

Platelet ADP-receptor antagonists for cardiovascular disease: past, present and future

Nina C Raju*, John W Eikelboom and Jack Hirsh

SUMMARY

Aspirin is the foundation antiplatelet therapy for patients at risk of cardiovascular events. The thienopyridine, clopidogrel, is modestly more effective than aspirin and in patients with stroke seems to be as effective as the combination of aspirin and dipyridamole. The addition of clopidogrel to aspirin further reduces the risk of cardiovascular events in patients with acute coronary syndromes and those who undergo percutaneous coronary intervention, but uncertainty remains about whether this combination has incremental efficacy over clopidogrel monotherapy in patients with stroke or peripheral arterial disease. Clopidogrel has pharmacological limitations that have prompted the search for more effective ADP-receptor antagonists. Promising results have been achieved with the thienopyridine, prasugrel, which has been compared with clopidogrel in patients treated with aspirin. The nonthienopyridine P2Y₁₂ inhibitors AZD6140 and cangrelor are presently being evaluated in phase III, randomized, controlled trials.

KEYWORDS aspirin, AZD6140, cangrelor, clopidogrel, platelets, prasugrel

REVIEW CRITERIA

We searched PubMed for articles published up to July 2008. The following search terms were used alone and in combination: "clopidogrel", "prasugrel", "AZD6140", "cangrelor", "S18886", "E5555", "PAR1", "PAR4", "ADP", "SCH530348", "cardiovascular disease", "angina", "myocardial infarction", "coronary syndromes", "P2Y12", "percutaneous coronary intervention", "randomized" and "clinical trials".

CME

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe the pharmacokinetics of clopidogrel.
- 2 Identify the clinical presentations that are best treated with dual antiplatelet therapy.
- 3 Review guideline recommendations for optimal duration of dual antiplatelet therapy following revascularization.
- 4 Identify key differences between clopidogrel and new adenosine diphosphate (ADP) receptor antagonists.

Competing interests

JW Eikelboom declared associations with the following companies: Bayer, Bristol-Myers Squibb, and sanofi-aventis. See the article online for full details of the relationships. The other authors and the Journal Editor H Camm declared no competing interests. The CME questions author CP Vega declared that he has served as an advisor or consultant to Novartis, Inc.

INTRODUCTION

Platelets have a central role in the pathogenesis of atherothrombosis. In addition to being major components of arterial thrombi, they contribute to all phases of atherosclerosis; activated platelets promote coagulation on their surface¹ and express mediators of inflammation and smooth-muscle-cell proliferation. Rupture of an atherosclerotic plaque exposes collagen and von Willebrand factor (vWF), both of which are ligands that initiate platelet adhesion and activation. Subendothelium-bound vWF binds to the platelet glycoprotein 1b-IX-V complex present on platelets, and thereby tethers platelets from passing blood² and strengthens the binding of subendothelial collagen to

platelets through glycoprotein VI and glycoprotein IIa/Ib receptors (Figure 1).³

Platelet agonists interact with their respective G-protein-coupled receptors via a series of intracellular signaling cascades to amplify platelet activation and aggregation. Binding of the three primary platelet agonists—vWF, collagen and thrombin—to their corresponding receptors on the platelet surface stimulates the extracellular release of secondary agonists such as ADP and thromboxane A₂ into the blood plasma. ADP binds the G_q-protein-linked P2Y₁ receptor on platelets, which causes a change in cell shape, mobilization of calcium, and initiation of reversible aggregation,⁴ and binds the G_i-linked P2Y₁₂ receptor to amplify aggregation via adenylyl-cyclase-mediated cyclic AMP production.⁵ The resulting platelet activation triggers a conformational change in glycoprotein IIb/IIIa receptors, which increases their affinity for fibrinogen and vWF. These ligands then bind to the receptors to form bridges between adjacent platelets, which results in aggregation. Sustained ADP-induced platelet aggregation requires activation of both P2Y₁ and P2Y₁₂ receptors.⁶ Of the two, however, the P2Y₁₂ receptor is the more attractive therapeutic target because its expression has a less widespread distribution and it has a dominant role in platelet aggregation. Activated platelets also promote the generation of thrombin—the most potent of all platelet agonists. Thrombin acts predominantly via protease-activated receptors 1 and 4 (PAR1 and PAR4) expressed on platelets.⁷ Thrombin cleaves a portion of these receptors' N-terminus, which unmask the sequence that serves as its ligand;⁸ this modification activates the receptor and triggers multiple signal transduction pathways that modulate thrombosis, coagulation and inflammation. Protease-activated receptors are widely distributed in the vascular system and occur on platelets, endothelial cells, leukocytes and vascular smooth muscle cells.⁹ PAR1 is more potent when activated than PAR4,⁷ and thus PAR1 is the preferred target for developing therapies.

Antiplatelet agents that target critical steps in thrombogenesis have been developed; drugs that block thromboxane A₂ synthesis, those that block receptors for ADP, thrombin and thromboxane A₂, and agents that block fibrinogen and other ligands from binding to activated glycoprotein IIb/IIIa receptors (Figure 2 and Box 1). However, as the pathways that promote thrombosis are also critical to hemostasis, treatment with antiplatelet drugs is usually associated with an increased risk of

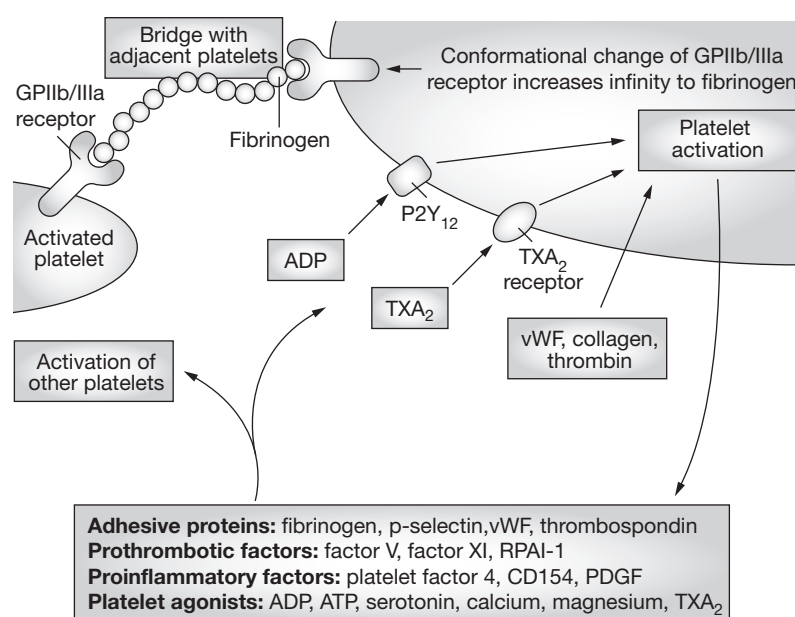


Figure 1 Mechanisms of platelet adhesion and activation. Abbreviations: GP, glycoprotein; PAI-1, plasminogen activator inhibitor 1; PDGF, platelet-derived growth factor; TXA₂, thromboxane A₂; vWF, von Willebrand factor.

bleeding. Furthermore, as several agonists can initiate platelet activation, increased antithrombotic efficacy can reasonably be expected to be obtained by blocking more than one pathway of platelet activation, but such strategies incur the cost of an increased risk of bleeding.

Antiplatelet agents are effective in the treatment of arterial thrombosis. Aspirin, the first antiplatelet agent to be evaluated, can reduce the risk of vascular death by 15%, nonfatal myocardial infarction (MI) by 30% and nonfatal stroke by 25% in a broad range of high-risk patients.¹⁰ However, room for improvement remains. Despite aspirin therapy, 10–20% of patients have recurrent vascular events in the 5 years after their incident event.¹¹ As aspirin inhibits the synthesis of only one platelet agonist (thromboxane A₂), its limited efficacy as an antithrombotic agent is not surprising. The thienopyridines—ticlopidine and clopidogrel—block ADP-mediated platelet activation. In patients with a broad spectrum of cardiovascular disease, these ADP antagonists are modestly more effective than aspirin in the prevention of major cardiovascular events (MI, stroke or death) and, in patients with stroke, clopidogrel is as effective as aspirin and dipyridamole in combination. In certain cardiovascular disorders clopidogrel combined with aspirin has additive beneficial effects when compared with clopidogrel alone. Of the two thienopyridines, clopidogrel is associated with

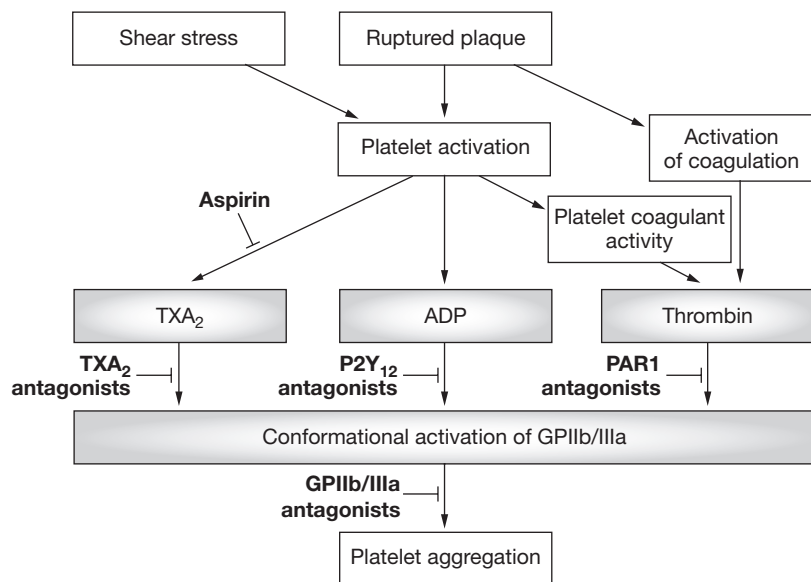


Figure 2 Sites of action of platelet inhibitors. Platelet aggregation can be inhibited by agents that target cyclo-oxygenase 1 and therefore block the production of thromboxane, or by agents that target platelet receptors (e.g. the TXA₂ receptor, P2Y₁₂, PAR1, and GP IIb/IIIa receptors) and thus block the action of platelet agonists. The various antiplatelet agents and their drug classes are listed in Box 1. Abbreviations: GP, glycoprotein; PAR, protease-activated receptor; TXA₂, thromboxane A₂.

Box 1 A summary of agents that inhibit platelet aggregation.

P2Y₁₂ antagonists

- Clopidogrel
- Prasugrel
- AZD6140
- Cangrelor

Thromboxane antagonists

- Terutroban

Protease-activated receptor 1 antagonists

- E5555
- SCH530348

Glycoprotein IIb/IIIa antagonists

- Abciximab
- Tirofiban
- Eptifibatide

fewer adverse effects. Clopidogrel does, however, have limitations, which has prompted the development of new ADP antagonists (Table 1). Over the past few years antiplatelet agents have also been developed that block thromboxane-A₂-mediated platelet activation (terutroban) and thrombin-mediated platelet activation (SCH530348 and E5555). In preliminary clinical trials, both classes of antiplatelet drugs show promise.

This Review focuses on the role of ADP-receptor antagonists in the treatment of cardiovascular disorders. We examine evidence for the effectiveness and safety of clopidogrel when used alone and in combination with aspirin, and address controversies over the optimum loading dose and duration of treatment with clopidogrel. We also explore the new ADP-receptor antagonists prasugrel, AZD6140 and cangrelor, and examine their therapeutic potential relative to each other and to clopidogrel.

THE THIENOPYRIDINES

The structure of ADP-receptor antagonists is provided in Supplementary Figure 1 online. Ticlopidine and clopidogrel irreversibly inhibit the P2Y₁₂ receptor. Early studies with ticlopidine demonstrated that it was more effective than aspirin in preventing stroke or death in patients with cardiovascular disease.¹² The results of clinical trials that evaluated ticlopidine in cardiovascular disease are summarized in Table 2. Ticlopidine alone or when combined with aspirin was shown to be more effective than oral anticoagulants in preventing stent thrombosis, more effective than aspirin or placebo in the secondary prevention of stroke, and more effective than placebo in patients with mixed atherothrombosis. However, because of the raised incidence of nonhemorrhagic adverse effects, ticlopidine has been replaced by clopidogrel.

After ingestion, the majority (85%) of clopidogrel molecules are metabolized by esterases to form an inactive, carboxylic-acid derivative.¹³ The remainder of the prodrug molecules are converted to the active form by hepatic CYP450 isoenzymes (predominantly CYP3A4).¹⁴ The active metabolite of clopidogrel is an unstable, reactive, thiol derivative that has a very short half-life. The active metabolite forms disulfide bridges between cysteine residues on the P2Y₁₂ receptor, which irreversibly modifies the receptor site and inhibits ADP-dependent platelet activation and aggregation.¹⁵⁻¹⁷ Clopidogrel has a relatively slow onset of action; daily maintenance doses of 75 mg administered for 4-5 days are required to achieve plateau levels of platelet inhibition. P2Y₁₂ receptor inhibition by clopidogrel is irreversible, which means that this drug has a permanent effect on platelet aggregation that lasts for the lifetime of the platelet (5-10 days). Recovery of systemic platelet function requires approximately 5 days off treatment.

On the basis of its pathway of metabolism, clopidogrel has the potential to influence the actions of other drugs that are metabolized via

Table 1 Properties of P2Y₁₂ receptor antagonists.

Drug	Route of administration	Frequency of administration	Activation via CYP450 metabolism	Time to peak platelet inhibition	Reversibility (half-life)
Clopidogrel	Oral	Once daily	Yes ^a	2–6 h ^b	No
Prasugrel	Oral	Once daily	Yes ^a	2 h	No
Cangrelor	Intravenous	Continuous	No	30 min	Yes (3–5 min)
AZD6140	Oral	Twice daily	No	2 h	Yes (12 h)

^aThese agents are prodrugs. ^bAfter 600 mg clopidogrel loading dose. Abbreviation: CYP, cytochrome P.

CYP3A4. Although concern has been raised about interaction with certain statins that are metabolized via CYP3A4,¹⁸ no clinical evidence of an adverse interaction between statins and clopidogrel has been seen in large, randomized, controlled trials.^{19,20}

Monotherapy versus dual antiplatelet therapy: clinical evidence

Major clinical trials of clopidogrel are summarized in Tables 3 and 4. The landmark Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study established the efficacy and safety of clopidogrel monotherapy for the treatment of cardiovascular disease and showed that this thienopyridine was modestly more effective than aspirin.²¹ Since that trial was published in 1996, a number of studies have evaluated the complementary inhibitory properties of aspirin and clopidogrel in several settings, including after percutaneous coronary intervention (PCI), in patients with acute coronary syndromes (ACS), stroke, or mixed atherothrombotic disorders, and for the prevention of cardiovascular events in patients at high risk of these outcomes (Table 2).

The combination of aspirin and clopidogrel is superior to aspirin in patients with ACS and across the spectrum of patients who undergo PCI. In patients with non-ST-segment elevation ACS, the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study²² established that a 300 mg clopidogrel loading dose (75 mg maintenance dose) with concomitant aspirin therapy significantly reduced the occurrence of MI and recurrent ischemia compared with aspirin alone, irrespective of baseline TIMI (Thrombolysis in Myocardial Infarction) risk score.²³ Combination therapy did not, however, provide a benefit in terms of stroke or cardiovascular death. An early effect of treatment was seen, with onset within 2 h of administration of the loading dose, and

benefits continued to accrue over 12 months of follow-up.

The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT)²⁴ and Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction 28 (CLARITY–TIMI 28) study²⁵ both showed that a combined clopidogrel and aspirin regimen was superior to aspirin alone in patients with acute MI, despite a short duration of therapy. COMMIT randomly allocated participants to receive clopidogrel (75 mg daily, no loading dose) or placebo within 24 h of suspected acute MI. A mean of 15 days of therapy with clopidogrel significantly reduced the occurrence of MI, stroke or death; these benefits were evident early in treatment, despite the lack of a loading dose, and were consistent across a wide range of patients. No excess bleeding events were observed in the clopidogrel group, despite the inclusion of patients older than 75 years. The CLARITY–TIMI 28 study assessed clopidogrel pretreatment against a background of standard fibrinolytic therapy that included aspirin. Patients aged 75 years or younger were randomly assigned either placebo or clopidogrel within 12 h of presentation with ST-segment elevation MI. Clopidogrel-treated patients received a median of four drug doses (300 mg loading dose, 75 mg maintenance dose). Treatment with clopidogrel was associated with a reduced rate of the primary composite outcome—occlusion of an infarct-related artery on angiography, cardiovascular-related death or recurrent MI before angiography—and, at 30 days, patients who received clopidogrel had a 20% reduction in their risk of cardiovascular-related death, recurrent MI or ischemia that required revascularization (14.1% in placebo-treated patients versus 11.6% in clopidogrel-treated patients; $P=0.03$). No excess of major or total bleeds occurred in the clopidogrel group.

Table 2 A summary of randomized, controlled, phase III trials of ticlopidine in cardiovascular disease.^a

Study	Ticlopidine dose (n)	Comparator therapy and dose (n)	Primary outcome measures	Comment
ACS				
STAMI	250 mg bid (734)	160 mg daily aspirin (736)	Composite of MI, stroke, angina, cardiovascular death, death from any cause	No significant difference in primary outcome
PCI and/or stent				
ISAR ^b	250 mg bid (257)	Phenprocoumon, INR 3.5–4.5 ^c (260)	Cardiac: composite of cardiovascular death, MI, CABG, TVR Noncardiac: noncardiac death, stroke, severe hemorrhage, peripheral vascular events	Better outcomes with ticlopidine than oral anticoagulation: 82% lower risk of MI, 78% lower need for TVR, lower rate of stent thrombosis (RR 0.14), less bleeding
STARS	250 mg bid plus 325 mg daily aspirin (546)	325 mg daily aspirin alone (557), or 325 mg daily aspirin plus warfarin, INR 2.0–2.5 ^c (550)	Composite of death, TVR, thrombosis on angiography or MI within 30 days	Less stent thrombosis with ticlopidine but more bleeding, compared with aspirin alone
Stroke				
TASS	250 mg bid (463)	650 mg bid aspirin (464)	Stroke or death from any cause	Ticlopidine more effective than aspirin (12% RR overall, 21% RR of stroke) but increased rate of adverse effects
TISS	250 mg daily (821)	200 mg daily indobufen (811)	Stroke, MI, death from any cause	Ticlopidine more efficacious than indobufen (49.6% RRR)
CATS	250 mg bid (525)	Placebo (528)	Stroke, MI, cardiovascular death	Ticlopidine more efficacious than placebo (30% RR in primary outcome)
AAASPS	250 mg bid (902)	650 mg daily aspirin (907)	Stroke, MI, cardiovascular death	No significant difference in primary outcome
Mixed atherothrombosis				
STIMS	250 mg bid (346)	Placebo (341)	MI, stroke, TIA	Ticlopidine reduced mortality and decreased need for vascular surgery by approximately 50%

^aOnly trials with >500 participants are shown; a full reference list of all the studies is provided in Supplementary Reference List 1, online. ^bBoth treatment arms received aspirin. ^cOral anticoagulation bridged with intravenous heparin. Abbreviations: AAASPS, African American Antiplatelet Stroke Prevention Study; ACS, acute coronary syndromes; bid, twice daily; CATS, Canadian American Ticlopidine Study; INR, international normalized ratio; ISAR, Intracoronary Stenting and Antithrombotic Regimen; MI, myocardial infarction; n, number of patients; PCI, percutaneous coronary intervention; RR, risk reduction; RRR, relative risk reduction; STAMI, Ticlopidine Versus Aspirin After Myocardial Infarction Trial; STARS, Stent Anticoagulation Restenosis; STIMS, Swedish Ticlopidine Multicenter Study; TASS, Ticlopidine Aspirin Stroke Study; TIA, transient ischemic attack; TISS, Ticlopidine Indobufen Stroke Study; TVR, target-vessel revascularization.

The Clopidogrel for the Reduction of Events During Observation (CREDO)²⁶ trial and two substudies of large, randomized, controlled trials^{27,28} demonstrated the superiority of aspirin and clopidogrel combined compared with aspirin alone in patients who underwent PCI. Early benefits of treatment were observed, which were sustained for up to 1 year after treatment allocation. The CREDO trial provided important information about the timing of the 300 mg clopidogrel loading dose; a prespecified subgroup analysis found that pretreatment with clopidogrel conferred a benefit of borderline statistical significance in patients who received the loading dose at least 6 h before PCI (relative risk reduction 38.6%, 95% CI –1.6% to 62.9%; $P=0.051$). Overall, however, clopidogrel pretreatment (i.e. a 300 mg loading dose administered 3–24 h before

PCI) did not reduce the combined risk of death, MI or target-vessel revascularization at 28 days.²⁶ Initially, the CREDO trial results led guidelines to recommend that the 300 mg loading dose should be given at least 6 h before PCI.²⁹ Subsequently, the recommended loading dose has changed to 600 mg.³⁰ In the CURE trial, 21.2% of patients (1,313 of whom received clopidogrel and 1,345 received placebo) underwent PCI a median of 10 days after treatment allocation and were included in the PCI-CURE study.²⁷ Although allocation to clopidogrel or placebo was random, the decision whether to perform PCI was made by the investigator, which provided a potential source of bias. Nevertheless, fewer patients in the clopidogrel group had an MI, or MI and refractory ischemia before PCI than in the control group, and at 30 days after PCI clopidogrel was

Table 3 Summary of phase III, randomized, controlled trials with clopidogrel in cardiovascular disease; part 1.^a

Study	Clopidogrel dose (n)	Comparator therapy and dose (n)	Primary outcome measure	Comment
ACS				
CLARITY-TIMI 28 ^{25,b}	300 mg LD, 75 mg daily (1,752)	Placebo (1,739)	Composite of occluded infarct-related artery on angiography, or death or recurrent MI before angiography	36% reduction in primary outcome with clopidogrel, no increase in TIMI major or total bleed
COMMIT ^{24,c}	75 mg daily (22,961)	Placebo (22,891)	First: composite of death, reinfarction or stroke Second: death from any cause during scheduled treatment period	Improved outcomes with clopidogrel: no increase in bleeding
CURE ^{22,c}	300 mg LD, 75 mg daily (6,259)	Placebo (6,303)	First: composite of cardiovascular death, nonfatal MI or stroke Second: composite of first primary outcome or refractory ischemia	Clopidogrel more effective than placebo in reducing both primary outcome measures (RR 0.8 and 0.86, respectively) but increased bleeding
PCI and/or stent				
CREDO ^{26,c}	300 mg LD pre-PCI, then 75 mg daily to day 28; 75 mg daily day 29–12 months (1,053)	Placebo 3–24 h pre-PCI, then 75 mg daily clopidogrel to day 28; placebo day 29–12 months (1,063)	First: 1-year composite of death, MI, stroke (intention to treat analysis) Second: composite of death, MI, urgent TVR (per-protocol analysis)	Improved outcomes with clopidogrel (26.9% reduction in first primary outcome)
PCI-CLARITY ^{28,c}	300 mg LD, 75 mg daily (933)	Placebo (930)	Composite of cardiovascular death, recurrent MI, stroke (measured from PCI to 30 days after randomization)	Improved outcomes with clopidogrel (OR 0.54); no significant increase in TIMI major or minor bleeds
PCI-CURE ^{27,c}	300 mg LD, 75 mg daily (1,313)	Placebo (1,345)	Composite of cardiovascular death, MI or urgent TVR, within 30 days of PCI	Clopidogrel more effective than placebo (31% reduction in cardiovascular death or MI); no difference in major bleeding
TRITON-TIMI 38 ^{71,c}	300 mg LD, 75 mg daily (6,795)	60 mg prasugrel LD then 10 mg daily prasugrel (6,813)	Composite of cardiovascular death, MI, stroke	Prasugrel more effective than clopidogrel but associated with increased major and fatal bleeds
CLASSICS ^{82,c}	300 mg LD, 75 mg daily (345), or 75 mg daily (335)	250 mg/bid ticlopidine (340)	Major bleeds, neutropenia, thrombocytopenia, drug discontinuation for noncardiac event	Clopidogrel had superior safety and tolerability to ticlopidine
Muller <i>et al.</i> (2000) ^{83,c}	75 mg daily (355)	250 mg bid ticlopidine (345)	Cardiac: cardiovascular death, urgent TVR, thrombotic stent occlusion on angiography, MI Noncardiac: noncardiac death, stroke, severe peripheral vascular or bleeding events, any adverse event resulting in stopping study drug	Comparable safety and efficacy, significant reduction in noncardiac events with clopidogrel; long-term follow-up found ticlopidine was associated with significantly reduced mortality (63% reduction in cardiovascular death)
TOPPS ^{84,c}	300 mg LD, 75 mg daily (494)	500 mg LD ticlopidine then 250 mg bid ticlopidine (522)	Failure to complete 2 weeks of treatment	Clopidogrel was better tolerated than ticlopidine

^aOnly trials with >500 participants are shown. ^bBoth treatment arms received aspirin and fibrinolysis. ^cBoth treatment arms received aspirin. Abbreviations: ACS, acute coronary syndromes; bid, twice daily; CLARITY, Clopidogrel as Adjunctive Reperfusion Therapy; CLASSICS, Clopidogrel Aspirin Stent International Cooperative Study; COMMIT, Clopidogrel and Metoprolol in Myocardial Infarction Trial; CREDO, Clopidogrel for the Reduction of Events During Observation; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; LD, loading dose; MI, myocardial infarction; n, number of patients; PCI, percutaneous coronary intervention; OR, odds ratio; RR, risk reduction; TIMI, Thrombosis in Myocardial Infarction; TOPPS, Ticlid or Plavix Post-Stent; TRITON, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel; TVR, target-vessel revascularization.

associated with reduced rates of the primary CURE study outcome (4.5% versus 6.4%; risk reduction 0.7, 95% CI 0.5–0.97; $P=0.03$). As both treatment groups received open-label thienopyridine for 2–4 weeks after PCI, the benefit seen in the clopidogrel group during the first 30 days after PCI can be primarily attributed to

pretreatment with clopidogrel.²⁷ In the PCI-CLARITY study all patients underwent mandatory coronary angiography 48–192 h after they started to take the study medication and 53.4% of patients ($n=1,863$) underwent PCI 2–8 days after starting the study drug at the discretion of the investigator.²⁸ The benefits of clopidogrel

Table 4 Summary of phase III, randomized, controlled trials with clopidogrel in cardiovascular disease; part 2.^a

Study	Clopidogrel dose (n)	Comparator therapy and dose (n)	Primary outcome measure	Comment
Stroke				
MATCH ³³	75 mg daily clopidogrel plus 75 mg daily aspirin (3,797)	75 mg daily clopidogrel (3,802)	Composite of ischemic stroke, MI, cardiovascular death, rehospitalization for acute ischemia	Increased major and life-threatening bleeding events but no significant incremental benefit in efficacy with dual therapy
PRoFESS ³⁴	75 mg daily clopidogrel (20,332) ^b	200 mg bid dipyridamole ER and 25 mg bid aspirin (20,332) ^b	First recurrent stroke	Increased major and intracranial bleeding events
Mixed atherothrombosis^c				
CAPRIE ²¹	75 mg daily clopidogrel (9,599)	325 mg daily aspirin (9,586)	Composite of ischemic stroke, MI, vascular death	Clopidogrel showed modest superiority (RRR 8.7%); no difference in bleeding events
CHARISMA ^{31,d,e}	75 mg daily clopidogrel (6,062)	Placebo (6,091)	Composite of MI, stroke or cardiovascular death	Suggestion of benefit with clopidogrel (RR 0.88)
Asymptomatic, high-risk patients				
CHARISMA ^{32,d,f}	75 mg daily clopidogrel (1,659)	Placebo (1,625)	Composite of MI, stroke or cardiovascular death	Suggestion of harm with clopidogrel

^aOnly trials with >500 participants are shown. ^bBoth groups combined. ^cCerebrovascular disease, coronary artery or peripheral arterial disease. ^dBoth treatment arms received aspirin. ^eSubgroup of patients with established cardiovascular disease. ^fSubgroup of patients with multiple risk factors. Abbreviations: bid, twice daily; CAPRIE, Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance; MATCH, Management of Atherothrombosis with Clopidogrel in High-Risk Patients; MI, myocardial infarction; n, number of patients; PRoFESS, Prevention Regimen For Effectively Avoiding Second Strokes; RR, risk reduction; RRR, relative risk reduction.

pretreatment were evident early and continued to accrue throughout 30 days of follow-up, with no excess of major or minor bleeding (defined according to TIMI criteria).²⁸

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial^{31,32} compared dual antiplatelet therapy with aspirin monotherapy in patients with either clinically evident cardiovascular disease or multiple risk factors. Overall, although a modest (albeit nonsignificant) trend towards a benefit with the combination of aspirin and clopidogrel was observed over aspirin alone, this benefit was countered by an increased risk of severe and moderate bleeding, although only the increase in moderate bleeding was statistically significant. Dual antiplatelet therapy seemed to benefit the subgroup of patients with symptomatic atherothrombosis; these patients had a reduced incidence of MI, stroke or cardiovascular death compared with the subgroup of patients with symptomatic atherothrombosis given aspirin alone (6.9% versus 7.9%, relative risk 0.88, 95% CI 0.77–0.998; $P=0.046$). However, unexpectedly, a significant increase in mortality occurred in asymptomatic participants with multiple risk factors. This increase in mortality is difficult to

explain. The main message from CHARISMA is that the combination of aspirin and clopidogrel does not provide incremental benefit compared with aspirin alone in asymptomatic patients at high cardiovascular risk, and that this regimen could even be harmful in these patients.

To date, four clinical trials have evaluated clopidogrel in stroke prevention. The CAPRIE²¹ study found clopidogrel had a modest benefit over aspirin in a mixed group of patients with atherothrombosis, some of whom had stroke (relative risk reduction 8.7%, 95% CI 0.3–16.5; $P=0.043$). The CHARISMA study³² showed a benefit of the combination of clopidogrel with aspirin compared with aspirin alone in the subgroup of patients with prior ischemic stroke (hazard ratio 0.78; 95% CI 0.62–0.98; $P=0.029$). The Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH) study³³ showed that the combination of clopidogrel with aspirin was no more effective than clopidogrel alone for the secondary prevention of stroke, but that combination therapy increased the risk of both major and life-threatening bleeding events. The fourth (and the largest) study of secondary stroke prevention, the Prevention Regimen For Effectively Avoiding Second Strokes (PRoFESS) trial,³⁴ randomly

allocated 20,332 patients to various treatment regimens within 90 or 120 days of acute ischemic stroke. The study found that in terms of the overall prevention of recurrent stroke and other ischemic events, 75 mg clopidogrel daily was as effective as Aggrenox® (Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT; this agent is a combination of 200 mg dipyridamole and 25 mg aspirin), given orally, twice daily; however, Aggrenox® caused significantly more intracranial bleeds than clopidogrel did (1.4% aspirin plus extended-release dipyridamole versus 1.0% clopidogrel; HR 1.42, 95% CI 1.11–1.83). As Aggrenox® has been shown to be more effective than aspirin alone in two large studies conducted in patients with stroke,^{35,36} the results of the PROFESS trial support the conclusion that clopidogrel monotherapy is more effective than aspirin monotherapy in patients following a stroke.

The definitions of bleeding used in clinical trials have not been standardized, which limits comparisons across trials. Nevertheless, most of the large trials reported an excess of bleeding with dual therapy compared with aspirin alone or clopidogrel alone.³⁷ This finding reinforces the concept that the improved efficacy achieved with intensive antiplatelet therapy is likely to be associated with bleeding, and that the combination of aspirin and clopidogrel should be limited to treatment of high-risk groups (patients with ACS or those undergoing stent implantation) in whom the benefits have been shown to outweigh the risks.

Unresolved issues

Duration of dual antiplatelet therapy in patients without stents

The optimum duration of combination aspirin and clopidogrel after an ACS event is uncertain—in the large trials that demonstrated a benefit of combined treatment, the duration of therapy did not extend beyond 12 months. On the basis of these studies, the European Society of Cardiology, the ACC and the AHA recommend combined aspirin and clopidogrel for up to 1 year.^{38–40}

Duration of dual antiplatelet therapy in stent recipients

PCI is associated with a high risk of thrombosis. When it occurs early after PCI and stent implantation, thrombosis seems to be primarily attributable to mechanical disruption of the endothelium, whereas late thrombosis (i.e. >30 days post-PCI) is attributable to delayed or incomplete

re-endothelialization. Dual antiplatelet therapy reduces the incidence of early stent thrombosis and observational studies indicate that the strongest predictor for stent thrombosis, including late thrombosis, is premature discontinuation of antiplatelet therapy.^{41,42} Premature termination of clopidogrel therapy is also associated with an increase in mortality.⁴³ The results of the Randomized Argentine Clopidogrel Stent (RACS) trial also support an extended duration of therapy.⁴⁴ This trial, which randomly allocated 1,004 patients to either a 30-day or 180-day dual therapy regimen after bare-metal stent implantation, reported that the longer duration of aspirin and clopidogrel therapy significantly reduced the incidence of death, MI or stroke (4.99% versus 1.74%, relative risk reduction 65%; $P=0.01$) without a significant excess of total bleeds (0.64% versus 1.52%; $P=0.34$). Pooled analysis of the results from three studies suggested that clopidogrel nonresponsiveness (discussed later) increases the risk of subacute stent thrombosis; however, these studies were small and the reported results had wide confidence intervals (odds ratio 7.0, 95% CI 0.6–79.0).⁴⁵

Despite the scarcity of data from randomized, controlled trials on the optimum duration of antiplatelet therapy after stent insertion, the consensus view among experts is that treatment with aspirin and clopidogrel (75 mg daily) should be continued for at least 12 months in patients with at least one drug-eluting stent who are not at high risk of bleeding. Dual therapy should be continued for at least 1 month and ideally for 12 months in patients with one or more bare-metal stent (Class I, Level B),³⁰ and indefinite therapy should be considered in patients with a drug-eluting device (or devices).

Limitations of clopidogrel

Although clopidogrel can effectively prevent MI, stroke or death in patients with ACS and those undergoing PCI, the following limitations compromise its clinical utility: delayed onset of action, delayed cessation of action, incomplete platelet inhibition and variability in patients' responses to this agent.

The addition of a loading dose to clopidogrel treatment regimens has considerably shortened the delay in onset of action. A 600 mg loading dose achieves more rapid and greater platelet inhibition than a 300 mg dose,⁴⁶ which enables peak inhibition of platelet aggregation to occur 2–4 h after administration instead of 4–6 h.⁴⁷

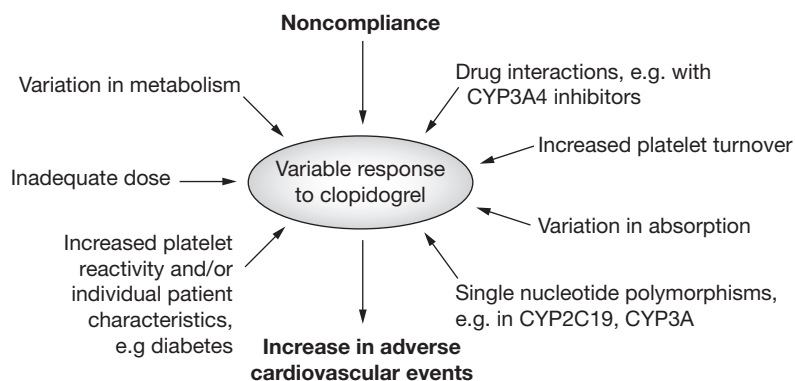


Figure 3 Causes of variation in responsiveness to clopidogrel.

A single 300 mg dose of clopidogrel inhibits approximately 40% of ADP-induced platelet aggregation, whereas a 600 mg dose inhibits approximately 50%, and 4–7 days of 75 mg clopidogrel daily inhibits 50–60%.^{48–50} However, an efficacy threshold exists; doses of more than 600 mg do not further increase concentrations of the active thiol metabolite⁴⁹ nor increase platelet inhibition. This maximum inhibition could possibly result from either a limit to the rate of intestinal absorption⁴⁹ or saturation of liver metabolic capacity.⁴⁸ The finding that two 600 mg loading doses of clopidogrel given within 24 h of one another achieve significantly greater platelet inhibition than a single 600 mg loading dose is consistent with the suggestion that saturation of hepatic metabolism may be the rate-limiting parameter.⁵¹ A 600 mg loading dose can also increase platelet inhibition in patients receiving long-term clopidogrel⁵² and might be associated with further clinical benefit.^{50,53}

The results of a meta-analysis of 10 trials (7 randomized and controlled, 3 nonrandomized) that involved a total of 1,567 patients indicated that a high loading dose (i.e. >300 mg) was superior to the standard loading dose (i.e. 300 mg) for prevention of cardiac death or nonfatal MI after PCI (odds ratio 0.54, 95% CI 0.32–0.9; $P=0.02$), and did not cause a significant increase in major or minor bleeds.⁵⁴ Regression meta-analysis also indicated that the high loading dose had a greater clinical effect than the 300 mg dose in high-risk patients. The current ACC/AHA/Society for Cardiac Angiography and Interventions guidelines recommend administration of a clopidogrel loading dose (“generally 600 mg”) before or at the time of PCI (Class I, Level C), and suggest that a reduced loading dose (300 mg) should be

considered for patients scheduled to undergo PCI within 12–24 h of fibrinolytic therapy.³⁰

Although the irreversible nature of clopidogrel’s antiplatelet effects has advantages for patients who miss one or more doses of the drug, this irreversibility is responsible for an increased risk of bleeding in patients who require CABG surgery within 5 days of stopping treatment.²² Consequently, interventional cardiologists in the US are often reluctant to pretreat patients with a loading dose of clopidogrel before the coronary anatomy has been examined.

Patients show a heterogeneous response to clopidogrel treatment, with a very wide range of platelet inhibition (from <5% to 90% with a roughly normal distribution).⁵⁵ Several mechanisms have been proposed to account for this variation in response: inadequate dosing, individual variability in absorption^{49,56} and metabolism of clopidogrel,¹⁴ genetic polymorphisms that affect CYP450⁵⁷ or the P2Y₁₂ receptor,⁵⁸ drug–drug interactions (e.g. with CYP3A4 inhibitors),¹⁸ increased platelet turnover, and high baseline platelet reactivity associated with comorbid diseases such as diabetes mellitus (Figure 3).

What proportion of patients should be classified as ‘nonresponsive’ to clopidogrel remains unclear. Nonresponsiveness is often defined as a less than a 10% reduction in platelet aggregation on light-transmission aggregometry (compared with baseline), but this definition has not been validated by use of rigorous methodology. Furthermore, the methods (assays and agonists) used to measure platelet inhibition vary substantially. Despite the lack of a standard definition for nonresponsiveness and the small size of studies that have investigated this phenomenon, suboptimal inhibition of platelet function has consistently been linked with an increased risk of cardiovascular events. In 2007, a systematic review of 25 studies that included 3,688 clopidogrel-treated patients who underwent PCI found that nonresponsiveness was common (mean prevalence 21%, 95% CI 17–25%) and associated with an increased risk of adverse cardiovascular outcomes (pooled odds ratio 8.0, 95% CI 3.4–19.0).⁴⁵ Although this review analyzed trials that used various definitions of nonresponsiveness, inverse correlations were observed between nonresponsiveness (defined as a <10% reduction in aggregation) and both the loading dose of clopidogrel used and the time elapsed between its administration and measurement of platelet function. The use of a 600 mg loading dose reduced

nonresponsiveness⁵⁹ but did not eliminate the wide variation in responses to clopidogrel.^{47,60} Similarly, increasing the maintenance clopidogrel dose from 75 mg to 150 mg reduced but did not eliminate nonresponsiveness.^{61,62}

New assays, such as flow cytometry (which measures vasodilator-stimulated phosphoprotein phosphorylation) and the Verify Now[®] platelet assay (Accumetrics, Inc., San Diego, CA), are more specific for P2Y₁₂-receptor-mediated aggregation than is light-transmission aggregometry. These new assays could be used to tailor clopidogrel doses to individual patients, which might improve clinical outcomes by reducing the variation in response to clopidogrel. Although preliminary results have been promising,^{63,64} the clinical benefit of using these P2Y₁₂-specific assays remains unproven. The efficacy of individualized antiplatelet therapy (tailored using the Verify Now[®] P2Y₁₂ assay) after drug-eluting stent implantation will be investigated by the Gauging Responsiveness With the Verify Now Assay—Impact on Thrombosis and Safety (GRAVITAS) trial, which is currently recruiting participants.

Despite progress in this field, the optimum loading dose of clopidogrel, its timing before PCI and the optimum maintenance dose all remain uncertain. Ongoing studies such as the Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events—Optimal Antiplatelet Strategy for Interventions (CURRENT—OASIS-7) trials might resolve some of these uncertainties. These studies will compare a high-dose regimen (600 mg loading dose, 150 mg daily maintenance dose for 1 week and 75 mg daily thereafter) with a low-dose regimen (300 mg loading dose, 75 mg maintenance dose daily thereafter) in patients with ACS.

NEW ADP-RECEPTOR ANTAGONISTS

The development of new ADP antagonists is justified by the limitations of clopidogrel, particularly its delayed onset and cessation of action, and suboptimal platelet inhibition.

Prasugrel

Prasugrel, a novel thienopyridine, is an irreversible inhibitor of P2Y₁₂ (Supplementary Figure 1 online). After absorption into the circulation this agent is metabolized by carboxyesterases and becomes rapidly undetectable in blood.⁶⁵ Unlike clopidogrel, which undergoes a two-step, CYP450-dependent conversion to its active metabolite, prasugrel only requires a single-step

activation.⁶⁵ Prasugrel is a more potent inhibitor of ADP-induced platelet aggregation than clopidogrel, and also achieves more consistent and faster inhibition,^{66,67} which presumably reflects its more efficient absorption and conversion to the active metabolite.^{67,68} The superiority of prasugrel has been confirmed in a panel of healthy volunteers,⁶⁹ in individuals with stable coronary artery disease⁷⁰ and ACS,⁷¹ and in patients who previously underwent PCI.⁷² In a phase II study that compared prasugrel with clopidogrel in patients with stable coronary artery disease, significantly fewer patients were pharmacodynamically defined as 'nonresponders' in the prasugrel group (40 mg or 60 mg loading dose, 10–15 mg maintenance dose) than in the clopidogrel group (300 mg loading dose, 75 mg maintenance dose).⁷⁰ Prasugrel irreversibly inhibits the P2Y₁₂ receptor, and so has the same drawbacks as clopidogrel when used preoperatively (i.e. prasugrel increases the risk of major bleeding in patients who undergo CABG surgery).⁷¹

The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation—Thrombolysis in Myocardial Infarction 44 (PRINCIPLE—TIMI 44) trial was a two-stage, crossover study of 201 patients who underwent coronary angiography with planned PCI.⁷³ During the loading-dose phase, patients were randomly allocated to receive 60 mg prasugrel or 600 mg clopidogrel. During the 28-day, maintenance-dose phase, patients who underwent PCI were randomly allocated to receive 10 mg prasugrel or 150 mg clopidogrel daily, with crossover to the alternative regimen after 15 days. Within 30 min of the loading dose, platelet inhibition was strongest in those who received prasugrel, a difference that remained evident during the maintenance phase. The prasugrel group also had a significantly lower incidence of hyporesponsiveness during both loading-dose and maintenance-dose phases than those treated with clopidogrel. Although no major bleeding events occurred, the study was not powered to assess clinical efficacy.

The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction 38 (TRITON—TIMI 38) study⁷³ explored the clinical efficacy of prasugrel in 13,608 patients with ACS who were scheduled to undergo PCI. Patients were randomly assigned to receive prasugrel (a 60 mg loading dose followed by 10 mg per day) or clopidogrel (a 300 mg loading dose

followed by 75 mg per day) for up to 15 months. The prasugrel group had significantly lower rates of the primary efficacy outcome than the clopidogrel group; the composite outcome of cardiovascular-related death, nonfatal MI or nonfatal stroke occurred in 9.9% of prasugrel-treated patients versus 12.1% of those treated with clopidogrel (hazard ratio 0.81, 95% CI 0.73–0.90; $P < 0.001$; median treatment duration 14.5 months). A benefit was evident within the first few days of treatment with prasugrel and was primarily attributable to a reduced incidence of nonfatal MI; no reduction in stroke or death occurred. Prasugrel also reduced the incidence of stent thrombosis for both patients with bare-metal and those with drug-eluting stents. Prasugrel did, however, increase the rate of major bleeding events (2.4% versus 1.8%; hazard ratio 1.32, 95% CI 1.03–1.68; $P = 0.03$), including fatal bleeding (0.4% versus 0.1%; $P = 0.02$). The rate of intracranial hemorrhage was similar (0.3%) in both groups. Both the improved efficacy and the increase in bleeding observed with prasugrel probably reflect the increased platelet inhibition achieved with this agent. Of note, the study drug was administered only after the coronary anatomy was known, and three-quarters of patients did not receive a first dose of thienopyridine until the PCI procedure had started. Thus, the more rapid onset of action of prasugrel (compared with clopidogrel) could have also contributed to its superior efficacy. On the basis of the increased bleeding risk with prasugrel seen in the TRITON-TIMI 38 study, a second phase III trial is under way to compare a reduced dose of prasugrel with clopidogrel in medically managed patients with ACS—the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) study.

AZD6140

AZD6140 is the prototype of a novel class of antiplatelet drugs, the cyclopentyltriazolopyrimidines, which also inhibit the P2Y₁₂ receptor (Supplementary Figure 1 online).⁷⁴ AZD6140 is derived from ATP and offers the advantages of oral administration, rapid onset of action, high potency, and reversibility. Although AZD6140 is processed to produce an active metabolite,⁷⁴ metabolic conversion is not essential as most of its antiplatelet activity is derived from the parent molecule, which directly inhibits the P2Y₁₂ receptor and has a half-life of 12 h. Near-complete inhibition of platelet aggregation is seen just 2 h after initial

administration of AZD6140, and its plateau level of inhibition of platelet aggregation is greater than that of clopidogrel (90–95% versus 60%).⁷⁴ A phase II study in 200 patients with atherosclerosis compared AZD6140 (50 mg, 100 mg and 200 mg twice daily, and 400 mg once daily) with 75 mg per day clopidogrel.⁷⁴ AZD6140 was associated with longer bleeding times than clopidogrel. Bleeding times in the AZD6140 group were dose-independent and associated with an increased rate of clinical bleeds, which included one major bleed in a patient who received the highest AZD6140 dose. Although platelet inhibition had declined 24 h after the final dose, the fact that substantial residual blood levels of this reversible inhibitor were present meant that even at 24 h after the final dose, the patients receiving the three highest doses of AZD6140 still had greater platelet inhibition than those receiving clopidogrel (~40% versus ~30%). From the standpoint of adherence to medication, this persistent action of AZD6140 is advantageous, and although such persistence could be problematic for some patients, this sustained antiplatelet activity is less of a concern with AZD6140 than it is with the irreversible inhibitors, if an urgent invasive procedure is required.

AZD6140 has been evaluated in the Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 Versus Clopidogrel in NSTEMI (DISPERSE-2) study,⁷⁵ a randomized trial that compared AZD6140 (90 mg or 180 mg twice daily) with clopidogrel (300 mg loading dose, 75 mg daily maintenance) for 4–12 weeks in 990 patients with non-ST-segment elevation ACS. Patients who received either clopidogrel or AZD6140 within 24 h of CABG surgery had a similar increase in their risk of bleeding; however, if surgery was performed 1–5 days after the last dose, the risk of major bleeding was significantly lower in patients treated with AZD6140 than in those who received clopidogrel (10 of 28 versus 9 of 14 patients; 36% versus 64%). Thus, although the reversible nature of AZD6140-mediated platelet inhibition does not eliminate bleeding risk should urgent surgery be required, use of this agent does provide more flexibility for the timing of surgery than is afforded by use of either clopidogrel or prasugrel. Importantly, although minor bleeds were more frequent with the highest AZD6140 dose in the DISPERSE-2 study, no significant difference in major bleeding events was observed between the two drugs: major bleeding rates were 6.9% with clopidogrel versus 7.1% with 90 mg AZD6140 ($P = 0.91$) and 5.1% with

180 mg AZD6140 ($P=0.35$). Although a trend was evident towards fewer MIs in the AZD6140 group (5.6% with clopidogrel, 3.8% with 90 mg AZD6140 and 2.5% with 180 mg AZD6140), the differences between these values did not reach statistical significance.

AZD6140 was associated with a dose-dependent increase in the rate of dyspnea, which occurred in 10% of patients given 100 mg daily and 20% of those given 400 mg daily. Overall, 6% of patients in each of the AZD6140 groups had persistent dyspnea compared with 2% of patients who received clopidogrel. The cause of dyspnea is uncertain but might be related to the ATP-like effects of AZD6140. The other major adverse effect of AZD6140 was prolonged, mainly asymptomatic, ventricular pauses. AZD6140 is currently being compared with clopidogrel in a large, phase III study in patients with non-ST-segment elevation ACS (A Study of Platelet Inhibition and Patient Outcomes [PLATO]). The findings are expected to be reported in 2009.

Cangrelor

Of the two intravenous receptor inhibitors presently in clinical development, the development of cangrelor is the furthest along. An ATP analog, this agent has biphasic elimination and possesses the advantages of high potency, rapid onset of action and reversibility (Supplementary Figure 1 online). Cangrelor's short half-life (3–5 min) enables platelet function to be re-established rapidly after the drug is discontinued; 60% of baseline platelet aggregation was restored within 1 h in 23 of 33 patients with ACS.⁷⁶ Cangrelor has a potent inhibitory effect on ADP-mediated platelet aggregation, and infusion rates of 2 $\mu\text{g}/\text{kg}/\text{min}$ and 4 $\mu\text{g}/\text{kg}/\text{min}$ cause near-complete inhibition of platelet aggregation.^{76,77} Not unexpectedly, at this level of inhibition, cangrelor is associated with prolonged bleeding times and an increase in injection site⁷⁷ and minor⁷⁸ bleeding events.

Cangrelor has undergone preliminary clinical evaluation in a randomized, two-part, phase II study that included 399 patients.⁷⁷ In the first part of this study, treatment with three different doses of cangrelor (1 $\mu\text{g}/\text{kg}/\text{min}$, 2 $\mu\text{g}/\text{kg}/\text{min}$ and 4 $\mu\text{g}/\text{kg}/\text{min}$) was compared with placebo treatment in patients who underwent elective PCI; in the second part of the study, 4 $\mu\text{g}/\text{kg}/\text{min}$ cangrelor was compared with abciximab. Patients assigned to receive cangrelor showed more rapid cessation of inhibition of platelet aggregation and shorter bleeding times than those given abciximab therapy.

All treatment groups had similar rates of the combined end point of major and minor bleeding (cangrelor 13% versus placebo 8% in the first part of the study, and cangrelor 7% versus abciximab 10% in the second part) and the incidence of adverse cardiac events was comparable.

Cangrelor has also undergone preliminary evaluation as an adjunct therapy to thrombolysis. In the Safety, Tolerability and Effect on Patency in Acute Myocardial Infarction (STEP-AMI) study,⁷⁹ 92 patients with ST-segment elevation MI received aspirin and heparin, and were randomly assigned to receive either an infusion of cangrelor alone, full-dose tissue plasminogen activator alone, or one of three doses of cangrelor plus half-dose tissue plasminogen activator. At 60 min, patients who were assigned to receive the combinations of cangrelor (all doses) and half-dose tissue plasminogen activator had similar coronary-artery patency on angiography to that seen in those who received full-dose tissue plasminogen activator alone. Patients who received combination therapy had greater coronary artery patency than those who received cangrelor alone, with no difference in adverse clinical or bleeding events between these groups. The rapid onset and cessation of action gives cangrelor an advantage over other ADP antagonists in patients who might soon require invasive procedures. Rapid cessation of action means that this P2Y₁₂ inhibitor can be used more safely than other such inhibitors if the coronary anatomy is unknown.

After initial treatment, patients given cangrelor will often require continued treatment with one of the oral P2Y₁₂ antagonists. However, a study by Steinhubl *et al.* has highlighted a potential problem when patients are switched from cangrelor to clopidogrel.⁸⁰ In this small study of 20 healthy volunteers, a 600 mg clopidogrel loading dose did not produce sustained platelet inhibition when administered simultaneously with a cangrelor infusion; however, inhibition was seen if clopidogrel was given immediately after the cangrelor infusion was discontinued. As the onset of action of clopidogrel is delayed for 2–6 h after administration, the initiation of clopidogrel after cangrelor infusion ceases will result in a short hiatus in platelet inhibition. The failure of clopidogrel to inhibit platelet function when administered simultaneously with cangrelor was attributed to binding-site competition between cangrelor and the unstable, rapidly cleared, active metabolite of clopidogrel. Results of *in vitro* experiments support the hypothesis that

cangrelor competes with the active metabolite of clopidogrel for the ADP receptor.⁸¹ As prasugrel and AZD6140 both have a more rapid onset of action than clopidogrel, the duration of ineffective platelet inhibition with sequential administration of cangrelor and either prasugrel or AZD6140 should be less than it is with clopidogrel.

The relative efficacy and safety of cangrelor and clopidogrel will be addressed in two large phase III trials. In the Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) trials, cangrelor will be compared with usual care after PCI (CHAMPION-PLATFORM) and with clopidogrel in patients with ACS who undergo PCI (CHAMPION-PCI).

CONCLUSIONS AND FUTURE PERSPECTIVES

Other P2Y₁₂ inhibitors are currently in early stages of development; these agents include reversible oral (e.g. BX667) and combined oral and intravenous formulations (PRT060128). Whether additional new drugs are clinically needed remains uncertain. Of course, we have focused solely on agents that inhibit the ADP receptor. Another potential source for improvements in medical care comes from the recent introduction of specific drugs that target other platelet receptors. Agents that target two such receptors are in early clinical development: a thromboxane-receptor antagonist and several thrombin-receptor antagonists.

The introduction of ADP antagonists into the clinic has had a major influence on the care of patients. Further improvements should come from optimization of clopidogrel dosages, and possibly from individualized dosing guided by accurate point-of-care measurements of platelet inhibition. The new ADP-receptor antagonists all have potential advantages over clopidogrel, including less variation in their antiplatelet effects, greater potency and, in the case of nonthienopyridine agents, more flexibility in their use if antiplatelet treatment is required before an invasive procedure. Whether these potential advantages will translate into actual clinical advantages will require additional head-to-head comparisons between clopidogrel and these new agents in properly designed, randomized, controlled trials.

Supplementary information in the form of a reference list and a Figure is available on the *Nature Clinical Practice Cardiovascular Medicine* website.

KEY POINTS

- Long-term clopidogrel is modestly more effective than aspirin
- Combined antiplatelet therapy with clopidogrel and aspirin reduces the risk of recurrent cardiovascular events in patients with acute coronary syndromes and those undergoing percutaneous coronary intervention
- Clopidogrel does have some limitations: slow onset of action; variable inhibition of platelet function; lack of reversibility; and undefined optimum loading dose
- When administered immediately before percutaneous coronary intervention, prasugrel—a more rapid and more potent P2Y₁₂ receptor inhibitor than clopidogrel—reduces nonfatal myocardial infarction but increases major bleeding events
- AZD6140 and cangrelor—reversible, nonthienopyridine P2Y₁₂ inhibitors currently being tested—have a more rapid onset and cessation of action than clopidogrel and could reduce acute bleeding risk in patients with acute coronary syndromes requiring early CABG surgery

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