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Review article

Platelet adenosine diphosphate receptor antagonists: ticlopidine to ticagrelor—a long continuing journey

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KEYWORDS

Anti-platelet therapy
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ABSTRACT

Platelet aggregation plays a central role in the pathogenesis of atherothrombosis. Platelet adenosine diphosphate (ADP) receptor antagonists (ticlopidine, clopidogrel, prasugrel, and ticagrelor) are a major advance in the treatment of atherothrombotic diseases, especially acute coronary syndromes (ACS). Ticlopidine was the first thienopyridine introduced into clinical practice, but its potentially serious haematological side-effects limited its use and it was quickly eclipsed by clopidogrel. Clinical trials established aspirin plus clopidogrel as the standard dual anti-platelet therapy in patients with ACS and patients undergoing percutaneous coronary intervention (PCI) with stenting. Clopidogrel was found to have pharmacokinetic and pharmacodynamic limitations. Prasugrel is the next approved thienopyridine that has shown superior efficacy in ACS patients undergoing PCI in comparison to clopidogrel, although at the cost of a higher bleeding risk. Ticagrelor is the latest non-thienopyridine ADP receptor blocker that is potent, effective, reversible, and relatively safer as compared to clopidogrel.

Both prasugrel and ticagrelor are more potent than clopidogrel. The data so far suggests that ticagrelor has a wider applicability in usage in patients with ACS as compared to prasugrel. Prasugrel however seems to be better tolerated. Search is on for newer more potent but safer anti-platelet agents.

Introduction

Platelets play a central role in the pathogenesis of atherothrombosis. Aspirin is the basic standard anti-platelet agent. Aspirin (acetylsalicylic acid) targets cyclo-oxygenase (COX-1), inhibiting thromboxane A_2 formation and inducing a functional permanent inhibition in platelets. The limited role of thromboxane A_2 in platelet activation explains why aspirin therapy, which effectively inhibits release of thromboxane A_2 by platelets is insufficient in high-risk conditions such as acute coronary syndromes (ACS) or percutaneous coronary intervention (PCI). The platelet $P2Y_{12}$ receptor, one of two adenosine diphosphate (ADP) receptors on platelets, plays a central and unique role in platelet activation through amplifying the effects of numerous platelet agonists. Platelet adenosine diphosphate receptor inhibitors are a class of agents that provide additional anti-aggregatory property to prevent initial platelet activation (Table 1). This mechanism has represented a major advance in the treatment of athero-thrombotic diseases especially ACS. Intravenous GP IIb/IIIa receptor antagonists (abciximab, eptifibatide, and tirofiban) target the final common pathway of platelet aggregation.

Ticlopidine

The first thienopyridine agent to be introduced in the clinical arena was ticlopidine. It was initially evaluated and found

Table 1
Platelet adenosine diphosphate receptor antagonists.

Thienopyridines
Ticlopidine
Clopidogrel
Prasugrel
Non-thienopyridines
Ticagrelor

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effective in the long-term management of ischaemic stroke and claudication. Its use was later extended to the prevention of cardiac thrombotic events. In a placebo-controlled trial of ticlopidine in unstable angina, there was a statistically significant 46% reduction in the risk of vascular death or myocardial infarction (MI) at 6 months.[1] It was the combination of aspirin and ticlopidine which facilitated the widespread use of coronary stenting.[2] However, the major shortfall of ticlopidine turned out to be the idiosyncratic and severe haematological illness associated with its clinical use. The potentially serious side-effects like leukopenia and thrombotic thrombocytopenic purpura requiring frequent monitoring was a drawback and this agent was replaced by clopidogrel, which showed better haematological and gastrointestinal tolerance besides being a once a day therapy.[3]

Clopidogrel

Clopidogrel monotherapy was shown to be modestly superior to aspirin monotherapy in preventing recurrent ischaemic events in patients with peripheral vascular disease, ischaemic strokes, and recent myocardial infarction in the CAPRIE study.[4] However, it did not replace aspirin because of its higher cost and was promoted as an alternative to aspirin in patients who could not tolerate it. Thereafter trials in patients with ACS and those undergoing coronary stenting showed that a combination of aspirin and clopidogrel was superior to aspirin alone during the 1 year follow-up of the treatment and it significantly improved the outcomes.[5,6] The combination of aspirin and clopidogrel became a standard of treatment in managing patients with acute coronary syndrome with or without STEMI.[7,8] Likewise patients with coronary stents especially drug-eluting stents are recommended this combination for at least a year.

The secondary analysis of HORIZONS AMI trial[9] concluded that among patients undergoing primary PCI for STEMI, a 600 mg dose of clopidogrel was superior to a 300 mg loading dose. Likewise the recently published CURRENT/Optimal Antiplatelet Strategy for Interventions (CURRENT-OASIS-7)[10] trial, clopidogrel given as a 600 mg loading dose followed by 150 mg daily for 7 days and 75 mg daily thereafter was compared with the conventional doses in patients with STEMI or NSTE-ACS. Overall, the higher dose regimen was no more effective than the conventional dose regimen, with a similar 30 day rate of the composite endpoint of cardiovascular death, MI, or stroke (4.2% vs 4.4%, respectively; hazard ratio [HR] 0.94; 0.83–1.06; $P=0.30$), but was associated with increased 30 day rates of major bleeding.

However, the same trial showed that doubling the loading and maintenance dose of clopidogrel for 1 week in ACS patients undergoing planned PCI significantly reduces stent thrombosis and cardiovascular events, largely driven by reductions in MI, without a significant increase in major bleeding.

The drawbacks of clopidogrel are shown in Table 2.[11] The two-step activation process involving a series of cytochrome P-450 (CYP) isoenzymes, is susceptible to the interference of genetic polymorphisms and drug–drug interactions.[12,13] Proton pump inhibitors that inhibit CYP2C19, particularly omeprazole, decrease clopidogrel-induced platelet inhibition ex vivo, but there is currently no conclusive clinical evidence that co-administration of clopidogrel and proton pump inhibitors increases the risk of ischaemic events in addition, clopidogrel (and prasugrel) absorption is regulated by P-glycoprotein (encoded by ABCB1), which is an ATP-dependent efflux pump that transports various molecules across extracellular and intracellular membranes. It is expressed, among other places, on intestinal epithelial cells, where increased expression or function can affect the bioavailability of drugs that are substrates. Patients with a poor response to clopidogrel have an increased risk of coronary thrombosis.[14,15] The increased risk of bleeding due to prolonged persistence of its effect is another concern when patients need urgent coronary artery bypass grafts (CABG).

Table 2
Limitations of clopidogrel.

- Delayed onset of action
- Requires metabolic biotransformation to active metabolite
- High interpatient variability in pharmacokinetics and pharmacodynamics (resistance/non-responders)
- Modest inhibition of platelet response ex vivo
- Irreversible $P2Y_{12}$ receptor binding

Prasugrel

This new member of the class is more effective than ticlopidine and clopidogrel at inhibiting the ADP receptor largely because it is more efficiently metabolised so more active metabolite is delivered to the platelet.

It is more rapid its onset of action and has a stronger inhibitory effect than clopidogrel.[16] As compared with clopidogrel, prasugrel shows lower variability in platelet response and no measurable vulnerability to genetic variation in CYP is-coenzymes. It was shown to have superior efficacy in reducing the ischaemic events in the TRITON-TIMI-38 clinical trial done in patients with acute coronary syndrome with moderate to high-risk.[17] However, this superior efficacy was associated with a higher bleeding risk. The study showed that prasugrel significantly reduced the risks of recurrent myocardial infarction and stent thrombosis as compared to clopidogrel. The benefits were particularly sizeable in patients with diabetes or ST-segment elevation. The benefits appeared to be continued over the 15-month trial period. The study pushes the standard for the appropriate duration of therapy beyond 12 months and it appears that an indefinite duration of dual anti-platelet therapy may be warranted after an acute coronary syndrome.[18]

The bleeding risk among those patients needing early CABG was 4 times higher than in the clopidogrel group. Thus, it is prudent to know coronary anatomy in non-STEMI (ST-segment elevation myocardial infarction) patients before initiating prasugrel. The finding of increased bleeding rates among patients undergoing CABG also raises the concern of increased

Table 3
Target population for prasugrel.

- Patients undergoing PCI for STE myocardial infarction
- Patients at risk of stent thrombosis and patients after stent thrombosis
- Diabetics undergoing PCI
- Patients with the presence of genetic variants related to non-responsiveness to clopidogrel

PCI: percutaneous coronary intervention, STE: ST-segment elevation.

bleeding in patients needing non-cardiac surgery who have been on prasugrel in the past 7 days.

Recent concerns regarding the risk of thrombosis with drug-eluting stents have captured the attention of interventional cardiologists.[19] It is felt that using prasugrel in patients undergoing complex stenting procedures may reduce the rates of stent thrombosis. The finding of an approximately 50% reduction in the rate of stent thrombosis held true in both the DES and BMS arm (TRITON-TIMI-38) both in early and late stent thrombosis. However, it is the patients with ACS who are at a greater risk for stent thrombosis and related events than patients undergoing elective PCI.[20] Therefore, caution is needed in recommending prasugrel routinely after elective PCI.

Prasugrel thus represents an advance in anti-platelet therapy for ACS. TRITON-TIMI-38 supports its use in patients with such syndromes when there is a very high probability of PCI such as in STEMI and in patients with non-STEMI after coronary angiography. Its use in other situations where clopidogrel is used at present is not recommended. Table 3 lists the patients who are potential candidates for prasugrel therapy.

The bleeding risks were seen to be higher in patients >75-year-old, with low body mass index, and history of stroke or transient ischaemic attacks.

Therefore, it would be best to avoid prasugrel in such patients. A reduction of the dose of prasugrel in these patients would probably reduce the bleeding risk. It is suggested that a dose of 5 mg instead of 10 mg as the maintenance dose may be more appropriate. This aspect is being studied in on-going clinical trials.

Concerns regarding bleeding led to several risk mitigation strategies: US FDA has put a boxed warning underscoring the increased risk of bleeding for patients >75 years of age or older and patients undergoing CABG. A statement in the label emphasises that choosing a therapy requires balancing the reduction in the risk of thrombotic event against the bleeding risk. Excess neoplasms which was another issue which had come out while analysing the data did not seem to be concerning after going through the details and it is felt that this possibly was a false positive finding of a very marginal statistical support. Studies conducted by the sponsor to evaluate tumour progression possibility of prasugrel in human colon, prostate, and lung have come out to be negative.

The use of prasugrel in patients of ACS in patients not intended for early invasive strategy is not recommended and is the subject of another on-going study TRIOLOGY.

The advantage of prasugrel over clopidogrel appears to be the prevention of non-fatal MIs, many of which would not have immediate overt clinical consequences. The cost of this prevention is excessive bleeding an important adverse effect but one that is transient and does not result in increase in strokes or deaths. The benefits of prasugrel over clopidogrel in patients with diabetes mellitus presenting as ACS were really spectacular and at no higher bleeding cost. Diabetics who constituted one-third of the patients of the TIMI Triton study have shown an absolute difference of 4.6% lower net clinical benefit (HR 0.74, $P=0.001$).

Ticagrelor

Ticagrelor belongs to a new chemical class cyclopentyltriazolopyrimidine (CPTP) that evolved in the process of developing an orally active mimetic of adenosine triphosphate (ATP), the natural antagonist at the $P2Y_{12}$ receptor. It is an orally active drug that binds reversibly to $P2Y_{12}$, with a stronger and more rapid anti-platelet effect than clopidogrel.[21,22] The PLATO study showed that as compared to clopidogrel, ticagrelor was associated with a 16% relative risk reduction with regard to the primary end point—a composite of death from cardiovascular causes, myocardial infarction and stroke—but no significant increase in the overall risk of major bleeding.[23]

The recommended dose is 180-mg loading dose, then 90 mg twice daily. It has not been determined whether continuing ticagrelor beyond 1 year (when clopidogrel is often discontinued) will lead to continued accrual of benefit. This issue will be addressed in the on-going phase 3 PEGASUS-TIMI 54 study which will compare the efficacy and safety of the PLATO maintenance regimen of ticagrelor (90 mg twice daily) and a lower dose regimen of ticagrelor (60 mg twice daily) with placebo in higher risk patients with a history of MI 1–3 years previously. The PLATO-INVASIVE study[24] (pre-specified invasively-treated subgroup of PLATO study) revealed a statistically significant reduction of ischaemic events including stent thrombosis without an increase in major bleeding.

The major trials of platelet ADP receptor antagonists in patients with ACS have been CURE, TRITON-TIMI-38, and PLATO. In CURE as well as the TRITON-TIMI-38 trial, a stronger platelet inhibition was associated with increased risk of bleeding. On the other hand PLATO has shown that the potent ticagrelor is not associated with increased incidence of major bleeding. Ticagrelor was safer than clopidogrel in patients undergoing CABG, although non-CABG-related bleeding was more frequent. Perhaps the reversibility in the mechanism of action of ticagrelor comes into play.[25] While clopidogrel and prasugrel showed no mortality benefit in association with a stronger anti-platelet effect, ticagrelor did confer a 22% mortality reduction despite being a potent anti-platelet agent.

The emerging concept is that agents with increased anti-platelet effect without an increase in bleeding complications may reduce the overall mortality. This interesting hypothesis needs to be confirmed in future investigations. In addition, the subset analysis of the PLATO study has shown that the benefits of ticagrelor over clopidogrel are consistent even in patients of ACS not intended for early invasive strategy.[26] The incidence of total major bleeding ($P=0.08$) and non-CABG-related bleeding ($P=0.10$) was numerically higher with ticagrelor as

compared to clopidogrel. However, in patients of ACS undergoing CABG within 7 days of the intake of last dose ticagrelor was associated with significantly lower total (9.7% vs 4.7%, $P<0.01$) and cardiovascular (CV) death (7.9% vs 4.1% $P<0.01$) without an increase in major bleeding as compared to clopidogrel.[27] This makes ticagrelor a drug of choice in wider indications in the treatment of ACS.

The newer side-effects seen with ticagrelor (dyspnoea, bradyarrhythmia, increased serum creatinine and uric acid levels) were not seen in the trials of clopidogrel and prasugrel. These effects are important and need to be pursued further since they would have negative effects on the quality of life.

In addition, there was also a trend towards increase in the risk of haemorrhagic strokes especially if unclassified strokes are included in the category of haemorrhagic strokes. The significance of these findings is not very clear at present.

With the availability of three platelet ADP receptor blockers, it may be possible to individualise anti-platelet therapy. If patients on clopidogrel or prasugrel require CABG it may be reasonable to switch them over to ticagrelor 5–7 days before surgery. Likewise ticagrelor may be preferred in non-STEMI ACS patients whose coronary anatomy is not known. It is also to be noted that the rapidly reversible effects of ticagrelor makes careful surveillance of patients' compliance mandatory. While as prasugrel should be avoided in the elderly, the underweight or those having a history of previous stroke or TIA (TRITON-TIMI-38), ticagrelor should be discouraged in patients who have chronic obstructive pulmonary disease, hyperuricemia, renal failure, brady-arrhythmias, or a history of syncope, as per the PLATO trial. Its use in patients who have high-risk for bleeding and multiple risk factors should be avoided. The peculiar side-effects of ticagrelor would require a watch in the post-marketing surveillance studies.

An important message for those involved in the anti-platelet drugs research is that increasing potency of anti-platelet agents does not always imply increased bleeding risk. Search for newer agents of this group must continue.

What do the guidelines say regarding the anti-platelet therapy in acute coronary syndromes?

American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) guidelines 2011 on PCI have made the following class I recommendations[28]: Patients already taking daily aspirin therapy should take 81–325 mg before PCI. Patients not on aspirin therapy should be given non-enteric aspirin 325 mg before PCI; after PCI, the use of aspirin should be continued indefinitely. A loading dose of a $P2Y_{12}$ receptor inhibitor should be given to patients undergoing PCI with stenting.

The different options include:

a. Clopidogrel 600 mg (ACS and non-ACS patients)
b. Prasugrel 60 mg (ACS patients)
c. Ticagrelor 180 mg (ACS patients).

The loading dose of clopidogrel for patients undergoing PCI after fibrinolytic therapy should be 300 mg within 24 hours and 600 mg >24 hours after receiving fibrinolytic therapy. Patients should be counseled on the need for and risks of DAPT before placement of intracoronary stents, especially DES, and alternative therapies should be pursued if patients are unwilling or unable to comply with the recommended duration of DAPT. The duration of $P2Y_{12}$ inhibitor therapy after stent implantation should generally be as follows: In patients receiving a stent (BMS or DES) during PCI for ACS, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. Options include:

a. Clopidogrel 75 mg daily
b. Prasugrel 10 mg daily
c. Ticagrelor 90 mg twice daily.

The European Society of Cardiology 2011 makes the following class I recommendations for anti-platelet use in NSTE-ACS.[29]

Aspirin should be given to all patients without contraindications at an initial loading dose of 150–300 mg, and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy. A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained >12 months, unless there are contraindications such as excessive risk of bleeding. A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (*Helicobacter pylori* infection, age ≥65 years, concurrent use of anticoagulants or steroids). Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate to high-risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).

Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high-risk of life-threatening bleeding or other contraindications.

Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel. A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option. A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding.

For our athero-thrombosis prone population these new additions are welcome. A careful balance between efficacy and risk however, would always be an important issue before making any recommendations. Table 4 shows a comparison of the efficacy and safety endpoints of the major trials of platelet ADP receptor inhibitors. $P2Y_{12}$ inhibitors have transformed the efficacy of pharmacotherapy for ACS and PCI, and further research is on-going.

Table 4
Major 'adenosine diphosphate receptor antagonists' trials with associated risks.

Trial	Group	Events					
		MI	Stroke	Vascular death	All-cause death	Vascular death MI, stroke	Major bleeding
CAPRIE	Clopidogrel group	3.20	5.44	1.19	3.05	_	_
(n=19,185)	Asprin group	3.92	5.69	2.06	3.11	_	_
	Relative risk reduction (95% CI)	_	_	7.6 (–6.9–20.1)	2.2 (–9.9–12.9)	7.0 (–0.9–14.2)	_
CURE	Clopidogrel group	5.2	1.2	5.1	5.7	–9.3	3.7
(n=12,562)	Placebo group	6.7	1.4	5.5	6.2	11.4	2.7
	Relavie risk with clopidogrel (95% CI)	0.77 (0.67–0.89)	0.86 (0.63–1.18)	0.93 (0.79–1.08)	0.93 (0.81–1.07)	0.80 (0.72–0.90)	1.38 (1.13–1.67)
TRITON-TIMI-38	Prasugrel group	7.3	1.0	2%	3.0	9.9	2.5
(n=13,608)	Clopidogrel group	9.5	1.0	2.4	3.2	12.1	1.7
	Relative risk with prasugrel (95% CI)	0.76 (0.67–0.85)	1.02 (0.71–1.45)	0.89 (0.70–1.12)	0.95 (0.78–1.16)	0.81 (0.73–0.90)	1.45 (1.15–1.83)
PLATO	Ticagrelor group	5.8	1.5	4.0	4.5	9.8	11.6
(n=18,624)	Clopidogrel group	6.9	1.3	5.1	5.9	11.7	11.2
	Relative risk with ticagrelor (95% CI)	0.84 (0.75–0.95)	1.17 (0.91–1.52)	0.79 (0.69–0.91)	0.78 (0.69–0.89)	0.84 (0.77–0.92)	1.04 (0.95–1.13)

MI: myocardial infarction; CI: confidence interval.

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