Review Article

P2Y12 inhibitors in acute coronary syndromes: Which and when?

PREM PAIS

ABSTRACT

Acute coronary syndromes (ACS) are the commonest acute manifestation of coronary artery disease and a major cause of hospitalization and death. Plaque rupture and subsequent platelet activation are the key factors in its pathogenesis. Platelet inhibitors are crucial in the management of ACS.

Aspirin remains the standard antiplatelet but use of dual antiplatelet drugs is beneficial in ACS. Platelet P2Y12 receptor inhibitors are an important group of antiplatelet compounds that can be combined with aspirin in the management of ACS. P2Y12 inhibitors may belong to the thienopyridine or non-thienopyridine group of compounds. The former (clopidogrel, prasugrel) combine irreversibly with the receptor and therefore have a prolonged duration of action. On the other hand, the non-thienopyridine compounds (ticagrelor, elinogrel) have a reversible action and hence a shorter duration of action.

Several new compounds in this group have become or are likely to become available. The newer agents have a more uniform and complete antiplatelet effect and are much less likely to be affected by genetic variability of CYP2C19 enzyme activity compared with that of clopidogrel. Large phase 3 trials have shown that ticagrelor and prasugrel reduce major cardiovascular events in ACS compared to clopidogrel when given in addition to aspirin. This is accompanied by some increase in bleeding.

This review discusses the properties, clinical profile and possible place of P2Y12 receptor inhibitors in clinical practice.

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ACUTE CORONARY SYNDROMES (ACS) AND THEIR MEDICAL MANAGEMENT

Acute ST elevation myocardial infarction (STEMI), acute non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA) are the most frequent acute presentations of ischaemic heart disease (IHD). They carry significant morbidity and mortality. In all three forms of ACS, plaque rupture followed by platelet activation, aggregation and subsequent triggering of the coagulation cascade is the key pathology. Since the pathophysiology in ACS involves platelet activation and the coagulation cascade, medical strategy targets both these systems. The use of a single agent is insufficient to address the 'hot plaque' and thus multiple agents are required. Drugs that target mainly the coagulation cascade include those that block factor X either via antithrombin 3 (heparin, low molecular weight heparin [LMWH], fondaparinux), directly (apixaban, rivaroxaban) or by blocking the action of thrombin (bivalirudin, dabigatran).

The antiplatelet drugs act by blocking various platelet receptors (Fig. 1) and when used in combination in ACS they can lead to better outcomes with acceptable safety. Aspirin, the earliest used antiplatelet agent in ACS, causes reduced synthesis of thromboxane A2 which is responsible for the platelet activation effect of collagen by inhibiting the cyclooxygenase enzyme. The P2Y12 receptor inhibitors (ticlopidine, clopidogrel, prasugrel, ticagrelor, cangrelor, elinogrel) block the effect of adenosine diphosphate (ADP) which acts by activating this receptor, while GPIIb/IIIa receptor inhibitors (abciximab, eptifibatide and tirofiban) block the final common pathway which involves fibrinogen and results in cross-linking of platelets. The last group is used mainly in conjunction with invasive management of ACS. In the setting of ACS, inhibition of platelet aggregation is related to clinical outcomes; therefore, greater inhibition with acceptable risk of

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Fig 1. Site of action of antiplatelet drugs

ADP adenosine diphosphate
bleeding should lead to better clinical efficacy. Seminal trials\(^1\)\(^\text{2}\) have shown that in ACS platelet aggregation should be blocked at two sites. The current guidelines for management of ACS recommend the use of aspirin with a P2Y12 inhibitor in most patients, with additional use of GPIIb/IIa receptor inhibitor in patients undergoing percutaneous coronary intervention (PCI).\(^1\)

Aspirin

Aspirin has been in use for over a century for its anti-inflammatory effects. Thirty years ago, it was discovered to have, in low doses, an antiplatelet effect by blocking the cyclooxygenase enzyme. Aspirin is rapidly absorbed and inhibits platelet aggregation in about 60 minutes, but it has a relatively weak antiplatelet effect. About one-third of patients are resistant to the effect of aspirin. Nevertheless, clinical trials of aspirin in ACS clearly showed that it reduced vascular mortality and recurrent myocardial infarction (MI). The ISIS 2 study\(^4\) showed a 23% reduction of vascular mortality among patients with STEMI given 162.5 mg of aspirin alone and 42% reduction when given with streptokinase compared to placebo. A meta-analysis of trials of aspirin in ACS involving 95 000 individuals in primary prevention trials and 17 000 in secondary prevention trials\(^5\) showed a 20% reduction of serious vascular events. In view of this, low-dose aspirin remains the key in the management of ACS and should always be used unless there is a specific contraindication.

P2Y12 RECEPTOR INHIBITORS

About a decade after aspirin came to be used as an antiplatelet agent, a new class of such agents, the thienopyridines, was introduced. Ticlopidine was the first such agent to be used in clinical practice.\(^6\) This group of drugs blocks platelet activation through ADP by blocking the platelet P2Y12 receptor. Ticlopidine was found to cause bone marrow suppression in a few patients resulting in leucopenia and occasionally thrombotic thrombocytopenic purpura.\(^7\) It has been largely replaced by clopidogrel, the second agent in this class. In the past 5 years large clinical trials have been conducted with newer P2Y12 inhibitors which are now entering the market. This review focuses on the P2Y12 inhibitors especially clopidogrel, prasugrel and ticagrelor and their place in the clinical management of ACS.

The P2Y12 receptor plays a key role in activation of platelets. Its activation by ADP leads to platelet degranulation, aggregation, procoagulant activity and platelet–leucocyte interaction leading to conversion of monocytes to macrophages and release of cytokines.\(^8\) These actions are blocked by the P2Y12 inhibitors. Based on their molecular structure, P2Y12 inhibitors are classified as being thienopyridine or non-thienopyridine. Drugs in the thienopyridine group (ticlopidine, clopidogrel and recently prasugrel) bind to the P2Y12 receptor irreversibly and hence have a prolonged action. A second and newer group of P2Y12 inhibitors is the non-thienopyridine compounds (ticagrelor and cangrelor). Unlike the thienopyridine compounds, the non-thienopyridine compounds bind reversibly to the P2Y12 receptor and therefore have a shorter duration of action. In the case of ticagrelor, the duration of action is about 3 days and in the case of cangrelor it is about an hour (Table I). Ticagrelor has recently been licensed in Europe and is being actively reviewed for licensing by the Food and Drugs Administration (FDA) in the USA and the Drug Controller General of India (DCGI) in India.

Clopidogrel

In stable IHD, clopidogrel does not seem to have a major advantage over aspirin. The CAPRIE study\(^9\) showed a borderline reduction (8%) in major adverse cardiovascular events (MACE) compared to aspirin, and the CHARISMA study\(^10\) showed no benefit of using dual antiplatelet agents (aspirin and clopidogrel) over aspirin alone in stable coronary artery disease. However, in ACS the role of clopidogrel is different. The CURE study,\(^1\) a placebo-controlled, double-blind study showed that in NSTEMI ACS the addition of clopidogrel to aspirin reduced adverse events (combination of cardiovascular death, non-fatal MI and non-fatal stroke) from 11.4% to 9.3%. This 20% relative risk reduction (RR) was homogeneous among all subgroups, i.e. even patients with no ST depression or enzyme elevation benefited. However, this benefit came at the cost of increased bleeding—a 34% (p=0.003) increase in major bleeds in the clopidogrel arm although there was no significant increase in life-threatening bleeds.

In the subgroup of participants in the CURE trial undergoing PCI (PCI-CURE)\(^11\) the benefit increased further (MACE reduced by 35% at 30 days and 28% at one year) with no increase in major bleeds. Subsequently, the CLARITY and COMMIT trials\(^12\) showed that the benefit of adding clopidogrel to aspirin was true for STEMI even when many patients were treated with thrombolysis. In both the CURE and CLARITY trials, a loading dose of 300 mg clopidogrel followed by 75 mg daily was used while in the COMMIT study from China the same daily dose was used but with no loading dose. The CLARITY trial, like the CURE trial, reported a 20% reduction in the composite end-point of cardiovascular death, non-fatal MI and non-fatal stroke while COMMIT with a large sample size of over 45 000 participants reported a smaller but still highly significant reduction of 9%. The lack of a loading dose in COMMIT could have been responsible for this smaller effect.

The antiplatelet effect of clopidogrel can be quite variable and the drug needs to be used in larger doses in critical situations such as ACS where PCI is intended. The CURRENT-OASIS 7 study\(^13\)\(^,\)\(^14\) compared two dosing regimens of clopidogrel—high dose (600 mg loading dose, 150 mg daily for 7 days followed by 75 mg daily) with low dose (300 mg loading dose followed by 75 mg daily) in patients with ACS where PCI was intended. All patients received aspirin too in one of two doses (300–325 mg or 75–100 mg). While in the entire study population there was no significant reduction in MACE (hazard ratio [HR] 0.95, 95% CI 0.83–1.06) or cardiovascular death (HR 0.95, 95% CI 0.81–1.13), in patients who actually underwent PCI there was a significant reduction (15%) in MACE (HR 0.86, 95% CI 0.74–0.99) and a 46% reduction in definite stent thrombosis (HR 0.54, 95% CI 0.39–0.74) but not in cardiovascular death alone (HR 0.96, 95% CI 0.79–1.19) in patients receiving the higher dose of clopidogrel (Table II). This benefit of the higher dose came at a cost of a 39% increase in major bleeds. Following OASIS 7, it seems reasonable to use the higher dose regimen in patients with ACS undergoing PCI but not in others. It is yet unclear how long the higher maintenance dose of 150 mg should be continued. In OASIS 7 it was given for

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**Table I. Characteristics of thienopyridine and non-thienopyridine antiplatelet compounds**

<table>
<thead>
<tr>
<th>Type of Compound</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thienopyridine compounds</td>
<td>(irreversible binding to P2Y12 receptor)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Slow onset of action, slow offset of action</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Fast onset of action, slow offset of action</td>
</tr>
<tr>
<td>Non-thienopyridine compounds</td>
<td>(reversible binding to P2Y12 receptor)</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>Fast onset of action, fast offset of action</td>
</tr>
<tr>
<td>Cangrelor</td>
<td>Very fast onset of action, very fast offset of action</td>
</tr>
</tbody>
</table>
confirmed by a recently published meta-analysis. As a result in increased event rate in those with this allele has also been shown.19 In a study of 1477 patients with ACS and a planned PCI, pharmacodynamic studies compared to those with an active metabolite, pharmacokinetic studies and reduced platelet aggregation on concomitantly with clopidogrel. Some areas of concern are its delayed onset of action, the variability in its antiplatelet effect and its long duration of action, increasing the risk of bleeding due to coronary artery bypass graft (CABG) surgery and non-CABG surgery. About 33% of patients on clopidogrel are ‘resistant’ and show only a low level of platelet inhibition. One of the main reasons for the variability and delayed onset of action of clopidogrel is that it is a prodrug that requires a two-step activation in the liver involving a series of cytochrome P-450 (CYP) isoenzymes.18 This activation is susceptible to reduction in enzyme action caused by genetic polymorphisms and to the effect of drug interaction when agents with metabolism involving these isoenzymes are used concomitantly with clopidogrel.

A reduced function allele of CYP2C19 is common and patients with this allele have been shown to have a reduced area under the curve (AUC) of the active clopidogrel metabolite on pharmacokinetic studies and reduced platelet aggregation on pharmacodynamic studies compared to those with an active allele. In a study of 1477 patients with ACS and a planned PCI treated with clopidogrel, over a year, there was a 50% increase in the composite of cardiovascular death, non-fatal MI and non-fatal stroke (relative risk [RR] 1.53, 95% CI 1.07–2.19, p=0.014) and a three-fold increase in stent thrombosis (RR 3.04, 95% CI 1.19–8.00, p=0.015) in those with the reduced function allele. This increased event rate in those with this allele has also been confirmed by a recently published meta-analysis. As a result in 2010, the US FDA required a black box warning to be added to the clopidogrel information leaflet to indicate that persons with ACS or those undergoing a PCI who have a reduced function allele of CYP2C19 can have increased events while on the standard dose of clopidogrel. Alternative treatment strategies may be considered where such patients are identified. The GRAVITAS trial20 in 2214 subjects with stable coronary artery disease or ACS undergoing PCI studied whether measuring the extent of platelet inhibition could be used to tailor the dose of clopidogrel. All subjects were given a loading dose of 600 mg of clopidogrel. Platelet function was tested using a point-of-care device (VerifyNow) 12–24 hours after PCI. Those with platelet reactivity >230 units were randomized to either 75 mg or 150 mg of clopidogrel daily for 6 months. In studying the whole cohort there was a 68% non-significant trend to increased events in patients with persistent high platelet reactivity. Although platelet reactivity was significantly reduced in patients receiving the higher dose of clopidogrel, the study could not show any clinical benefit of the higher doses of clopidogrel. The reasons for this are unclear. The authors hypothesized that perhaps platelet reactivity is a marker but not necessarily the cause of higher events. The dose used may not have been high enough (although CURRENT showed definite benefit in cases of ACS undergoing PCI with 150 mg for just 7 days). The fact that all patients received a similar loading dose of 600 mg may have masked any effect of the difference in the maintenance dose. Finally, including stable coronary artery disease with ACS may have had an impact on the results.

The irreversibility of clopidogrel action gives it a prolonged antiplatelet effect until a new generation of platelets is developed. This can lead to bleeding problems when surgery particularly CABG surgery is done in patients on the drug. Clopidogrel needs to be discontinued at least 5 days before any major surgery. On the other hand, the advantage of the prolonged action is that, even if a dose or two is missed, some antiplatelet effect remains.

There has also been concern about the bioavailability of clopidogrel in patients receiving the proton pump inhibitor omeprazole. Proton pump inhibitors can inhibit the CY2C19 that is required for the activation of clopidogrel. Some studies on platelet aggregation have shown that use of clopidogrel with omeprazole results in a reduction in the effect of clopidogrel in inhibiting platelet aggregation. The COGENT trial21 studied 3873 patients on aspirin who were randomized to receive either a fixed-dose combination of clopidogrel 75 mg and omeprazole 20 mg, or clopidogrel and placebo. The combination therapy group had a 70% reduction in gastrointestinal bleeding (HR 0.30, p=0.001) and there was no increase in MACE (HR 0.99, p=0.96). A cohort study of a general practice database of 24 471 patients in Britain also did not find any clinical consequence of the use of proton pump inhibitors with clopidogrel.

**Prasugrel**

Prasugrel is a thienopyridine P2Y12 receptor inhibitor that has been licensed and marketed recently. It shares the class effect of thienopyridines in being a non-reversible inhibitor of the P2Y12 receptor. In fact its duration of action is longer than that of clopidogrel. However, it has a more rapid onset of action and more uniform and complete inhibitory effect on the receptor. It requires a one-stage activation that is much less dependent on the CYP

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**Table II. Comparison of high-dose versus low-dose clopidogrel in patients undergoing percutaneous coronary intervention (PCI): Data from CURRENT-OASIS7 study**

<table>
<thead>
<tr>
<th>Event</th>
<th>All patients RR (95% CI)</th>
<th>PCI RR (95% CI)</th>
<th>No PCI RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major adverse cardiovascular events*</td>
<td>0.94 (0.83–1.06)</td>
<td>0.86 (0.74–0.99)</td>
<td>1.14 (0.92–1.40)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>0.95 (0.81–1.13)</td>
<td>0.96 (0.77–1.19)</td>
<td>0.99 (0.70–1.39)</td>
</tr>
<tr>
<td>Definite stent thrombosis</td>
<td>1.24 (1.05–1.46)</td>
<td>1.39 (1.07–1.81)</td>
<td>1.09 (0.88–1.35)</td>
</tr>
</tbody>
</table>

* major adverse cardiovascular events (composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke)
enzyme and its action does not seem to be affected in patients who have a reduced function CYP2C19 allele.

The definitive study on which prasugrel’s regulatory approval was based was the TRITON-TIMI 38 study. TRITON-TIMI 38 was a double-blind, double-dummy, randomized clinical trial of patients with ACS (STEMI, NSTEMI and UA) and planned PCI; 13,600 patients were enrolled and randomized either to clopidogrel (300 mg loading dose/75 mg daily) or prasugrel (60 mg loading dose/10 mg daily). All patients received aspirin. The median duration of follow-up was 14.5 months. The study reported a significant 20% reduction in the composite of cardiovascular death, non-fatal MI and non-fatal stroke with prasugrel compared to clopidogrel. This applied equally to STEMI and NSTEMI ACS. The absolute risk reduction was 1.9% for NSTEMI and 2.4% for STEMI. Stent thrombosis was reduced by over 50%. This benefit was seen both for drug-eluting stents (2.2% stent thrombosis rate with clopidogrel vs. 0.8% with prasugrel, p<0.0001) and bare metal stents (2.3% stent thrombosis rate with clopidogrel vs. 1.2% with prasugrel, p=0.0014). However, these benefits came at the cost of increased bleeding. Prasugrel led to significant increase in both major (30% increase) and minor bleeds and in CABG surgery and non-CABG surgery bleeding. CABG surgery-related major bleeding rate was 13.4% with prasugrel vs. 3.2% with clopidogrel. In some subgroups excess bleeding nullified the benefit of prasugrel—those >75 years of age, <60 kg in weight or those who had a stroke in the past. It would be wiser to avoid prasugrel in such patients or to use a lower dose. On the other hand, TRITON confirmed that prasugrel retains its efficacy even in those with reduced activity CYP2C19 allele. The event rate was similar in the prasugrel arm for such patients while it was 53% higher in the clopidogrel arm. If such patients could be identified, prasugrel would be especially beneficial for them. Another subgroup in which prasugrel could be useful is those at high risk. In TRITON, patients with diabetes in the prasugrel arm had a highly significant reduction in events (30%) with no increase in bleeding compared to those in the clopidogrel arm.

Prasugrel was approved by the US FDA in 2009 as an alternative to clopidogrel for patients with ACS who are to undergo PCI. The recommended dosage is a loading dose of 60 mg followed by a maintenance dose of 10 mg daily (5 mg in those >75 years of age or <60 kg in weight). In patients with STEMI who are to be treated with thrombolytic therapy clopidogrel is preferred. Prasugrel should be stopped 7 days earlier where CABG surgery and non-CABG surgery bleeding. CABG surgery-related major bleeding rate was 13.4% with prasugrel vs. 3.2% with clopidogrel. In some subgroups excess bleeding nullified the benefit of prasugrel—those >75 years of age, <60 kg in weight or those who had a stroke in the past. It would be wiser to avoid prasugrel in such patients or to use a lower dose. On the other hand, TRITON confirmed that prasugrel retains its efficacy even in those with reduced activity CYP2C19 allele. The event rate was similar in the prasugrel arm for such patients while it was 53% higher in the clopidogrel arm. If such patients could be identified, prasugrel would be especially beneficial for them. Another subgroup in which prasugrel could be useful is those at high risk. In TRITON, patients with diabetes in the prasugrel arm had a highly significant reduction in events (30%) with no increase in bleeding compared to those in the clopidogrel arm.

Ticagrelor

Ticagrelor is a non-thienopyridine P2Y12 receptor inhibitor and as such blocks this receptor reversibly. It has a rapid onset of action (within an hour) and a relatively quicker offset of its antiplatelet effects. It is a direct-acting drug that does not require activation in the liver and hence its action is not affected in patients with the reduced activity CYP2C19 allele. Its platelet inhibition effect is dose-dependent and is more complete than that of clopidogrel. Phase 1 studies in humans showed that ticagrelor at a dose of 100 mg twice daily produced a uniform near 100% impaired platelet aggregability (IPA) while clopidogrel at a dose of 75 mg once daily produced 60% IPA.

The pharmacodynamic sub-study from the DISPERSE trial showed that 90 mg of ticagrelor b.i.d. produced a 75% inhibition of platelet function while 75 mg of clopidogrel produced a 64% inhibition. Moreover, ticagrelor could produce an additional suppression of platelet function even in those patients previously treated with clopidogrel. The ONSET-OFFSET study compared the pharmacodynamics of ticagrelor 180 mg followed by 90 mg twice daily and clopidogrel 600 mg followed by 75 mg daily over 6 weeks on platelet aggregability in 123 patients with stable coronary artery disease on aspirin. Ticagrelor produced significantly greater IPA within 30 minutes, greater degree of impairment of platelet function and faster return to baseline platelet function compared with that of clopidogrel.

Early phase studies also showed some unusual symptoms in patients on ticagrelor. There was an increase in dyspnoea without evidence of cardiac or pulmonary decompensation as well as increased episodes of bradycardia. These symptoms do not seem related to its antiplatelet effect but may be related to its similarity in structure to adenosine.

The PLATO study was a phase 3 trial of ticagrelor in a broad range of ACS. It included patients with either STEMI or NSTEMI and those managed with an invasive or conservative strategy. However, the use of fibrinolytic therapy was a contraindication for inclusion in the trial. The PLATO study randomized 18,624 patients to either 180 mg loading dose of ticagrelor followed by 90 mg twice daily or to 300/600 mg of clopidogrel followed by 75 mg daily. The study medication was continued for a median of 277 days. It showed that patients randomized to ticagrelor had a significant 16% RRR in the composite of cardiovascular death, non-fatal MI and non-fatal stroke (p=0.001). The use of ticagrelor was associated with a significant reduction in the pre-specified secondary end-point of MI (HR 0.84, 95% CI 0.75–0.95, p=0.005) and cardiovascular death (HR 0.79, 95% CI 0.69–0.91, p=0.001). The latter is a unique finding for not since aspirin has an antiplatelet agent been shown to reduce mortality as an independent event. Neither CURE nor TRITON-TIMI 38 showed a significant reduction in mortality (Table III). In PLATO, the rates of all-cause mortality were 4.5% with ticagrelor and 5.9% with clopidogrel—a significant 22% RRR. The mechanism for this reduction in mortality is unclear. It could be related to the increased antiplatelet effect without an increase in overall major bleeding (see below). It could also be related to the adenosine-like effect the molecule has which also explains its unusual adverse symptoms of bradycardia and dyspnoea. In PLATO, ticagrelor also led to a 23%
reduction in any stent thrombosis (p=0.01) and 33% reduction in definite stent thrombosis (p=0.009). The benefits were seen regardless of an invasive or non-invasive strategy. In patients in whom a conservative strategy was planned, compared to those on clopidogrel, those on ticagrelor had a 15% reduction in MACE (p=0.04), 24% reduction in cardiovascular death (p=0.02) and 25% reduction in total mortality (p=0.01). A pre-planned subgroup analysis of PLATO showed that patients intended for medical management did not differ in outcome from the entire population. 35

One would expect a drug with increased antiplatelet effect to result in increased bleeding. The results in PLATO showed that overall major bleeding was not significantly increased by ticagrelor compared to clopidogrel (HR 1.04, 95% CI 0.95–1.13, p=0.43). However, on closer scrutiny, it was evident that major bleeding not related to surgery did in fact increase in the ticagrelor arm—4.5% v. 3.8%, p=0.03. However, CABG surgery-related bleeding was not increased and in fact it showed a trend towards reduction in the ticagrelor arm—7.4% v. 7.9%. The explanation for this could lie in the shorter duration of action of ticagrelor compared to clopidogrel allowing more complete recovery of platelet function by the time of CABG surgery. However, there was a small increase in intracranial bleeding with ticagrelor—0.3% v. 0.2%, p=0.06.

Early phase studies had reported bradycardia and dyspnoea with ticagrelor, hence these were closely monitored in the PLATO study. Episodes of bradycardia were assessed by Holter monitoring. In patients receiving ticagrelor during the first week, 5.8% showed ventricular pauses of over 3 seconds versus 3.6% of those receiving clopidogrel (p=0.01). By 30 days, the difference was no longer significant—2.1% and 1.7%, respectively (p=0.52). Bradycardia-related clinical events (pacemaker insertion and sudden death) were not significantly different. In the case of syncope, there was a non-significant trend towards increase in the ticagrelor arm—0.8%, p=0.08. Patients with conduction defects and bradyarrhythmias not protected by a pacemaker were excluded from the trial and hence the effect of ticagrelor in this subgroup could not be assessed from the PLATO study.

In the case of dyspnoea, symptomatic dyspnoea (13.8% v. 7.8%) and discontinuation of medication for dyspnoea (0.9% v. 0.1%) were both significantly more in patients on ticagrelor compared with those on clopidogrel but the absolute numbers were small.

OTHER P2Y12 ANTIPLATELET AGENTS (Table IV)

**Cangrelor**

Cangrelor is an investigational, ultra-short-acting, non-thienopyridine P2Y12 platelet receptor inhibitor that has to be given intravenously. It is being tested as a bridge therapy in ACS being managed medically a combination of aspirin and clopidogrel (300–600 mg loading dose followed by 75 mg daily) or 80 mg elinogrel i.v. followed by one of three arms (50, 100 or 150 mg of elinogrel orally twice daily) for at least 60 days. The 100 mg and 150 mg doses had greater platelet inhibitory effect than clopidogrel with no increase in bleeding.

Some new receptor inhibitors are in the pipeline but are still far from clinical use—protease-activated receptor (PAR) inhibitors vorapaxar and compound E555.

**Elinogrel**

Elinogrel is a direct-acting P2Y12 receptor inhibitor that is unique in being available in both i.v. and oral forms. This should give it an advantage for use in both the acute setting in the catheterization laboratory or in preparation for surgery. It has a reversible action, a half-life of 12–14 hours and no major interaction with CYP agents or proton pump inhibitors. The INNOVATE-PCI trial, a double-blind, double-dummy trial randomized patients with ACS going for PCI to cangrelor (bolus 30 µg/kg followed by an infusion of 4 µg/kg/hour) or clopidogrel 600 mg loading dose. Both arms were given clopidogrel after the PCI. At 48 hours, there was no difference between the two arms as far as the primary end-point was concerned (death, MI, ischaemia-driven revascularization [IDR]). At the same time, there was an increase in bleeding with cangrelor although there was no increase in the requirement for transfusion. The BRIDGE trial recently published its results on the use of cangrelor in the setting of CABG surgery. In this study, 210 patients going for elective CABG surgery had their antiplatelet medication discontinued 5–7 days before surgery. They were then randomized to receive cangrelor or placebo infusion during these days. Those receiving cangrelor were able to maintain over 60% platelet inhibition with no significant increase in CABG-related bleeding. The study was not powered to assess ischaemic or mortality end-points.

**TABLE IV. Properties of different P2Y12 receptor inhibitors**

<table>
<thead>
<tr>
<th>Property</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
<th>Cangrelor</th>
<th>Elinogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversibility</td>
<td>Irreversible</td>
<td>Irreversible</td>
<td>Reversible</td>
<td>Reversible</td>
<td>Reversible</td>
</tr>
<tr>
<td>Formulation</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Intravenous</td>
<td>Intravenous and oral</td>
</tr>
<tr>
<td>Onset</td>
<td>4–6 hours</td>
<td>1–2 hours</td>
<td>2–3 hours</td>
<td>Immediate</td>
<td>Immediate (i.v.)</td>
</tr>
<tr>
<td>Half-life</td>
<td>5 days</td>
<td>5 days</td>
<td>12 hours</td>
<td>5 minutes</td>
<td>Intravenous: 50 minutes Oral: 12 hours</td>
</tr>
</tbody>
</table>
be appropriate. In medically managed patients, prasugrel has no benefit over clopidogrel.\textsuperscript{27} On the other hand, the PLATO study showed prasugrel to be appropriate. In medically managed patients, prasugrel has no benefit over clopidogrel.\textsuperscript{27} In the TRITON study, there were 13.4% major bleeds in patients on prasugrel undergoing CABG surgery as against 3.2% in those on clopidogrel. Hence, it may be better to avoid prasugrel in those likely to require CABG surgery or to wait until the coronary anatomy is known. Since prasugrel acts quickly it could be given soon after coronary angiography has delineated the vascular anatomy and CABG surgery is unlikely to be needed. Ticagrelor may be preferred in those that are more likely to require CABG surgery. In view of the relatively short antiplatelet effect of ticagrelor, it would be reasonable for patients on clopidogrel or prasugrel needing elective surgery to switch to ticagrelor 5–7 days before surgery. A corollary about ticagrelor is that while the shorter antiplatelet effect is an advantage in so far as reducing the chances of surgical bleeding, it makes compliance with twice daily dosing schedule important as a missed dose can lead to loss of antiplatelet effect.

Should there be testing of platelet response to clopidogrel and using prasugrel or ticagrelor in non-responders? There is as yet no evidence with clinical outcomes to support this strategy. The RESPOND trial\textsuperscript{46} gave patients with stable coronary artery disease 300 mg of clopidogrel and then studied platelet function. Non-responders were randomized to either 600 mg clopidogrel loading dose followed by 75 mg maintenance dose or to ticagrelor 180 mg loading dose followed by 90 mg twice daily. After 14 days, patients were crossed over to the other arm. Platelet function tests showed a 30%–40% increased inhibition of platelet aggregation during the ticagrelor phase. However, there was no measure of clinical events in this short-term mechanistic study. Doubling the dose of clopidogrel is an easy option for clinicians before other antiplatelets, including the investigational oral antiplatelet agent ticagrelor and the newly approved prasugrel—are available or in more widespread use.

Both prasugrel and ticagrelor are best avoided in patients with a history of stroke or transient ischaemic attacks because of the increased risk of haemorrhagic stroke. Based on the findings of TRITON, prasugrel could be avoided in patients who are over 75 years of age or under 60 kg in weight. As ticagrelor may cause dyspnoea, bradycardia and increase in serum uric acid, it may be best to avoid it in patients with hyperuricaemia, chronic obstructive pulmonary disease, history of syncope or with bradycardia/bradyarrhythmias without a pacemaker.

**Conflict of interest.** I was the National Coordinator for India for the PLATO study.

**REFERENCES**
