

Management of Antiplatelet Therapy During Acute Percutaneous Coronary Intervention: New Strategies and Therapeutics

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Abstract

Aggressive intravenous and oral dual antiplatelet therapy has established primary percutaneous coronary intervention (PCI) as the standard of care for acute myocardial infarction. Clopidogrel is currently the thienopyridine of choice for dual antiplatelet therapy in patients treated with PCI. The dose regime and duration of therapy of clopidogrel has undergone multiple refinements. Recently, 2 novel third generation oral inhibitors of P2Y₁₂ receptors, prasugrel and ticagrelor, have undergone clinical evaluation with promising results. This article is a non-exhaustive review of the literature, concentrating on the role of current and novel oral antiplatelet agents for acute myocardial infarction particularly highlighting the limitations and issues associated with clopidogrel use.

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Introduction

Platelet adhesion, activation, and aggregation are stimulated during an acute coronary syndrome (ACS), the result of intimal injury due to rupture of an atherosclerotic plaque. This triggers a cascade of events leading to the catastrophic formation of an occlusive clot. Antiplatelet agents assume the cornerstone role in modern pharmacotherapy for ablating this process in the management of ACS. After plaque rupture or stent placement, the resulting endothelial injury exposes the thrombogenic surfaces of the subendothelial collagen, von Willebrand factor and other proteins to circulating platelets. Following platelet adhesion, multiple metabolic pathways are initiated within the platelet complex. This results in the production and release of thromboxane A₂ (TXA₂) and adenosine diphosphate (ADP) from platelet granules. These platelet products stimulate vasoconstriction, with further platelet recruitment and activation. Platelet aggregation is compounded by activating the glycoprotein IIb/IIIa (GP IIb/IIIa) complex, which binds platelets to one another, through linkage fibrinogen molecules. Aggregating platelets form the core of the growing thrombotic mass, aiding the propagation of the fibrin and red blood cell-rich clot. This process finally culminates in the formation of an occlusive

thrombus and acute myocardial infarction (MI). The platelet-rich thrombus is relatively resistant to fibrinolytic activity and predisposes to the development of reocclusion even after initial successful clot lysis.¹

The resistance of platelet-rich thrombi to clot lysis is particularly important in patients with an ST-elevation myocardial infarction (STEMI) who are treated with fibrinolytic therapy.² The current standard-of-care practice of primary percutaneous coronary intervention (PCI), with stent implantation³ for treatment of patients with an acute STEMI, mandates aggressive antiplatelet therapy to prevent stent thrombosis.⁴ This review focuses on the actions of antiplatelet agents, the evidence that they are beneficial in patients with an STEMI treated with acute PCI, and new therapeutic strategies soon to be available for use in this evolving field.

Current Antiplatelet Agents

The 3 main classes of antiplatelet agents in use are aspirin or acetylsalicylic acid (ASA), thienopyridines and GP IIb/IIIa inhibitors. These agents can be classified according to their mechanism of action. ASA act by blocking the enzyme cyclooxygenase that mediates the biosynthesis of prostaglandins and TXA₂ from arachidonic acid.⁵

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Thienopyridines, including ticlopidine, clopidogrel and prasugrel, block the binding of ADP to the platelet receptor P2Y₁₂, thereby inhibiting activation of the GP IIb/IIIa complex and platelet aggregation.⁶ GP IIb/IIIa antibodies and receptor antagonists inhibit the final common pathway of platelet aggregation (Fig. 1). GP IIb/IIIa inhibitors also prevent the initial adhesion of platelets to the vessel wall. Agents in this class of GP IIb/IIIa inhibitors include abciximab, tirofiban, and eptifibatid. These agents can only be administered intravenously, and are used in the initial 24 to 48 hours of an ACS episode. Among patients undergoing PCI with stenting, peri-procedural administration of GP IIb/IIIa inhibitors improves the outcomes of patients with high risk non-ST elevation ACS and STEMI. The role of GP IIb/IIIa inhibitors, in combination with current oral antiplatelet agents, or in combination with other anti-thrombotic agents during acute PCI, is beyond the scope of this review.

Aspirin

ASA was the first discovered member of the class of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs) with analgesic, antipyretic, anti-inflammatory and antiplatelet effects. This wonder drug was first discovered by the French chemist Charles Frédéric Gerhardt in 1853 and marketed by Bayer as Aspirin since 1899. ASA’s use as a NSAID declined due to Reye’s syndrome⁷ but it continues to be the corner stone agent for primary and secondary treatment of cardiovascular diseases.⁸ The antiplatelet activity of ASA appears to be mediated principally through inhibition of the synthesis of TXA₂. Aspirin irreversibly acetylates and inactivates cyclooxygenase, which catalyses the first step of the conversion of arachidonic acid to TXA₂. Platelets do not synthesize new cyclooxygenase. As a result, the functional defect induced by ASA persists for the life of the platelet, typical 7 days.

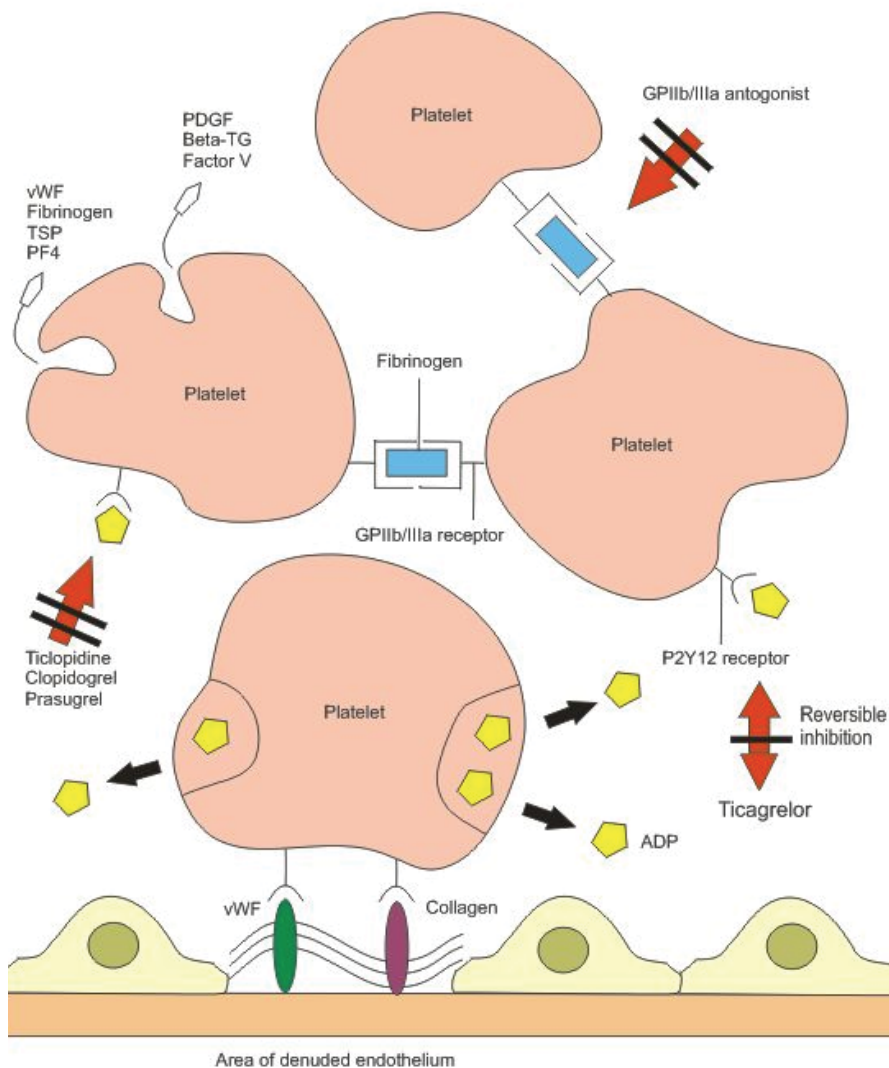


Fig. 1. Mechanism of antiplatelet agents.

The efficacy of ASA therapy was initially demonstrated in the Second International Study of Infarct Survival (ISIS-2) for acute STEMI.⁹ ISIS-2 randomly assigned 17,187 patients in a “2-by-2 factorial” design to oral aspirin (160 mg/day for 30 days), intravenous streptokinase, both agents, or neither drug. Aspirin therapy resulted in a highly-significant 23% relative reduction in 5-week vascular mortality, which was equivalent to that seen with streptokinase (25% reduction) and additive when streptokinase and aspirin were administered together (42% reduction). The absolute mortality reduction was 2.4 vascular deaths prevented per 100 patients treated. ASA’s additive effect with streptokinase was in the prevention of reocclusion after successful recanalisation.

An initial loading dose of 150 to 300 mg of uncoated or chewable ASA produces a rapid antithrombotic effect due to immediate and almost complete inhibition of TXA₂ production within 15 minutes of administration. A daily dose of at least 75 mg/day is then continued indefinitely. In the local context, ASA 100 mg is the standard dose. Early clinical trials did not demonstrate additive benefits of adding dipyridamole to ASA as compared to the addition of thienopyridines.¹⁰ Thus, dipyridamole has no role as a second agent in addition to ASA post-PCI. The 2007 ACC/AHA guidelines for the management of ST-elevation MI recommend high-dose ASA 162 to 325 mg/day for at least 1 month in patients who received a bare metal stent and for 3 to 6 months in those who received a drug eluting stent.¹¹ This is the regimen used in all of the relevant trials. The recently presented CURRENT-OASIS-7 trial randomised 25,087 unstable angina or acute MI patients who were scheduled to undergo angiography within 72 hours of hospital arrival to a “2-by-2 factorial” design for high- versus low-dose clopidogrel and high- (300 to 325 mg once daily) versus low-dose (75 to 100 mg once daily) ASA. A little more than two-thirds of the study patients underwent PCI. There were no significant differences in outcome between these 2 groups. What this implies is that the usual low doses of aspirin may be the optimal treatment strategy in PCI patients.¹²

Low-dose ASA at 75 to 150 mg is recommended indefinitely for all patient post-MI for secondary prevention.¹³ The Antiplatelet Trialists’ Collaboration concluded that, in patients with an acute MI treated with ASA, the combined outcome of any serious vascular event was reduced by about one quarter; non-fatal myocardial infarction was reduced by one-third, non-fatal stroke by one quarter, and vascular mortality by one-sixth with no apparent adverse effect on other deaths. The absolute reductions in the risk of having a serious vascular event were 36 per 1000 treated for 2 years among patients with previous myocardial infarction; 38 per 1000 patients treated for 1 month among patients with acute MI.¹³

Aspirin and Bleeding Risk

Low-dose aspirin increased the risk of any major bleeding by 1.7 to 2.1 times compared to placebo. The absolute annual increase attributable to aspirin for all major bleeding episodes was 0.13%. This was predominantly for major gastrointestinal (GI) bleeding (0.12%) and much less so for intracranial bleeding (0.03%).¹⁴ Essentially the benefits from secondary prevention far outweigh the annual increase in major bleeding risk of 1.3 per 1000 patients. There is a belief amongst physicians and patients that buffered, or enteric coated rather than regular ASA helps decrease gastrointestinal side effects. Enteric coated aspirin is designed to resist disintegration in the stomach, dissolving in the more neutral-to-alkaline environment of the duodenum and although this preparation may reduce erosions on endoscopy, enteric coating does not protect against the clinically relevant end point of gastrointestinal bleeding.¹⁵ Proton pump inhibitors (PPIs) reduce the risk of recurrent upper gastrointestinal bleeding from long-term low-dose ASA use.¹⁶ However, the evidence to support their use for prevention of a first episode (primary prevention) of ASA-induced GI bleeding in low-risk individuals is limited. Increased risks that would recommend PPIs for secondary prevention of GI bleeding include a history of peptic ulcer disease, dual antiplatelet therapy, concomitant anticoagulant therapy, or more than one of the following risk factors: age ≥ 60 years, concurrent glucocorticoid or high-dose NSAID use, or dyspepsia and reflux symptoms. Switching to clopidogrel alone without PPIs cover for these high GI risk patients is not recommended. ASA plus esomeprazole was superior to clopidogrel in the prevention of recurrent ulcer bleeding in randomised studies, thereby demonstrating the importance of GI protection for this group of patients who have a history of GI complications.^{17,18}

Clopidogrel 75 mg/day or ticlopidine 250 mg twice a day are effective alternatives in approximately 5% of patients who cannot tolerate aspirin, primarily due to reasons such as allergy, dyspepsia, gastrointestinal bleeding diathesis and bronchospasm.^{19,20} The benefit of this approach was suggested by results from the CAPRIE trial,¹⁹ which was not limited to STEMI, and the STAMI trial,²⁰ which showed that clopidogrel and ticlopidine are at least as effective as aspirin. The ACC/AHA guidelines and the 2008 ACCP guideline prefer clopidogrel in such patients because it is at least as effective as ticlopidine and has fewer side effects, particularly because of far fewer haematologic complications.

Thienopyridines

Ticlopidine and Clopidogrel

Thienopyridine derivatives irreversibly modify platelet P2Y₁₂ receptors by covalently binding to cysteine residues

of the receptor. The proportion of ADP receptors sensitive to the effects of thienopyridines is limited to 60% to 70%. Currently, the 2 available thienopyridines for clinical use are ticlopidine and clopidogrel. These 2 agents are equally potent and effective but with differing pharmacokinetics and side effects. Clopidogrel has few adverse effects and more conveniently administered as a once daily dosage compared to ticlopidine. As a result, clopidogrel has rapidly replaced ticlopidine as the thienopyridine of choice for dual antiplatelet therapy in patients undergoing PCI to decrease the incidence of coronary stent thrombosis. Moreover, it has proven efficacy in the secondary prevention of myocardial infarction, stroke, and vascular death in patients with atherosclerotic vascular disease. This was demonstrated in the CURE study which randomly assigned 12,562 patients who had presented within 24 hours after the onset of ACS, excluding STEMI patients, to receive clopidogrel (300 mg immediately, followed by 75 mg once daily) or placebo in addition to aspirin for 3 to 12 months.²¹ In the follow-up PCI-CURE study for the subgroup of NSTEMI patients who had PCI performed, prolonged dual antiplatelet inhibition (DAI) with clopidogrel versus placebo in combination with ASA up to 9 months continue to demonstrate beneficial effects²² for both the stented and non-stented groups.

Clopidogrel Loading and Maintenance Dosing

Clopidogrel as a pro-drug has an onset of action of between 4 to 6 hours after a loading dose. In the PCI-CURE study, pretreatment was administered for a median of 6 days. Subsequently, the CREDO trial addressed the effect of preloading with 300 mg of clopidogrel versus placebo. The study randomised 2116 ACS patients. The clopidogrel loading was administered 3 to 24 hours before PCI. Thereafter, all patients received clopidogrel, 75 mg per day, through day 28. From day 29 through 12 months, patients in the loading-dose group received clopidogrel, 75 mg per day, and those in the control group received placebo. Both groups received aspirin throughout the study. Patients who received clopidogrel at least 6 hours before PCI experienced a relative risk reduction of 38.6% (95% CI, -1.6% to 62.9%; $P=0.051$) compared with no reduction with treatment less than 6 hours before PCI. Similar to the CURE study (9 months), long-term dual antiplatelet inhibition in CREDO study (1 year) for this group of ACS patients following PCI with clopidogrel therapy significantly reduced the risk of adverse ischaemic events.²³ The CREDO trial, however, could not discriminate benefit between clopidogrel loading versus long-term maintenance therapy with clopidogrel. In the follow-up CURRENT-OASIS 7 trial which randomised 25,087 unstable angina or acute MI patients who were scheduled to undergo angiography within 72 hours of hospital arrival to a high- versus low-dose clopidogrel loading and maintenance dose. Patients received

either high-dose clopidogrel 600 mg loading followed by 150 mg daily for 7 days and 75 mg daily thereafter versus standard dose 300 mg clopidogrel loading followed by 75 mg daily. In the PCI subgroup of 17,232 patients, there was a significant reduction in the combined outcome of death, myocardial infarction and stroke driven by reduction in myocardial infarction (2.6% vs 2.0%; HR, 0.78; 95% CI, 0.64-0.95; $P=0.012$). There was also a significant reduction in the risk of stent thrombosis. (2.3% vs 1.6%; 95% CI, 0.57-0.89; $P=0.002$). This was achieved at an increased risk of CURRENT defined major and severe bleeds but no difference in Thrombolysis in Myocardial Infarction (TIMI) major bleeds, intracranial haemorrhage, fatal bleeds or coronary artery bypass grafting (CABG)-related bleeds. There was no additional benefit for increased dose clopidogrel for patients not undergoing PCI and patients should continue with standard dose clopidogrel.

Clopidogrel Pharmacokinetics, Genetics and Limitations

The use of dual antiplatelet therapy with aspirin and a thienopyridine is an integral adjunct pharmacologic regimen for ACS patients undergoing acute PCI, enshrined in current guidelines. To achieve levels of the active metabolite sufficient to inhibit the P2Y₁₂ receptor around the time of PCI, the thienopyridine dosing strategy begins with a loading dose followed by long-term therapy with a daily maintenance dose. Premature termination can lead to catastrophic ischaemic complications, especially acute stent thrombosis. Despite its established efficacy as the thienopyridine element of the dual antiplatelet regimen, clopidogrel has several limitations. These limitations of clopidogrel include a delayed onset of action, only a modest antiplatelet effect, considerable patient-to-patient variability and irreversibility of its platelet inhibition effects. Clopidogrel is an inactive pro-drug of thienopyridine, which needs to be metabolised by the cytochrome P450 (CYP450) system in the liver into the active metabolite. However, only a small percentage of administered clopidogrel is metabolised by CYP450. The majority of clopidogrel is hydrolysed to an inactive derivative that accounts for 85% of the inactive clopidogrel-related compounds circulating in plasma. The need for metabolisation of the pro-drug delays the onset of antiplatelet activity. Additionally, patient variability to clopidogrel effect has been demonstrated and shown to follow normal curve distribution. In a study conducted by the French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction (FAST-MI) investigators report on a cohort of more than 2200 clopidogrel-treated patients who presented with acute myocardial infarction.²⁴ The investigators, who looked at the relationship between genetic variants that are potentially relevant to platelet function and clinical outcome during a 1-year period, found that patients carrying any 2 *CYP2C19* loss-of-function

alleles (*2, *3, *4, or *5) had a higher event rate. Carriers of the *ABCB1* variant that modulates clopidogrel absorption also had a modestly increased rate of events. However, they found no association with polymorphisms of P2Y₁₂ or GP IIb/IIIa or with co-administration of omeprazole. In another study, Mega et al²⁵ examined the association between CYP genetic variants and cardiovascular outcomes in nearly 1500 patients who presented with an acute coronary syndrome and who were treated with clopidogrel during the earlier Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 study. They found that in healthy subjects, carriers of at least one *CYP2C19* loss-of-function allele had decreased levels of the active clopidogrel metabolite and less reduction in platelet aggregation, as compared with non-carriers. In clopidogrel-treated subjects from TRITON-TIMI 38, carriers of the loss-of-function alleles had an increased risk of death from cardiovascular causes, myocardial infarction, or stroke, as compared with non-carriers. In addition, subjects in TRITON-TIMI 38 who carried the *CYP2C19**2 allele had a risk of stent thrombosis that was 3 times that of non-carriers. In this study, the event curves diverged soon after treatment with clopidogrel, a finding that was consistent with the potential immediate loss of a platelet-inhibitory effect. Patients on clopidogrel therapy with lower responsiveness to clopidogrel had an increased rate of recurrent cardiovascular events. The best antiplatelet effects occurred at loading doses of 600 mg and maintenance doses of 150 mg a day. Non-responsiveness to high loading doses has also been reported in clinical studies. One particular study reported that “non-responsiveness” to a clopidogrel 600 mg loading dose was a strong independent predictor of stent thrombosis in patients receiving drug-eluting stents (DES).

Two small Japanese studies using angioscopy showed incomplete coverage of sirolimus-eluting stents in 20% to 87% of the stent segments and this was associated with the presence of strut-related thrombus material.²⁶ Furthermore, an intravascular ultrasound (IVUS) study in patients with sirolimus-eluting stents found no or almost absent neointimal coverage in 75% of the stents. However, the resolution of IVUS is too limited to accurately discern thin neointima. Therefore, in a recent study, Matsumoto et al have used optical coherence tomography (OCT) together with IVUS and angiography to examine neointimal coverage of sirolimus eluting stents at the 6-month follow-up for 36 patients.^{27,28} OCT is an imaging modality based on the back reflection of infrared light where IVUS is based on the back reflection of ultrasound. The axial resolution of OCT is superb (10 to 20 μm) compared with the axial resolution of IVUS (100 to 150 μm). In the study, ticlopidine was discontinued 3 months after stent implantation. Using IVUS,

no or almost no neointimal layer could be found. When looking with OCT at every separate stent strut, 91% of the struts were well-apposed to the vessel wall and covered with neointima, 7% of the struts were well apposed without neointimal coverage, and 1% was malapposed to the vessel wall without neointimal coverage. These OCT data show convincingly that only 16% of all stents were completely covered. Therefore, in a majority of stents, portions of the stent remain susceptible for thrombosis. Although in this study no thrombus-related clinical events were reported, thrombus formation was found in several sirolimus-eluting stents. For non-responders or clopidogrel resistant patients, it is not unforeseeable that this would greatly increase the rate of stent thrombosis for this cohort of patients.

These studies raise many pivotal questions. However, in the Asian population, the prevalence of clopidogrel resistance is unknown. The impact on the incidence of myocardial infarction and stent thrombosis post-implantation of DES is also unclear. The data currently available cannot answer these questions.²⁹ Until a prospective study is completed demonstrating how best to treat patients, particularly those who have poor metabolism of clopidogrel, it is not clear that routine genetic testing will be clinically or fiscally advantageous. It is currently also unknown if a point of care testing itself which is technically and fiscally more appealing is sufficient to guide clinical practice and change the current standard of care post-implantation of DES.

Clopidogrel and Omeprazole Interactions

Omeprazole (Prilosec, Procter & Gamble) is a PPI commonly used in combination with dual antiplatelet regimes for gastric ulcer prophylaxis. Omeprazole and other potent inhibitors of the CYP2C19 enzyme such as cimetidine, fluconazole, ketoconazole, fluoxetine, and fluvoxamine would be expected to retard the metabolism of pro-drugs such as clopidogrel that is dependent on the CYP2C19 system for conversion into the active metabolite. The Food and Drug Administration (FDA) has issued a new public-health warning on the possible interaction between clopidogrel and the PPI omeprazole. The alert states: “*New data show that when clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel is reduced. Patients at risk for heart attacks or strokes who use clopidogrel to prevent blood clots will not get the full effect of this medicine if they are also taking omeprazole*”. The alert quotes a reduction in active metabolite levels of about 45% was found in people who received clopidogrel with omeprazole compared with those taking clopidogrel alone. The effect of clopidogrel on platelets was reduced by as much as 47% in people receiving clopidogrel and omeprazole together. These reductions were seen whether the drugs were given at the same time or 12 hours apart.³⁰ The agency advises

patients using clopidogrel who need a medication to reduce stomach acid to use antacids or H₂ antagonists such as ranitidine and famotidine except cimetidine because the FDA does not believe that these medicines will interfere with the anti-clotting activity of clopidogrel.

However, current endpoint based randomised studies with proper subgroup analyses including CREDO, TRITON, PRINCIPLE, and preliminarily data from PLATO and CURRENT, all indicate that no interaction exists between clopidogrel and omeprazole for hard outcome end points. The recently presented COGENT (Clopidogrel and the Optimization of GI Events Trial) study was dedicated to specifically address this issue. The study enrolled 3627 patients to clopidogrel 75 mg along with omeprazole 20 mg versus clopidogrel 75 mg daily with a placebo. There was no difference in the incidence of the primary endpoint (Composite of cardiovascular death, non-fatal MI, CABG or PCI and ischaemic stroke) between the clopidogrel plus omeprazole and clopidogrel alone arms (3.8% vs 3.7%; HR, 1.02; 95% CI, 0.70-1.51). However, the incidence of composite GI events was significantly lower in the combination arm (2.0% vs 3.5%; HR, 0.55; 95% CI, 0.36-0.85, $P = 0.007$). This randomised study failed to suggest even a negative interaction as suggested by ex vivo platelet assays and observational studies. Furthermore, the combination is associated with a reduction in composite GI events when used in patients who are not at an especially high risk for GI bleeding. These data thus indicate that the concomitant use of omeprazole in patients on dual antiplatelet therapy should not be discouraged, but probably encouraged. Although these data are promising, it is still preliminary and unfortunately the trial was terminated early when the sponsor declared bankruptcy.³¹ Long-term data are also awaited. Similar concerns from ex vivo platelet assays had been raised for atorvastatin when used with clopidogrel, but had not borne out when tested for clinical outcomes in randomised controlled trials. Calcium channel blockers such as diltiazem, verapamil and nifedipine induce changes in intracellular calcium concentrations that play a crucial role in platelet activation.³² However, in double-blind trials, involving patients with hypertension and following acute myocardial infarction, verapamil failed to alter circulating platelet aggregates, inhibit agonist-induced aggregation in platelet-rich plasma or prolong bleeding time, although an antiplatelet effect has been demonstrated when ex vivo whole blood techniques are used for measurement.³³ Other agents that have a negative association in vitro include nitrates and beta blockers at high concentrations but again not borne out in clinical studies. This reinforces the necessity of changing clinical practice in response to good randomised trials with clinical endpoints in contrast to preliminary ex vivo studies.

Duration of Dual Antiplatelet Therapy for Drug Eluting Stents (DES)

In the past 2 years, concerns have been raised about a possible increase in the incidence of death and myocardial infarction in patients treated with DES due to the occurrence of stent thrombosis.³⁴ The incidence of stent thrombosis in the bare metal stent (BMS) era is low after the introduction of dual antiplatelet therapy. Stent thrombosis for BMS is associated with technical considerations such as persistent dissection, stent length, and final diameter and typically occurs within 6 weeks of the index procedure. With paclitaxel and sirolimus-eluting stents, premature discontinuation of thienopyridine therapy has become the most important risk factor for stent thrombosis, a catastrophic event that can occur late. This impact on outcome of clopidogrel discontinuation was not observed in patients who received a BMS. The current consensus opinion is for at least 1 year of dual antiplatelet use post-DES implantation. A recent post-hoc analysis of the CHARISMA trial showed that at least in some DES recipients, extending dual antiplatelet therapy beyond 1 year may be beneficial, without putting them at undue risk of bleeding, although how much stent-thrombosis risk is reduced remains unclear.³⁵ Without any input from randomised studies, there is debate regarding the strategy of extending dual antiplatelet therapy beyond 12 months. Numerous studies suggest that the risk of late and very late stent thrombosis continues in a linear fashion, without any clustering of events when clopidogrel is stopped. In BASKET-LATE study,³⁴ credited with first stirring widespread concern for the late stent-thrombosis problem, events occurred throughout the follow-up period, long after clopidogrel was stopped. We should bear in mind that long-term clopidogrel administration has disadvantages such as allergic reactions, cost, drug interactions and major life-threatening bleeding risk annually in the range of between 1% and 2%. The contrarian view amongst experts is that indefinite dual antiplatelet use beyond 12 months in select patients reduced thrombotic events that are not limited to stent thrombosis. This so called select group of CAPRIE-like cohort, characterised as higher-risk secondary-prevention patients with documented prior MI, ischaemic stroke, or symptomatic peripheral arterial disease that were treated with clopidogrel plus aspirin had significantly reduced rates of cardiovascular death, MI, stroke, or hospitalisations for ischaemia, as compared with those who received placebo plus aspirin.³⁵

The answer without any targeted randomised study to guide us probably lie somewhere in between. Late stent thrombosis post-DES implantation can be prevented to a certain degree by arbitrary administration of the dual

antiplatelet regime up to 12 months. Beyond this, a certain cohort of high atherosclerotic risk patients with high threshold for GI bleeding complication might benefit from indefinite dual antiplatelet use to reduce thrombotic events. Picking the right horse to bet on so to speak remains challenging.

Prasugrel and Ticagrelor: New and More Potent Inhibitors of P2Y₁₂ Receptors

Prasugrel

Prasugrel like clopidogrel is an inactive pro-drug of thienopyridine; however, the active metabolite is generated more efficiently after administration due to its rapid absorption and extensive metabolism. Prasugrel is rapidly hydrolysed into thiolactone and oxidised by intestinal and hepatic cytochrome CYP-450 system into the active metabolite. The active metabolites of prasugrel and clopidogrel have similar potency at the platelet level, but due to the pharmacokinetic profile of prasugrel, higher peak plasma levels lead to significantly greater exposure of circulating platelets to the prasugrel active metabolite. This permits a dosing regimen that yields significantly greater levels of inhibition of platelet aggregation (IPA) after both the loading as well as the maintenance dose. The percentage of prasugrel non-responders, in patients with stable coronary artery disease was only 3% after the 40 mg and 60 mg doses of prasugrel as compared to 30% for 300 mg clopidogrel loading.³⁶

The TRITON-TIMI 38 trial (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction) was performed for 13,608 moderate- to high-risk ACS patients undergoing PCI, including 3534 with STEMI.³⁷ The trial demonstrated that a prasugrel regimen of a loading dose of 60 mg and 10 mg once a day maintenance dose was significantly superior to the standard regimen of clopidogrel 300-mg loading dose and 75-mg daily maintenance dose in preventing the composite endpoint of death from cardiovascular causes, non-fatal MI, or non-fatal stroke during a median duration of therapy of 15 months. The reduction in the primary endpoint was driven by a significant 24% reduction in MI. Additionally, significant reductions of other ischaemia driven end points were shown. These include a 34% and 52% reduction in urgent target vessel revascularisation and stent thrombosis, respectively. The rate of definite or probable stent thrombosis was significantly reduced in the prasugrel group (1.6% vs 2.8%). These benefits of prasugrel over clopidogrel in preventing ischaemic events were achieved at the cost of an increased rate of TIMI major non-CABG-related bleeding. Net clinical benefit (death from any cause, non-fatal MI,

non-fatal stroke, and non-fatal TIMI major bleeding) significantly favoured the use of prasugrel over the course of the trial in spite of the elevated bleeding risks. The safety end point of major bleeding was not significantly greater in STEMI patients treated with prasugrel (2.4% vs 2.1%). This finding differed from that in the entire cohort in which there was significantly more episodes major bleeding event not associated with CABG with prasugrel. Both the loading and maintenance doses of prasugrel studied in TRITON-TIMI 38 yield greater levels of platelet inhibition than a standard dose of clopidogrel due to the higher and more rapid availability of the active metabolite of prasugrel. Needless to say, agents with higher levels of platelet inhibition, such as prasugrel, have lower cardiovascular event rates but higher rates of bleeding.

Ticagrelor

Ticagrelor is an oral, reversible, direct-acting inhibitor of the adenosine diphosphate receptor P2Y₁₂ that has a more rapid onset and more pronounced platelet inhibition than clopidogrel. This was demonstrated in the PLATElet inhibition and patient Outcomes (PLATO) trial. The study compared ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) to clopidogrel (300-to-600-mg loading dose, 75 mg daily thereafter) among 18,624 patients with an ACS with or without ST-segment elevation.³⁸ Patients were randomised in a double-blind manner with the study drug treatment to continue for up to 12 months. Median time from symptom onset to treatment was 11.3 hours. The ACS diagnosis comprised STEMI (38%), NSTEMI (43%), and unstable angina (17%). PCI was performed in the majority of patients (61%) during the index hospitalisation. The mode of revascularisation was cardiac surgery in 4.5% of patients. Nearly half of all patients in both arms had received clopidogrel during the index hospitalisation prior to randomisation. The primary endpoint at 12 months, a composite of death from vascular causes, MI, or stroke occurred less frequently in the ticagrelor group compared with the clopidogrel group (9.8% vs 11.7%; HR, 0.84; 95% CI, 0.77-0.92; $P < 0.001$). This finding was evident by 30 days, and was also evident among patients in whom an invasive treatment was planned (8.9% vs 10.6%; HR, 0.84; 95% CI, 0.75-0.94; $P = 0.003$). Results were consistent in the prespecified subgroups, with the exception of patients weighing less than gender-specific median, those on lipid-lowering drugs at randomisation, and those enrolled in North America, for whom the benefit of ticagrelor was attenuated. Among 8430 STEMI patients, the primary outcome occurred in 9.3% vs 11.0% ($P = 0.02$), respectively. The rate of death from any cause was also reduced with ticagrelor (4.5%, vs 5.9% with clopidogrel; $P < 0.001$) as was definite or probable stent thrombosis (2.2% vs 2.9%; HR, 0.75; 95%

CI, 0.59-0.95; $P = 0.02$). No significant difference in the rates of major bleeding was found between the ticagrelor and clopidogrel groups (11.6% and 11.2%, respectively; $P = 0.43$), but ticagrelor was associated with a higher rate of major bleeding not related to CABG (4.5% vs 3.8%; $P = 0.03$). Fatal bleeding was equivalent in both groups (0.3%; $P = 0.66$). The secondary safety endpoint of non-CABG-related major bleeding was higher in the ticagrelor group using both the trial defined endpoint (4.5% vs 3.8%; $P = 0.03$) and the TIMI criteria (2.8% vs 2.2%; $P = 0.03$). CABG-related major bleeding did not differ between groups (7.4% vs 7.9%; $P = 0.32$). Discontinuation of study drug was slightly higher in the ticagrelor group (23.4% vs 21.5%; $P = 0.002$), as was discontinuation due to an adverse event (7.4% vs 6.0%; $P < 0.001$).

Ticagrelor and prasugrel are 2 of the novel oral P2Y₁₂ receptor antagonist to have undergone large-scale clinical trial validation with promising results compared to clopidogrel. Although prasugrel was associated with an increase in bleeding rates in the trial, ticagrelor at the study doses had overall bleeding rates that were comparable to clopidogrel, although there were some increases in non-CABG-related bleeding, but not in CABG-related bleeding.

Conclusions and Recommendations

Platelet aggregation plays a central role in the development of an acute occlusive disease causing STEMI. Antiplatelet agents have been shown to improve the clinical outcomes for patients receiving treatment with acute PCI. The evidence supports the early initiation of dual antiplatelet therapy with aspirin and clopidogrel loading, followed by maintenance dosing in all patients with STEMI.

For the initial presentation of STEMI, patients should receive at least 300 mg of ASA and asked to chew the tablets. For patients planned for acute PCI, 600 mg of clopidogrel should be loaded as early as possible. Post-PCI with stent implantation, patients should be on a regime of 75 mg twice a day for 1 week followed by a 75-mg daily maintenance dose. ASA 100 mg is continued indefinitely for secondary prevention. Clopidogrel is continued for at least 1 month and up to 9 months for patients implanted with a BMS. Patients who are implanted with DES should receive a minimum of 1 year of dual antiplatelet therapy. Patients at high risk of GI events should be covered with ulcer prophylaxis with either a H₂ antagonist or PPIs. There is a FDA caution about the possible metabolic antagonism of PPIs with clopidogrel efficacy but this is not currently advised by clinical practice guidelines.

Potent novel antiplatelet agents such as prasugrel and ticagrelor show promise as a step forward in antiplatelet therapy. These newer agents overcome most of the issues associated with clopidogrel non-responsiveness. The initial

uptake will be dependent on cost considerations and the bleeding risk incurred for the local population. Further dose-ranging studies for the Asian population would be welcome to refine their usage in ACS patients undergoing PCI, so that patients can derive the benefits of antiplatelet therapy, while minimising the risks of stent thrombosis and bleeding.

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