

Novel antithrombotic agents 2



Clinical evidence for oral antiplatelet therapy in acute coronary syndromes

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Platelet-mediated thrombosis is a major pathophysiological mechanism that underlies acute coronary syndromes, and therefore, antiplatelet therapy is an important foundation in the treatment and prevention of recurrence of these syndromes. Nearly 30 years ago, aspirin was the first agent to show a benefit for acute coronary syndromes and is still a key therapeutic agent. The landmark CURE trial showed that the addition of a P2Y₁₂ antagonist, clopidogrel, to aspirin was beneficial in the treatment of acute coronary syndromes. Despite substantial benefits with clopidogrel, limitations include the slow speed of onset, variable response, and a modest antiplatelet effect. Next-generation P2Y₁₂ antagonists, prasugrel and ticagrelor, overcome these limitations and have been shown, in large-scale clinical trials for acute coronary syndromes, to reduce ischaemic events more than clopidogrel, at the expense of an increase in bleeding. Additional agents that target platelets by alternate mechanisms, including the protease-activated receptor-1 antagonist vorapaxar, have shown ischaemic benefit. These large-scale trials inform treatment decisions that need to balance ischaemic benefit and bleeding risk in patients with acute coronary syndromes. This Series paper describes major trial results, implications for clinical practice, and summarises continuing controversy.

Introduction

Acute coronary syndromes are a leading cause of mortality, morbidity, and loss of productivity. The major pathophysiological mechanism underlying unstable angina and myocardial infarction is atherosclerotic plaque rupture with resultant coronary thrombosis. Platelets adhere to ruptured plaques, aggregate, and release secondary messengers, which result in further thrombosis and vasoconstriction, and serve as a surface for activation of the clotting cascade. As a result, antiplatelet therapies have led to major advances in the treatment of acute coronary syndromes and the prevention of recurrent events. With key components of the thrombotic process targeted, obligate increases in bleeding exist. The past 25 years has seen the completion of various large-scale clinical trials that have investigated the efficacy and safety of several pharmaceutical agents, including aspirin and P2Y₁₂ antagonists, alone or in combination (table 1). These trials provide evidence to guide patient management in balancing the efficacy and safety of pharmaceutical compounds, the pharmacology of which is described in detail in a companion Series paper.⁸

Aspirin

Historically, the first antiplatelet agent to show benefit in acute myocardial infarction was aspirin, which blocks the production of thromboxane A₂. The first major trial,¹ ISIS-2, showed the additive benefits of thrombolysis and low-dose aspirin in patients with ST-segment elevation acute myocardial infarction. The Antithrombotic Trialists' collaboration summarised the evidence for the benefit of aspirin in vascular disease, and showed that low-dose aspirin reduced vascular events (6·7% vs 8·2% per year; $p < 0·001$) and total stroke events (2·08% vs 2·54% per year;

$p = 0·002$).¹³ Reductions were consistent in men and women. Since then, aspirin has been the foundation of antithrombotic therapy for all acute coronary syndromes. Even rare patients with a history of hypersensitivity to aspirin can be desensitised rapidly to tolerate chronic treatment with low-dose aspirin.¹⁴ After an initial oral-loading dose of 150–300 mg, patients should receive a maintenance dose of 75–100 mg daily (table 2) since there is no evidence of a benefit from any higher aspirin doses, but a substantial reduction in gastrointestinal bleeds with the lower doses.²

Combination of clopidogrel with aspirin

The CURE trial² was the landmark trial that established the benefits of addition of the P2Y₁₂ receptor blocker, clopidogrel, to aspirin in patients with non-ST-segment elevation acute coronary syndromes, showing a 20% reduction in the composite outcome of cardiovascular death, myocardial infarction, and stroke, compared with placebo over 9–12 months of therapy. No increase in TIMI major bleeding was noted with the combination of aspirin and clopidogrel, but a 38% increase in the trial primary endpoint of CURE major bleeding was reported. The benefits of clopidogrel were established early, well before angiography and percutaneous coronary intervention were done,¹⁵ thereby lending support to the value of early therapy. The benefits of addition of clopidogrel (with a 300 mg loading dose and a 75 mg maintenance dose) to aspirin were also seen in patients with ST-segment elevation acute myocardial infarction (aged ≤ 75 years) who had been treated with thrombolysis in the CLARITY trial.³ In this trial, the primary efficacy composite endpoint of an occluded infarct-related artery on angiography, or death or recurrent myocardial infarction before angiography, was reduced in absolute

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	Population	Groups	Background therapy	Primary efficacy outcome	Primary efficacy results	Primary safety outcome	Primary safety results
ISIS-2 (1988) ¹	17 187 patients with suspected AMI	Streptokinase, aspirin, both, and placebo	None	Vascular mortality at 5 weeks	10.4%,* 10.7%,* 8.0%,*† 13.2%	Bleeding that needs transfusion	0.51%,* 0.16%, 0.56%,* 0.26%
CURE (2001) ²	12 562 patients with NSTEMI-ACS	Clopidogrel 300 mg then 75 mg once a day and placebo	Aspirin	Cardiovascular death, MI, stroke at 12 months	9.3%, 11.4%, p<0.001	CURE major bleeding	3.7%, 2.7%, p=0.001
CLARITY-TIMI 28 (2005) ³	3491 patients with STEMI	Clopidogrel 300 mg then 75 mg once a day and placebo	Aspirin (and heparin when appropriate)	Occluded infarct-related artery, death, myocardial infarction at 30 days	15.0%, 21.7%, p<0.001	TIMI major bleeding	1.3%, 1.1%, p=0.64
COMMIT (2005) ⁴	45 852 patients with suspected AMI	Clopidogrel 75 mg/day and placebo	Aspirin	Death, reinfarction, stroke (all-cause death) at 28 days	9.2% (7.5%), 10.1% (8.1%), p=0.002 (p=0.03)	All fatal, transfused, or cerebral bleeding	0.58%, 0.55%, p=0.59
CURRENT-OASIS 7 (2010) ⁵	25 086 patients with NSTEMI-ACS or STEMI	Clopidogrel 600 mg then 150 mg/day for 7 days then 75 mg/day, clopidogrel 300 mg then 75 mg/day	Aspirin	Cardiovascular death, MI, stroke at 30 days	4.2%, 4.4%, p=0.30	CURRENT major bleeding	2.5%, 2.0%, p=0.01
TRITON-TIMI 38 (2007) ⁶	13 608 patients with NSTEMI-ACS or STEMI undergoing PCI	Prasugrel 60 mg then 10 mg/day, and clopidogrel 300 mg then 75 mg/day	Aspirin	Cardiovascular death, MI, stroke at 450 days	9.9%, 12.1%, p<0.001	Non-CABG-related TIMI major bleeding	2.4%, 1.8%, p=0.03
TRILOGY ACS (2012) ⁷	7243 patients aged <75 years with STEMI or UA without revascularisation	Prasugrel 10 mg/day and clopidogrel 75 mg/day	Aspirin	Cardiovascular death, MI, stroke at 17 months	13.9%, 16.0%, p=0.21	GUSTO (TIMI) non-severe/life-threatening (major) bleeding	0.4% (1.1%), 0.4% (0.8%), p=0.87 (p=0.27)
PLATO (2009) ⁸	18 624 patients with NSTEMI-ACS or STEMI	Ticagrelor 180 mg then 90 mg twice a day and clopidogrel 300–600 mg then 75 mg/day	Aspirin	Cardiovascular death, MI, stroke at 12 months	9.8%, 11.7%, p<0.001	PLATO major bleeding	11.6%, 11.2%, p=0.43
PEGASUS-TIMI 54 (2015) ^{9,10}	>21 000 patients with MI 1–3 years previously	Ticagrelor 90 mg twice a day, ticagrelor 60 mg twice a day and placebo	Aspirin	Cardiovascular death, MI, stroke	Pending	TIMI major bleeding	Pending
TRACER (2012) ¹¹	12 944 patients with NSTEMI-ACS	Vorapaxar 40 mg then 2.5 mg/day and placebo	Standard therapy	Cardiovascular death, MI, stroke, hospitalised recurrent ischaemia, urgent revascularisation at 2 years	18.5%, 19.9%, p=0.07	GUSTO moderate-severe bleeding	7.2%, 5.2%, p<0.001
TRA 2P-TIMI 50 (2012) ¹²	26 449 patients with a history of MI, ischaemic stroke or PAD	Vorapaxar 2.5 mg/day and placebo	Aspirin	Cardiovascular death, MI, stroke at 3 years	9.3%, 10.5%, p<0.001	GUSTO moderate-severe bleeding	4.2%, 2.5%, p<0.001

ACS=acute coronary syndromes. AMI=acute myocardial infarction. NSTEMI=non-ST-segment elevation. MI=myocardial infarction. STEMI=ST-segment elevation myocardial infarction. CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention. UA=unstable angina. PAD=peripheral artery disease. *p<0.001 versus placebo. †p<0.001 versus single drug.

Table 1: Large-scale clinical trials on the efficacy and safety of treatments in ACS

terms by 6.7% with clopidogrel compared with placebo. Likewise, in the COMMIT trial,⁴ in 45 852 Chinese participants with ST-segment elevation myocardial infarction, many of whom had not received thrombolysis, 75 mg/day of clopidogrel for 16 days or placebo added to aspirin reduced both coprimary endpoints. The COMMIT trial showed a reduction of 9% in the triple composite outcome of mortality recurrent myocardial infarction and stroke, and a reduction in all-cause mortality by 7% at 28 days.⁴ A double-loading dose of 600 mg instead of 300 mg increased the speed of onset and the magnitude of the antiplatelet effect.¹⁶ The large CURRENT-OASIS 7 double-blind trial,⁵ subsequently compared a regimen of 600 mg loading followed by 150 mg clopidogrel for 1 week, with the conventional regimen of 300 mg loading followed by 75 mg for 1 week,

in 25 086 patients with acute coronary syndromes and intended invasive management. The double dose did not reduce adverse cardiac outcomes overall,⁵ but in a prespecified analysis of the 17 263 patients treated with percutaneous coronary intervention,¹⁷ it reduced the primary outcome (3.9% vs 4.5%; adjusted hazard ratio [HR] 0.86, 95% CI 0.74–0.99; p=0.039) at the expense of an increase in major bleeding (1.6% vs 1.1%; adjusted HR 1.41, 95% CI 1.09–1.83; p=0.009).

Notably, the evidence for the benefits of the aspirin and clopidogrel combination in acute coronary syndromes somewhat predated the routine use of percutaneous coronary intervention in acute coronary syndromes. In parallel with acute coronary syndromes studies, clinical trials^{18–20} established the key role of dual inhibition of cyclooxygenase-1 and the P2Y₁₂ platelet receptor with the

	Indication	Loading dose (mg)	Maintenance dose (mg)	Duration of treatment (years)	Recommended delay between last dose and CABG surgery in stabilised patients (days)
Aspirin	All types of ACS	150–300	75–100 once a day	Indefinite	No interruption recommended
Prasugrel	ACS treated with PCI (including primary PCI) no previous history of stroke or TIA	60	10* once a day	1	7
Ticagrelor	STEMI treated with primary PCI	180	90 twice a day	1	3–5
Ticagrelor	NSTE-ACS regardless irrespective of management (invasive or conservative)	180	90 twice a day	1	3–5
Clopidogrel	STEMI treated with thrombolysis	300†	75 once a day	1	5
Clopidogrel	All types of ACS if little access to ticagrelor or prasugrel, or if high risk of bleeding (including chronic treatment with oral anticoagulants)	300–600	75 once a day	1	5
Vorapaxar	History of MI or PAD, no previous history of stroke or TIA	NA	2.5 once a day‡	3	No interruption recommended

ACS=acute coronary syndromes. CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention. TIA=transient ischaemic attack. STEMI=ST-segment elevation myocardial infarction. NSTE=non-ST-segment elevation. MI=myocardial infarction. PAD=peripheral artery disease. *5 mg, if bodyweight <60 kg or age ≥75 years. †No loading dose, if age 75 years or more. ‡Vorapaxar sulfate (equivalent to 2.08 mg vorapaxar).

Table 2: Dosing and indications for the main oral antiplatelet drugs used during or after ACS

combination of aspirin and either ticlopidine (at the time) or clopidogrel, in the striking reduction of the risk of stent thrombosis after percutaneous coronary intervention. Other randomised trials²¹ also established primary percutaneous coronary intervention as the standard of care for reperfusion therapy in patients with ST-segment elevation myocardial infarction. Since then, ticlopidine use has been abandoned, with its rare but severe haematological side-effects, and the combination of aspirin and a P2Y₁₂ inhibitor has become the standard of care for patients who receive stents. Although the data in ST-segment elevation myocardial infarction were restricted to the first month after the acute phase, guidelines universally endorsed the recommendation of aspirin and clopidogrel use for up to 12 months after acute coronary syndromes, with a loading dose of 300 mg at the start (which can be increased to 600 mg in patients managed with an invasive strategy) and a maintenance dose of 75 mg/day. In lytic-treated patients, no loading dose is to be used in those older than 75 years based on the designs of CLARITY³ and COMMIT.⁴

Limitations of clopidogrel

Clopidogrel has substantial limitations in the management of acute coronary syndromes with a modest inhibition of platelet aggregation and a delayed onset and offset of action. Although no accepted test or specific target goal exists for platelet inhibition, variability in response to clopidogrel is substantial,^{22,23} with estimations that 4–34% of patients have an inadequate response dependent on the method and cut point used. These patients are at high risk of subsequent clinical events including stent thrombosis, recurrent myocardial infarction, and death,^{24–26} although evidence of the benefit of a platelet function-based treatment strategy has proven elusive.^{27–29} High on-treatment platelet reactivity with clopidogrel is related to clinical (eg, acute coronary syndromes and diabetes), behavioural (eg, adherence), and genetic factors. Clopidogrel is a prodrug

that needs to be transformed into an active metabolite; the transformation process relies on a multistep conversion by hepatic cytochrome P450 enzymes including CYP2C19, 3A4, 2B6, and 2C9,⁸ whereas much of the parent molecule is inactivated and a proportion is metabolised to the key active metabolite. Reduced effectiveness of clopidogrel has been shown in carriers of reduced-function alleles of these enzymes, particularly in the common variant *CYP2C19*2*. Carriers of *CYP2C19*2* have worse clinical outcomes with clopidogrel treatment than patients without this variant,^{30–32} but the restricted antiplatelet response to clopidogrel in carriers of the reduced-function alleles can, in part, be overcome with increased dosing of clopidogrel.³³ However, it has been difficult to show the ability to modulate clinical outcomes with a genetic-based strategy.³⁴ Finally, clopidogrel has a slow onset of action with a peak effect after 6–12 h, dependent on the dose, and a slow offset of action (3–5 days) because the active metabolite of clopidogrel irreversibly binds to the platelets, which could potentially limit the use of this drug in some clinical scenarios, such as when the need for surgery is uncertain before use. These limitations have led to the development of alternative P2Y₁₂ antagonist strategies that are discussed in detail later in this Series paper.

Prasugrel

Prasugrel is a second-generation thienopyridine that, similarly to clopidogrel, needs conversion from an inactive form to an active metabolite by use of cytochromes.³⁵ Unlike clopidogrel, however, prasugrel is rapidly and more wholly metabolised to its active components. This metabolic difference allows prasugrel to have a more rapid onset, higher levels of platelet inhibition, and less interpatient response variability than clopidogrel.³⁶

The major clinical outcomes trial of prasugrel, TRITON-TIMI 38 trial,⁶ compared prasugrel (60 mg loading dose and 10 mg daily) with clopidogrel (300 mg

loading dose and 75 mg daily) in patients with acute coronary syndromes and treatment at the time of planned percutaneous coronary intervention. Prasugrel had a 19% reduction in relative risk compared with clopidogrel in the primary efficacy endpoints of cardiovascular death, myocardial infarction, or stroke (figure 1),⁶ with a 24% reduction in myocardial infarction, a 52% reduction in stent thrombosis, and no differences in cardiovascular or overall mortality. Stent thrombosis and myocardial infarction reductions were recorded early after the procedure and throughout the 15-month follow-up.^{37,38} Consistent with the increased inhibition of platelets, higher overall bleeding was noted with prasugrel than clopidogrel, including a 32% increase in TIMI major bleeding that was not associated with coronary artery bypass grafting (CABG), higher rates of fatal bleeding, and bleeding associated with CABG. No excess in intracranial haemorrhage was reported.⁶

In TRITON-TIMI 38, there were notable subgroups that have shaped the use of prasugrel in clinical practice. Patients with a reported history of stroke or transient ischaemic attack were at higher risk of serious bleeding complications, including intracranial haemorrhage, and showed lesser efficacy with prasugrel than the overall trial population. As a result, regulatory agencies worldwide (eg, US Food and Drug Administration and the European Medicines Agency) have recommended against the use of prasugrel in patients with previous stroke or transient ischaemic attack. In patients aged 75 years or more, or who weigh less than 60 kg, the balance of risk and benefit with prasugrel was less favourable than in the overall trial population, and caution is generally recommended for the use of this agent in such patients, with the exception of the use of a lower 5 mg maintenance dose.³⁹⁻⁴¹ By contrast, a better clinical benefit and risk profile of prasugrel compared with the overall trial population tended to be seen in patients with ST-segment elevation myocardial infarction or diabetes.^{42,43}

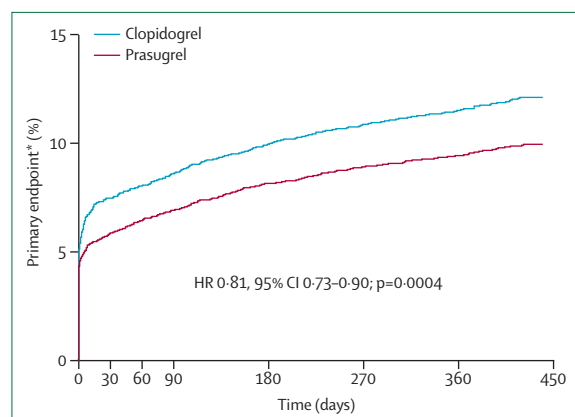


Figure 1: Kaplan-Meier estimates of the primary endpoints for prasugrel and clopidogrel in the TRITON-TIMI 38 trial

*Cardiovascular death, myocardial infarction, and stroke. Adapted with permission from Wiviott and colleagues.³¹

The TRILOGY ACS trial⁷ compared prasugrel with clopidogrel in 9326 patients with acute coronary syndromes managed medically without planned revascularisation. The primary endpoints of cardiovascular death, myocardial infarction, and stroke were not reduced and bleeding did not differ between groups.⁷ Prasugrel had better results in the subset of patients with angiographically proven coronary artery disease.⁴⁴ However, because of the little reduction in the primary composite endpoint in the full trial cohort, prasugrel has not been approved or recommended for the treatment of acute coronary syndrome without percutaneous coronary intervention.

Ticagrelor

Ticagrelor is a direct-acting P2Y₁₂ antagonist that does not need metabolic activation and is therefore not dependent on cytochrome P450 enzymes. The drug acts rapidly and has more potent and consistent antiplatelet effects than clopidogrel. Ticagrelor was compared with clopidogrel in patients with acute coronary syndromes in the PLATO trial,⁴⁵ which enrolled 18 624 patients with moderate to high risk of unstable angina, or non-ST-segment elevation myocardial infarction, or patients with ST-segment elevation myocardial infarction with planned primary percutaneous coronary intervention. Patients were randomly assigned, and treated as soon as possible, before percutaneous coronary intervention was attempted. Patients were given aspirin and could be clopidogrel naive or not. Ticagrelor was given with a loading dose of 180 mg and a maintenance dose of 90 mg twice daily, and clopidogrel with a loading dose of 300 mg (unless patients were previously on clopidogrel) and a maintenance dose of 75 mg daily. Physicians had the option to reload patients before percutaneous coronary intervention with an additional 300 mg. Ticagrelor reduced the primary outcome of cardiovascular death, myocardial infarction, and stroke by 16% compared with clopidogrel (HR 0.84, 95% CI 0.77-0.92; $p=0.0003$).⁴⁵ A prespecified hierarchical analysis of secondary outcomes showed that ticagrelor also reduced cardiovascular mortality (HR 0.79, 95% CI 0.69-0.91; $p=0.001$).⁴⁵ Ticagrelor reduced the occurrence of definite stent thrombosis by around 33%, irrespective of stent type, patient profiles, and cotherapies used.⁴⁶ The benefits of ticagrelor were consistent for invasive or conservative management strategies (figure 2).⁴⁷⁻⁴⁹ Likewise, these benefits were consistent across subgroups defined by age,⁵⁰ risk factors, bodyweight, previous medical history (including transient ischaemic attack),⁴⁷ type of acute coronary syndrome,⁵¹ and genotype.⁵² A noteworthy interaction ($p=0.045$) was present between treatment effect and enrolment region of the trial, with no benefit from ticagrelor in patients enrolled in North America. This interaction might result from a negative interaction between ticagrelor and the higher doses of aspirin (more

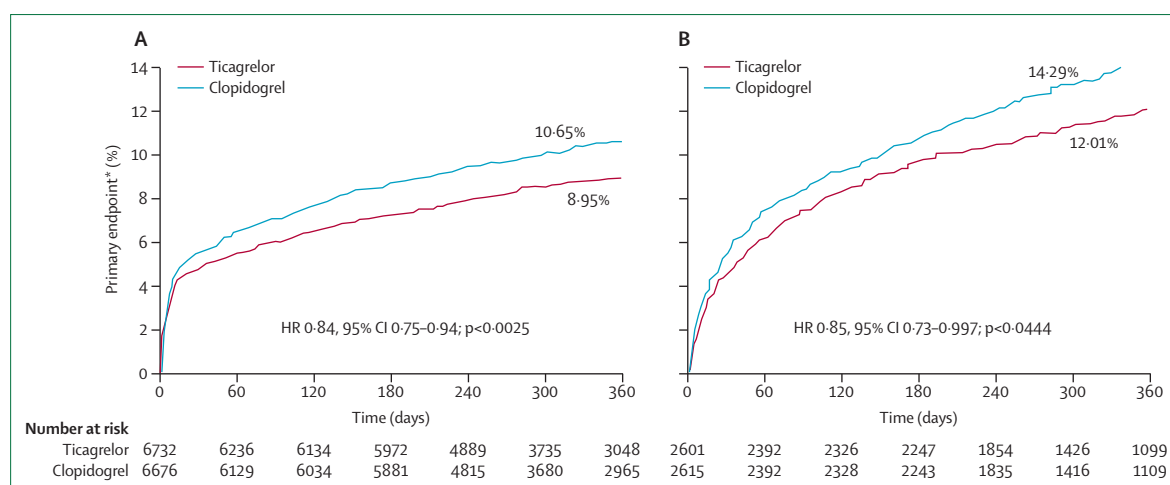


Figure 2: Kaplan-Meier estimates of the primary endpoint for patients given ticagrelor or clopidogrel in PLATO in relation to the management strategy planned at the time of randomisation

(A) Invasive strategy (72% of patients in PLATO). (B) Conservative strategy (28% of patients in PLATO). Adapted with permission from James and colleagues.⁴³

*Cardiovascular death, myocardial infarction, and stroke.

than 150 mg/day) often used in the USA compared with other regions, although a chance variation cannot be formally excluded. This has led to the recommendation to use ticagrelor with low-dose aspirin (up to 150 mg).³³ In PLATO,⁴⁵ ticagrelor did not increase major or fatal bleeding, although there was an increase in bleeding not related to CABG surgery (by around 20%) and a borderline increase in the proportion of intracranial bleeding (0.3 vs 0.2%, $p=0.06$). Combined major and minor PLATO bleeding rates increased by 11% ($p=0.008$), although TIMI major and minor bleeding rates did not increase. Dyspnoea was twice as frequent in patients given ticagrelor compared with patients given clopidogrel and led to treatment discontinuation in around 1% of patients. Dyspnoea was generally mild and transient, occurring early after therapy started, and was not associated with abnormalities on physical examination, chest radiograph, or lung-function tests.⁵⁴ Discussions on the risk of shortness of breath with patients before their discharge are important to avoid unplanned disruption of antiplatelet therapy.⁵⁵ The reduction in cardiovascular mortality seen in PLATO might be related to the fact that ticagrelor reduces ischaemic outcomes without an increase in fatal bleeding, or might stem from non-platelet mediated effects of ticagrelor (for which inhibition of adenosine reuptake in erythrocytes by ticagrelor has been postulated),^{56,57} or could be a chance finding.

Vorapaxar

Vorapaxar is a competitive antagonist of the protease-activated receptor, which is a major thrombin receptor on human platelets. Vorapaxar has been studied in two major trials of patients with acute coronary syndromes: TRACER¹¹ and TRA 2P-TIMI 50.¹² TRACER enrolled 12 944 patients with non-ST-segment elevation

acute coronary syndromes and compared vorapaxar with placebo, in addition to standard therapy, which included aspirin plus clopidogrel in 92% of patients. The combination primary endpoint of cardiovascular death, myocardial infarction, stroke, recurrent ischaemia, or urgent revascularisation tended to be lower (HR 0.92; $p=0.07$) than the placebo group but was not significant. The prespecified combination secondary endpoint of cardiovascular death, myocardial infarction, and stroke was marginally reduced (HR 0.89; $p=0.02$). GUSTO severe and TIMI major bleeding were significantly increased with vorapaxar. TRA 2P-TIMI 50¹² was a trial of 26 449 patients with a history of atherosclerotic vascular disease including myocardial infarction, stroke, or peripheral arterial disease within 2 weeks to 12 months of enrolment. The trial compared daily vorapaxar with placebo in addition to standard therapy. Use of dual antiplatelet therapy differed from 78% of patients with myocardial infarction to 37% of those with stroke. The stroke arm of the trial was stopped early because of an increased risk of intracranial haemorrhage. Overall, vorapaxar reduced the risk of the combined primary endpoint of cardiovascular death, myocardial infarction, and stroke by 13% (HR 0.87; $p<0.001$) compared with the placebo group, although non-CABG-related TIMI major bleeding increased (HR 1.48; $p<0.001$). Clinical events were fewer with vorapaxar in patients with previous-myocardial infarction and those with peripheral arterial disease. On the basis of these data, the US Food and Drug Administration approved vorapaxar for the secondary prevention of vascular events in patients with myocardial infarction, or peripheral arterial disease, but without previous stroke or transient ischaemic attack, but not for acute management of patients with acute coronary syndromes. The European

Medicines Agency also approved vorapaxar, but only in post-myocardial infarction patients. Importantly, vorapaxar has not been studied in combination with prasugrel or ticagrelor.

Cilostazol

Cilostazol is an orally available cyclic adenosine monophosphate phosphodiesterase III inhibitor that has vasodilatory and antiplatelet effects. This agent is predominantly used for the management of intermittent claudication associated with peripheral arterial disease. Cilostazol has been studied in small studies (predominantly in Asia) as a component of triple antiplatelet therapy with aspirin and clopidogrel. One meta-analysis⁵⁸ suggests that a strategy of cilostazol, in addition to standard dual antiplatelet therapy, could improve clinical outcomes, including cardiovascular events and stent thrombosis. These data are important but need confirmation in large-scale clinical trials before formal recommendation for use in acute coronary syndromes can be made.

Combined therapy with aspirin and either prasugrel or ticagrelor

Since both prasugrel and ticagrelor have shown superior outcomes to clopidogrel in pivotal trials, these novel agents are now preferred to clopidogrel as a first-line therapy in conjunction with aspirin, for most patients with acute coronary syndromes, as endorsed by both European and US guidelines.^{39–41} Prasugrel is a preferred option for patients undergoing percutaneous coronary intervention (except for patients with a previous history of stroke or transient ischaemic attack, with a bodyweight less than 60 kg, or at an age of 75 years or more), while ticagrelor is a preferred option for moderate-to-high risk patients with acute coronary syndromes, irrespective of the management strategy.^{39–41} Clopidogrel is now the preferred second-line therapy when there is a high risk of bleeding, in patients who have received thrombolysis, or in patients who need long-term oral anticoagulation (dependent on the availability of more data with prasugrel and ticagrelor), when the novel agents are unavailable, or when cost or specific patient issues exist.

Although the novel P2Y₁₂ blockers are more effective than clopidogrel for most patients, they also have limitations: they increase the risk of bleeding; they do not abolish the residual ischaemic risk; their cost is substantially higher than clopidogrel (which is now available as a generic drug); and the rapidity of onset, although quicker than clopidogrel, could be insufficient in some settings such as ST-segment elevation myocardial infarction.⁵⁹ For patients with ST-segment elevation myocardial infarction, particularly those receiving morphine, the antiplatelet efficacy of ticagrelor and prasugrel could be delayed for several hours, leaving patients without adequate protection against platelet aggregation during the first crucial hours of treatment.

In that setting, injectable agents with immediate efficacy, such as glycoprotein IIb and glycoprotein IIIa inhibitors⁶⁰ or, in the future, cangrelor,^{61,62} could provide immediate efficacy (particularly as bail out therapy in patients with high-thrombus load or recurrent-thrombotic events during percutaneous coronary intervention), although this increases costs and, at least for glycoprotein IIb/IIIa inhibitors, the bleeding risk.

Personalised antiplatelet therapy

In view of the high cost and bleeding risk of the novel agents, and the availability of clopidogrel as a generic drug, it might seem important to identify patients with a poor clopidogrel response (based on platelet-function testing or genotyping) and give them either a high dose of clopidogrel or the novel agents, and use the standard dose of clopidogrel in good responders. However, this approach is currently not recommended in routine practice, by guidelines;^{39,40} first, a large genotypic analysis from PLATO has shown that ticagrelor provides consistently better clinical outcomes compared with clopidogrel, irrespective of the presence, or absence, of loss-of-function alleles for genes encoding for clopidogrel metabolism.⁵² Additionally, randomised trials testing a personalised antiplatelet strategy have so far not shown any clinical benefit of this approach compared with a conventional approach,^{27,28,34} although trials so far have largely used high-dose clopidogrel rather than the novel P2Y₁₂ inhibitors. To achieve the desired antiplatelet effect consistently in patients carrying loss-of-function alleles for clopidogrel metabolism, prasugrel or ticagrelor might be preferable to an increase in the dose of clopidogrel.³³

When to start therapy with oral-antiplatelet agents

Substantial diagnostic uncertainty often exists in patients with suspected acute coronary syndromes in the early phases of management, and some patients might either eventually have other final diagnoses (including some contraindications to antiplatelet therapy, such as aortic dissection) or need urgent surgery (in which case, after the patients have received a potent oral antiplatelet agent, the risk of bleeding would be increased). The diagnostic uncertainty is greatest in patients with non-ST-segment elevation acute coronary syndromes and has prompted the administration of any antiplatelet agent other than aspirin to be delayed in some patients until a coronary angiogram has been done, and a decision to proceed with percutaneous coronary intervention can then be made. This is particularly true for prasugrel because its benefits were shown in PCI-treated patients with acute coronary syndromes in TRITON-TIMI 38, but not among medically managed patients in TRILOGY ACS. The ACCOAST randomised trial⁶³ showed no benefit of upstream loading with prasugrel compared with prasugrel given after angiography in patients with non-ST-segment elevation myocardial infarction, but did

show a substantial increase in bleeding risk. Note, however, that the time difference between treatment administration in the two strategies was only 4 h, which minimised any potential disparity between trial arms. By contrast, a meta-analysis⁶⁴ of clopidogrel trials has shown a reduction in cardiac events when clopidogrel was given before PCI in patients with acute coronary syndromes and, in the PLATO trial, treatment with ticagrelor was started at the time of diagnosis and always before PCI. Randomised trials of pretreatment with clopidogrel and ticagrelor are scarce. Overall, these findings suggest that in patients with suspected non-ST-segment elevation acute coronary syndromes, it is prudent to delay loading with oral-antiplatelet agents in case of diagnostic uncertainty or, if the P2Y₁₂ receptor antagonist planned is prasugrel, until a decision to proceed to PCI is made (provided that angiography is planned within hours of presentation). If ticagrelor or clopidogrel are used, then treatment can be started as soon as a diagnosis is established, particularly if the expected delay to coronary angiography exceeds a few hours.

In patients with ST-segment elevation acute coronary syndromes, less diagnostic uncertainty exists and the risk of urgent surgery is low. Routine practice has often been to load these patients with aspirin and a P2Y₁₂ agent as soon as possible, including clopidogrel, prasugrel, or ticagrelor. The ATLANTIC double-blind trial⁶⁵ randomly assigned patients with ST-segment elevation myocardial infarction, identified in the pre-hospital setting and triaged to primary PCI, to receive ticagrelor at the time of diagnosis. No differences were recorded between treatment arms in the two coprimary outcomes of the trial: ST-segment resolution and coronary flow in the infarct-related artery. However, there was a substantial reduction in definite stent thrombosis at 30 days (0·2 vs 1·2%; $p=0\cdot02$), even though there was only a 31 min difference between the administration of ticagrelor in the two treatment arms. There was no increase to the risk of bleeding. These results lend support to the early loading of antiplatelet agents in the pre-hospital setting in patients with ST-segment elevation myocardial infarction triaged to primary PCI.

Optimum duration of therapy

Patients with acute coronary syndromes are at high risk of recurrence⁶⁶ and therefore should receive combined antiplatelet therapy for the initial post-acute coronary syndrome period and subsequently remain indefinitely on single antiplatelet therapy. In addition to the prevention of recurrences, combined antiplatelet therapy also contributes to the prevention of stent thrombosis in the large proportion of patients with acute coronary syndromes who have stents. There is, however, some uncertainty regarding the optimum duration of combined antiplatelet therapy. In view of the costs and ease of use of aspirin, this drug is generally advised for indefinite therapy as secondary prevention. With respect to P2Y₁₂ antagonists, both American and European guidelines

suggest the use of these drugs for a duration of 12 months after acute coronary syndromes.^{39–41}

Although the CHARISMA trial⁶⁷ did not show an overall benefit for long-term clopidogrel for secondary prevention of events in patients with atherosclerosis (coronary artery disease, peripheral arterial disease, or cardiovascular disease), a reduction in recurrent events was observed in patients with a history of prior ischaemic events, such as myocardial infarction.⁶⁸

In the DAPT trial of dual antiplatelet therapy (aspirin with clopidogrel or prasugrel),⁶⁹ patients with stents who were free of clinical events (myocardial infarction, stent thrombosis, or bleeding) 12 months after stent placement were randomly assigned to discontinue or remain on thienopyridine therapy for an additional 18 months. Overall, the occurrence of major adverse cardiac events was 29% lower and that of stent thrombosis was a remarkable 71% lower in patients who continued thienopyridine than in those who discontinued, although, major bleeding was also 61% higher.⁶⁹ A marginally higher rate of overall mortality was noted in the persistent dual antiplatelet therapy group than in the discontinuation group, driven predominantly by non-cardiovascular mortality, an effect not seen in a meta-analysis of the persistent dual antiplatelet therapy trials.⁹ The risk of spontaneous (non-stent-related) myocardial infarction was reduced in the persistent therapy trials, suggesting a secondary preventive benefit, beyond stent protection. Overall, these results suggest that persistent antiplatelet therapy might be warranted in patients with acute coronary syndromes who have not had complications in the first year and who are not at high risk of bleeding. The PEGASUS trial⁷⁰ has tested long-term use of ticagrelor (at two doses 90 mg bid and 60 mg bid) in stable patients at high risk 1–3 years after acute myocardial infarction. Preliminary results show that both doses of ticagrelor reduced the primary outcome of cardiovascular death, myocardial infarction, or stroke, providing evidence of a continued benefit of the combined ticagrelor and aspirin after the initial 12 months.⁷⁰

Patients needing oral anticoagulation

A subset of patients with acute coronary syndromes need permanent oral anticoagulation (eg, because of a prosthetic heart valve or atrial fibrillation). In these patients, the treatment of combined antiplatelet therapy and oral anticoagulation is complex. Typically, management of acute coronary syndromes will entail an initial period of triple therapy, combining aspirin, clopidogrel, and oral anticoagulation, which increases the risk of bleeding.^{71,72} To minimise bleeding, it seems reasonable to avoid prasugrel or ticagrelor use, at least until prospective trials have established the best regimens and duration in this setting.^{73,74} Therefore, clopidogrel is the antiplatelet agent of choice for these patients. Another consideration is to shorten the duration of triple therapy and stop use of one antiplatelet agent as soon as possible. The optimum

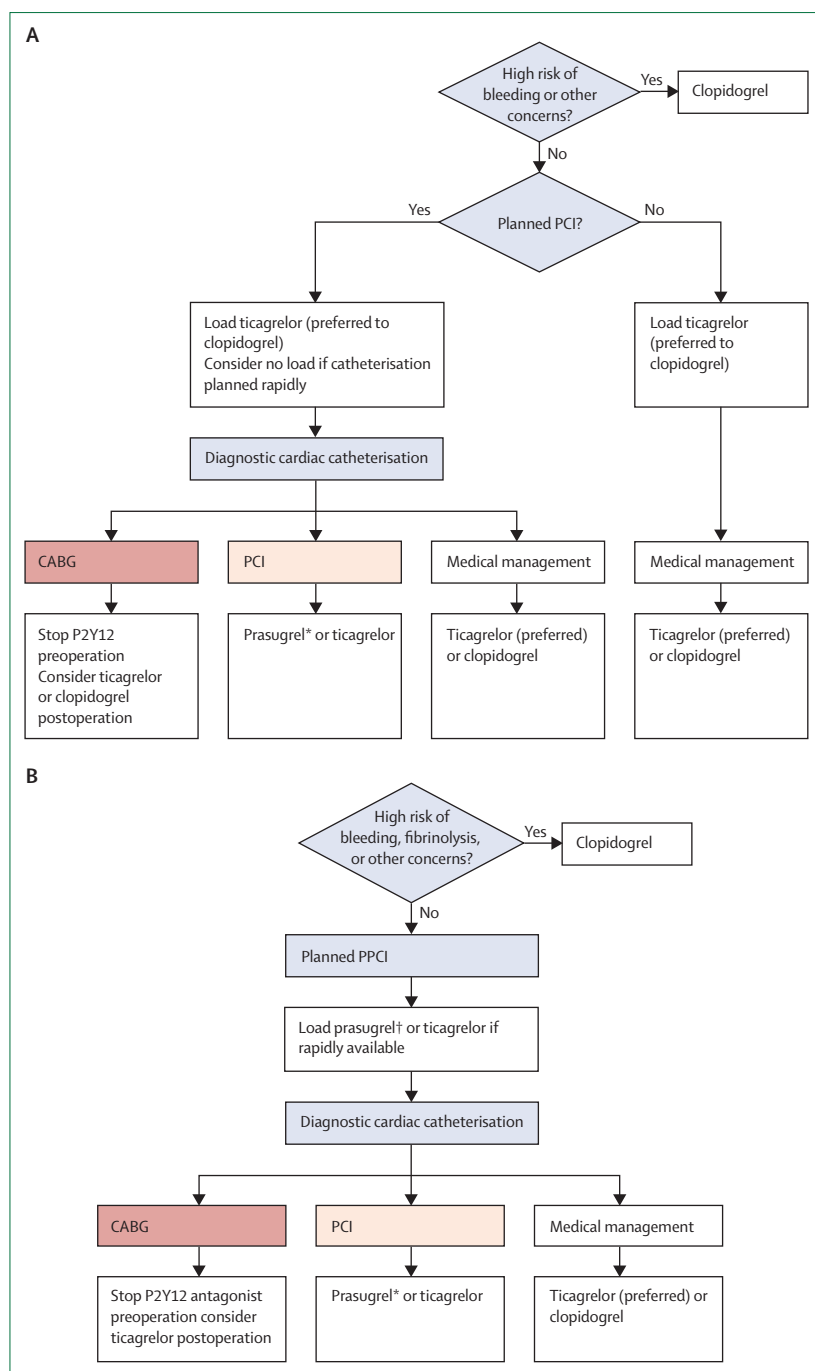


Figure 3: Framework for choice of P2Y12 antagonist in acute coronary syndromes based on US and European Guidelines.³⁴⁻³⁶

(A) Unstable angina or non-ST-segment elevation myocardial infarction. (B) ST-segment elevation myocardial infarction. CABG=coronary artery bypass graft. PCI=percutaneous coronary intervention. PPCI=primary percutaneous coronary intervention. *Without contraindication (stroke or transient ischaemic attack), if no pre-load. †Without contraindication (stroke or transient ischaemic attack).

duration of antiplatelet therapy remains uncertain, although fairly complex recommendations based on expert consensus have been proposed.⁷⁵ One trial showed no difference in efficacy or safety between 6 weeks and

6 months of clopidogrel,⁷⁶ but was somewhat underpowered. The WOEST trial⁷⁷ suggested that it might be possible to use clopidogrel without aspirin in patients who are receiving oral anticoagulation and undergoing stent placement. This strategy reduced the risk of bleeding without an increase in the risk of ischaemic events.

Management of patients undergoing CABG

In patients with acute coronary syndromes, a few will need CABG surgery. Although it is recommended to continue aspirin throughout the perioperative period, it is desirable, in most patients, to withhold P2Y12 receptor blockers before and during surgery to minimise bleeding (unless patients are highly unstable). In very unstable patients or those with new stents, injectable reversible antiplatelet agents, such as glycoprotein IIb/IIIa receptor blockers or, in the future, cangrelor, might allow maintenance of platelet inhibition until surgery, although the exact clinical safety and efficacy of these bridging approaches has not been formally assessed. Surgery sooner than 5 days after stopping of clopidogrel, or 7 days after stopping of prasugrel, is associated with an increased bleeding risk. For ticagrelor, the recommendations on the label suggest a delay of 7 days, although in PLATO, discontinuation for 3–5 days before surgery was not associated with an increased bleeding risk. Therefore, in stabilised patients, it seems prudent to wait for this minimum amount of time before surgery. Long-term outcomes of patients with acute coronary syndromes who underwent CABG after having previously received ticagrelor or prasugrel showed substantially lower mortality compared with patients who had received clopidogrel.^{78,79} Whether to restart P2Y12 receptor antagonists after surgery is uncertain, although it seems reasonable to judge whether therapy should resume once the risk of surgical bleeding has abated.

With respect to vorapaxar, in view of its very long half-life with residual platelet inhibition remaining up to 4 weeks after discontinuation, withholding for brief periods is not helpful for the management or prevention of bleeding. Results from TRACER suggest that patients with acute coronary syndromes undergoing CABG on vorapaxar had a substantial reduction in ischaemic events (HR 0.55, 95% CI 0.36–0.83; $p=0.005$ for the primary composite outcome of death, myocardial infarction, stroke, recurrent ischaemia with readmission to hospital, or urgent coronary revascularisation during index hospital admission) without a significant increase in major CABG-related bleeds.⁸⁰

Conclusions

Antiplatelet therapy improves cardiovascular outcomes after acute coronary syndromes. A broad and comprehensive dataset from large-scale trials allows for evidence-based decisions regarding these therapies (figure 3). The combination of aspirin with a potent inhibitor of the P2Y12 receptor (prasugrel or ticagrelor) is recommended in most patients with acute coronary syndromes, but patient factors and bleeding risk should

be considered in the choice of agents. Additional data from trials of novel agents, strategies, combinations of drugs, and for duration of therapy continue to emerge to help to refine recommendations. Personalised therapy based on genetics or platelet-function testing remains an elusive goal that needs additional research.

Contributors

SDW and PGS wrote the paper and are responsible for its content.

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