor was used as pretreatment; the benefit over clopidogrel was consistent in patients managed conservatively and with an invasive strategy [10]. Current ESC guidance, and our practice, is to treat patients with aspirin and ticagrelor as soon as NSTEMI-ACS is clinically diagnosed, consistent with the protocol of the PLATO study.

In PPCI for STEMI, the ATLANTIC trial ($n = 1875$) assessed whether pre-hospital ticagrelor loading was

superior to delayed in-hospital ticagrelor [26]. The co-primary outcomes were related to arterial patency at angiography (the absence of ST resolution or less than TIMI III flow), and were no different between the two groups. The difference in timing of loading dose was approximately 30 min. Interestingly, there was a lower rate of the secondary end-point acute stent thrombosis in the pre-hospital treatment arm (0.2% vs. 1.2%; HR 0.19 (95% CI: 0.04–0.86), $P = 0.02$). This potential benefit should be balanced against the risks of pre-hospital treatment; misdiagnosis of STE-ACS was identified in 10% of patients. Rarely, in conditions such as aortic dissection, early administration of DAPT could be potentially catastrophic. Further, it was also noted that opiate administration impaired oral absorption of ticagrelor—a potential limitation of all oral P2Y₁₂ receptors in the STEMI setting [26].

Glycoprotein IIb/IIIa inhibitors

Parenteral preparations overcome the potential problem of oral drug absorption. Intravenously administered glycoprotein inhibitors (GPI) block the final common pathway of platelet activation producing potent and rapid platelet inhibition. (Figure 1) Three GPIs are commercially available—the monoclonal antibody abciximab and the small molecules eptifibatide (peptide) and tirofiban (non-peptide). (Table 1) Routine GPI use had been in decline, in part due to the availability of more potent oral antiplatelet therapy and the increasing recognition of the importance of bleeding complications [27].

Many of the large GPI studies in NSTEMI-ACS were in the pre-DAPT era; meta-analysis of almost 30 000 patients showed a 1% absolute reduction in ischemic end-points and a 1% absolute excess in bleeding [28]. The major clinical trials in NSTEMI-ACS also examined “upstream” pre-catheter lab use and “downstream” use during PCI. The EARLY-ACS ($n = 9406$) study showed no benefit in routine “upstream” administration of eptifibatide in the NSTEMI-ACS setting, where patients were largely pretreated with clopidogrel [29]. In NST-ACS, current practice is to reserve GPI use for “bail-out” indications during PCI (Figure 2) [7].

In the PPCI setting, GPI were established as clearly beneficial in early trials and became the standard of care. Pooled patient level data from three PPCI studies with 3 year follow-up found that death or reinfarction was less common with abciximab compared to placebo (19.0% vs. 12.9%; RR 0.633 [95% CI: 0.452–0.887], $P = 0.008$) [30–32]. The benefits of GPI in the modern PPCI era with high dose clopidogrel preloading, or more potent P2Y₁₂ inhibitors is less clear. The BRAVE-3 trial found no difference between STEMI patients given abciximab or

placebo [33]. Conversely, a 2.8% absolute reduction in infarct size was seen following intracoronary abciximab in the INFUSE-AMI trial [34]. Further, ON-TIME 2 showed a significant 2.8% absolute reduction in major adverse cardiovascular events (MACE) with GPI, this time a high-bolus dose tirofiban/heparin combination [35].

Interpretation of the GPI evidence is further complicated by the choice of anticoagulant. Bivalirudin was shown to be superior to the heparin/GPI combination in HORIZONS AMI and EUROMAX, predominantly due to lower bleeding complications [36, 37]. However, when heparin was directly compared to bivalirudin in the HEAT-PPCI trial, heparin was found to be superior. There were approximately equal rates of “bail-out” GPI in both groups in HEAT PPCI, leading to the suggestion that routine GPI was not required in the era of modern P2Y₁₂ inhibition, and may simply contribute to additional bleeding events [38]. Thus, it may be reasonable in the modern PPCI era to use GPI for bail-out indications only, although direct evidence for this practice is weak. Figure 2 summarizes the current ESC levels of evidence for GPI.

Cangrelor

The newer intravenous antiplatelet Cangrelor may provide an answer to the problems of slow drug absorption during STE-ACS. Cangrelor has a fast onset and offset through reversible inhibition of the P2Y₁₂ receptor. It has a very short half-life (<10 min), thus platelet function can be restored within a couple of hours of discontinuation of the infusion. Cangrelor has been studied in three large trials, 70% of whom had presented with an ACS [39–41]. A meta-analysis of these trials demonstrated a reduction in periprocedural death, MI, ischemia-driven revascularization and stent thrombosis (cangrelor 3.8% vs. clopidogrel 4.7%; HR 0.81 (95% CI: 0.71–0.91) $P = 0.007$) [42]. Although theoretically cangrelor may have advantages—IV administration, rapid onset and offset—it has not been compared against either prasugrel or ticagrelor, and is therefore not currently standard therapy in STE-ACS or invasively managed NST-ACS.

Pretreatment—one size fits all or a tailored approach?

NSTEMI-ACS patients undergoing PCI should have prasugrel administered only after coronary anatomy is known. Prasugrel is not recommended as a pretreatment option in NSTEMI-ACS or in medically managed patients. Ticagrelor administration in PLATO was “up-stream”, and patients were ultimately managed with medical therapy, PCI or CABG with a primary end-point benefit and

overall mortality reduction. No specific trial of preloading versus delayed loading is available with ticagrelor, but the different mechanism of action to prasugrel would argue against assuming a P2Y₁₂ inhibitor “class effect” [25]. Patients should therefore be managed with ticagrelor loading at NSTEMI-ACS diagnosis as per the original PLATO study. In STEMI-ACS, pre-hospital administration of P2Y₁₂ inhibitors is not currently supported by the ESC guidelines and should be avoided where the diagnosis is uncertain [43].

Duration of Antiplatelet Therapy

The standard 1-year recommendation for DAPT stems from the duration of P2Y₁₂ inhibition in pivotal early antiplatelet trials, such as CURE [13]. In patients treated with first generation drug eluting stent (DES), reports of late stent thrombosis associated with the premature discontinuation of DAPT, prompted the empirical recommendation to prolong DAPT duration to 12 months in these patients [7]. Subsequently, TRITON-TIMI 38 and PLATO demonstrated superiority of prasugrel and ticagrelor, respectively, for a reduction in MACE over a 12 month period [10, 11]. CREDO further supported this recommendation; 12 months of DAPT led to a 27% relative risk reduction in MACE compared with 1 month therapy [44]. The CHARISMA trial ($n = 15\,603$) included a mixed population of stable patients; there was no benefit with aspirin and clopidogrel over aspirin alone. However, subgroup analysis suggested possible differential effects between patients treated as secondary versus primary prevention [45]. Further, the pattern of ischemic events in landmark trials diverges beyond the first month of therapy, suggesting the possibility of a longer term benefit with DAPT.

Until recently, however, prospective assessment of prolonged DAPT was lacking. The largest RCT in this area is PEGASUS-TIMI 54 ($n = 21\,162$) which enrolled patients with a prior history of MI, to ticagrelor at either 90 mg twice daily, or a reduced dose of 60 mg twice daily, in addition to aspirin [46]. PEGASUS demonstrated that prolonged DAPT reduced ischemic events with both doses of ticagrelor, leading to statically significant reduction in MACE compared with placebo, (HR 0.85 (95% CI: 0.75–0.96), $P = 0.008$) and (HR 0.84 [95% CI: 0.74–0.95] $P = 0.004$) for 90 mg and 60 mg of ticagrelor, respectively). Again, this was associated with a 1.54% (90 mg ticagrelor) and 1.24% (60 mg ticagrelor) absolute increase in major bleeding ($P < 0.001$ both doses). All-cause mortality did not differ overall.

The DAPT trial ($n = 9961$) assessed the specific question of longer term DAPT in DES-treated patients. [47] Patients were eligible if an FDA approved DES had been

implanted 12 months previously, and they had tolerated DAPT with no major bleeding or ischemic events. Randomization was to either continued DAPT, or aspirin monotherapy for a further 18 months. It should be noted that a large proportion of enrolled patients ($n = 22\,866$) were not randomized due to an ischemic or bleeding event ($n = 5261$) in the first 12 months, or other reasons ($n = 7644$). Prolonged DAPT therapy was associated a significant reduction in MI, stroke and death (4.3%, vs. 5.9%; HR 0.71 (95% CI: 0.59–0.85) $P < 0.001$). The ischemic benefit was predominantly due to a reduction in MI (2.1% vs. 4.1%; HR 0.47 (95% CI: 0.37–0.61) $P < 0.001$), that was both stent related (very late stent thrombosis (0.4% vs. 1.4% HR 0.29 [95% CI: 0.17–0.48] $P < 0.01$) and at other sites. However, prolonged DAPT was associated with a statistically significant increase in moderate to major bleeding (2.5% vs. 1.6%; HR 1.61 [95% CI: 1.21–2.16] $P = 0.001$) but not fatal bleeding. Despite the reduction in myocardial infarction, overall mortality (a secondary end-point) was higher in the prolonged DAPT group (2% vs. 1.5%; HR 1.36 (95% CI: 1.00–1.85) $P = 0.05$).

The finding of increased all-cause mortality was mirrored in a subsequent meta-analysis, which included a large proportion of patients from the original DAPT trial [48]. The analysis included 10 RCTs ($n = 32\,287$) that compared different durations of DAPT after DES, and allowed a comparison of both short-term (3-months) or extended DAPT duration on outcomes versus 12-month therapy [48]. Compared with 12-month DAPT, a shorter course of treatment was associated with a significant reduction in major bleeds, but no difference in ischemic outcomes or stent thrombosis. This population included a proportion of stable patients and low risk ACS. Extended DAPT, compared with 12-month treatment, yielded similar results to the DAPT trial discussed above.

Bleeding risk

Clearly demonstrated in all antiplatelet trials is the unavoidable trade-off between the reduction in ischemic events, and an excess of bleeding. There does appear to be a tipping point whereby more potent antithrombotics leads to major bleeding complications that outweigh any benefit from a reduction in ischemic events. Indeed, newer antiplatelets in development have shown promise in reducing ischemic events, but their integration into clinical practice has been limited by excess bleeding. One such example is the protease-activated receptor-1 (PAR-1) antagonists. (Figure 1, Table 1) Vorapaxar has been studied in large phase III RCTs. The TRA-CER and TRA 2P-TIMI 50 trials enrolled almost 40 000 patients comparing

vorapaxar with placebo, in addition to contemporary standards of care [49, 50]. Both demonstrated a modest reduction in MACE, however, there was significantly more severe bleeding including intracranial hemorrhage. While approved by the FDA, the use of vorapaxar in the setting of ACS will be limited because of the risk–benefit balance. Vorapaxar used alongside prasugrel or ticagrelor has not been studied; given the potential for synergistic bleeding risks such combinations should be avoided at present.

The clinical consequence of bleeding should not be downplayed. Several studies have shown an association between bleeding and mortality [3, 51, 52]. Thus, guidelines clearly encourage the weighing of ischemic and bleeding risk [7]. Well-established bleeding scores, such as

CRUSADE and ACUITY, have been derived from RCTs, however, their use in guiding patient management remains uncertain [53–56]. A limitation of this approach is that key aspects of ischemic and bleeding risk appear inseparable. For example, renal function, hemodynamic variables and signs of heart failure are key components of both the GRACE score, and the CRUSADE score [57]. Nonetheless, current guidelines encourage the use of a more systematic approach, rather than a gut feeling or intuitive assessment. Furthermore, bleeding risk can be minimized by performing angiography and PCI via the radial artery approach, consideration of bleeding risk during stent selection, limiting the duration of antiplatelet therapy where appropriate, and the use of proton pump inhibitors [58–60].

Table 2. Summary of selected antiplatelet therapy randomized controlled trials that have influenced current recommendations in acute coronary syndromes.

Trial acronym	Study description	Summary results	Practice change
ACCOAST [22]	NSTE-ACS patients; prasugrel pretreatment versus prasugrel at time of LHC but pre PCI	No change in primary ischemic outcomes; significant increase in bleeding with pretreatment	Prasugrel recommended following angiography and before planned PCI; pre-treatment discouraged
ATLANTIC [26]	STE-ACS patients; ticagrelor pre-hospital versus ticagrelor at time of PPCI	No change in primary outcomes related to vessel patency; pretreatment reduced post PPCI stent thrombosis	Ticagrelor not routinely recommended pre-hospital
CURE [13]	NSE-ACS/UA patients; clopidogrel versus placebo with aspirin	Clopidogrel led to a significant reduction in death from CV causes, non-fatal MI, and stroke	Cemented the importance of DAPT in treatment of NSTE-ACS
CURRENT-OASIS 7 [6]	NSTE-ACS and STE-ACS patients; evaluated clopidogrel loading dose of 600 mg versus 300 mg	No benefit of higher dose overall; PCI subgroup benefit in reducing MACE and stent thrombosis	Clopidogrel 600 mg loading can be considered for patients undergoing planned PCI or PPCI
DAPT [47]	Patients with previous PCI with DES; 12 Months DAPT versus 30 months DAPT	Prolonged DAPT reduced MI, stroke and death; significant increase in major, but not fatal, bleeding	DAPT duration can be extended in patients thought to have low bleeding/high ischemic risk
ISIS-2 [2]	Acute STEMI; aspirin alone versus streptokinase alone versus combination	Combination reduced mortality. Benefits extended over 10 years	Aspirin routinely administered in patients with acute MI.
PEGASUS-TIMI-54 [46]	Previous MI 1–3 years; aspirin versus aspirin plus ticagrelor 60 mg BD or 90 mg BD	Prolonged DAPT reduced CV death, MI and stroke; increased major, but not fatal, bleeding	DAPT duration can be extended beyond 12 months in patients with low bleeding risk
PLATO [10]	NSTE-ACS and STE-ACS patients; ticagrelor versus clopidogrel in addition to aspirin	Ticagrelor reduced CV death, non-fatal MI and stroke; Increase in non-fatal bleeding	Ticagrelor recommended over clopidogrel in patients with acute MI.
TRILOGY-ACS [22]	Patients with NSTE-ACS not undergoing PCI; prasugrel versus clopidogrel in addition to aspirin	No change in the primary endpoint of CV death, non-fatal MI or stroke	Prasugrel not indicated if patient with MI not undergoing invasive strategy
TRITON TIMI 38 [11]	Patients with UA, NSTE-ACS undergoing PCI; prasugrel versus clopidogrel in addition to aspirin	Prasugrel reduced CV death, non-fatal MI, stroke and stent thrombosis.	Prasugrel preferred to clopidogrel in patients undergoing PCI if bleeding risk not excessive. Avoid in patients >75, weight <60 kg and previous TIA

BD, Twice Daily; CV, Cardiovascular; DAPT, Dual Antiplatelet Therapy; ICH, Intracranial Hemorrhage; LHC, Left Heart Catheterization; MACE, Major adverse cardiovascular events; MI, Myocardial Infarction; NSTE-ACS, Non ST Elevation Acute Coronary Syndrome; PCI, Percutaneous Coronary Intervention; PPCI, Primary Percutaneous Coronary Intervention; RCT, Randomized Controlled Trial; STE-ACS, ST Elevation Acute Coronary Syndrome; TIA, Transient Ischemic Attack; TIMI, Thrombolysis in Myocardial Infarction; UA, Unstable Angina.

Duration of therapy—an individual assessment

The standard recommendation for patients with NSTEMI-ACS or STEMI-ACS, or following PCI with a modern DES, is 12 months DAPT. In patients with high bleeding risk or a need for surgery, this can safely be reduced to 3–6 months. Extended DAPT can also be considered in appropriate patients, such as those with previous stent thrombosis or those thought to have a high ischemic/low bleeding risk, although no overall mortality benefit has been shown with this strategy. The exact duration of antiplatelet therapy should be made on a case-by-case basis. Current ESC guidance for antiplatelet therapy in NSTEMI-ACS and STEMI-ACS is summarized in Figure 2 and the landmark trials that have shaped these guidelines are summarized in Table 2.

Conclusion

Antiplatelet therapy has revolutionized management of ACS, and facilitated major advances in PCI. An increasing number of antiplatelet medications are available; interpreting the evidence in this rapidly progressing field can be challenging. Newer drugs with more potent antiplatelet effects not only have the potential to reduce ischemic events, but also for serious bleeding complications when used in combination. There is often very limited data on the interpolation of new agents into established regimes. Controversies in the timing and duration of antiplatelet therapy remain, though current guidelines provide assistance in clinical decision-making. As in all areas of medicine, an individual assessment is required.

Conflicts of Interest

Dr. Brown and Dr. Austin have nothing to disclose.

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