Review

What is the risk of intensifying platelet inhibition beyond clopidogrel? A systematic review and a critical appraisal of the role of prasugrel

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Summary

Thienopyridines are a class of drug targeting the platelet adenosine diphosphate 2 receptor. They have been shown to significantly reduce platelet activity exerting an important role in those clinical settings in which such an effect is beneficial. Ticlopidine was first to be introduced several years ago but it was quickly replaced by clopidogrel as it had a better risk/benefit profile. Recently, prasugrel has been developed and tested in several ex vivo studies and clinical trials showing able to provide a more powerful antiplatelet effect at the expense of a higher risk of bleeding complications. Great debate rose around its recent approval in the US as well as in Europe. This review aims at exploring the development and available clinical data of this third-generation thienopyridine while discussing its practical implementation in routine practice.

Introduction

Thienopyridines, which include clopidogrel, ticlopidine and more recently prasugrel, are an antiplatelet class of drugs which selectively target the adenosine diphosphate (ADP) 2 receptor on the surface of platelets. Blockage of this receptor results in impaired platelet activation thus playing a pivotal role in clinical settings where such an effect is beneficial. Ticlopidine was the first member of this class to be used. Owing to concerns relating to neutropenia and thrombotic thrombocytopenic purpura, its
Clinical application has been largely superseded by clopidogrel. Conceivably, thienopyridines form an integral part of cardiovascular specialists’ drug regimen in several scenarios including the wide spectrum of patients with stable angina, acute coronary syndromes and/or treated with percutaneous coronary intervention (PCI) where they reduce the incidence of restenosis, thrombosis and major adverse cardiac events. Of note, in patient with stable angina, clopidogrel administration alone is advisable only when there is contraindication to or aspirin intolerance. In acute myocardial infarction, for patients who have undergone diagnostic cardiac catheterization and for whom PCI is planned, clopidogrel should be started and continued for at least 1 month after bare metal stent implantation and for several months after drug-eluting stent implantation, up to 12 months in patients who are not at high risk for bleeding. In patients with unstable angina, clopidogrel should be started on admission and administered at least 1 month, up to 9 months (with a level of evidence B). Overall, for those patient treated with PCI the co-administration of aspirin (permanently) and clopidogrel is mandatory. Clopidogrel is administered after implantation of bare metal coronary stents and drug eluting stents for at least 1 month and 12 months, respectively. In the latter case, such a prolonged co-administration seemed a sensible choice following the evidence of delayed endotelialization of stents and its subsequent risk of late stent thrombosis.

However, recent literature has emphasized the presence of ‘clopidogrel non-responders’ and significant inter-individual variability in response to clopidogrel. This has been attributed to clinical, cellular and genetic factors. It has been reported that between 4% and 34% of patients have an inadequate anti-platelet response to clopidogrel on the basis of ex vivo platelet function test and, on the basis of some pivotal studies, these individuals have a higher likelihood of adverse clinical events in both acute and chronic coronary heart disease.

These concerns acted as a spur for the development of more efficacious and reliable antiplatelet therapies. Prasugrel, the third generation thienopyridine, has been introduced in order to overcome the drawbacks of its predecessors. Aim of this article is to investigate its evolution and clinical application.

**Mechanism of action**

Prasugrel is a potent antiplatelet drug which exerts its activity inhibiting the via-ADP platelet activation. Like other members of the thienopyridine class, it is a prodrug absorbed via the gut and undergoes metabolism, first by hydrolysis via esterases in the gut wall, liver and plasma into a thiolactibe R-95913. This is then oxidized by the cytchrome p450 system, mainly through the CYP3A and CYP2B6 isoenzymes, into the active thiol metabolite R-138727 (Figure 1). The latter irreversibly binds the G-protein linked P2Y12 ADP receptors on the platelet surface (Figure 1). As a consequence, the release of ADP by the platelet, which in turn activates the platelet itself, is permanently impaired. As with other thienopyridines, the metabolites of prasugrel are excreted via the kidney.

**Preclinical studies**

It has been shown in several animal models that orally administered prasugrel is completely absorbed and then rapidly metabolized to an active thiol metabolite with no selective tissue uptake. Daily repeated oral prasugrel dosing was associated with a more potent inhibition of thrombic and platelet activity compared with ticlopidine or clopidogrel. A dose-dependent inhibition of ADP-induced platelet aggregation has been also shown to be exerted by the active hepatic metabolite rather than by prasugrel itself. Such active metabolite also inhibits ADP-induced inflammatory markers of platelet activation and interferes with platelet procoagulant activity in whole blood resulting in impairment of clot formation. The (R, S)-isomer of the active thiol metabolite R-138727 showed a more potent inhibiting platelet activity compared with other isomers, suggesting a stereo-selective effect. In a rat model, a single oral-dose of prasugrel has been shown to be more potent in inhibiting platelet activity and thrombotic activity through the inhibition of platelet function test. Furthermore the onset of action was quicker and was associated with less variation in platelet inhibition in comparison to other thienopyridines. Consistently, Sugidachi and colleagues demonstrated that prasugrel itself was 10-fold more potent than clopidogrel in inhibiting ADP induced platelet aggregation. Of note, the concentration of the prasugrel active metabolite was significantly higher in plasma compared to the active clopidogrel metabolite. Each drug’s active metabolite, however, produced an equivalent degree of platelet inhibition. Taken together these findings would suggest that the superior potency of prasugrel compared to clopidogrel in platelet inhibition reflects greater efficiency of the former in generating its active metabolite and not because of a difference in the platelet
inhibiting properties of the metabolites themselves.  

**Phase 1 studies**

Asai et al. randomized patients to receive either placebo or 2.5, 10, 30, or 75 mg of prasugrel (n = 5 per group). ADP-induced platelet aggregation and plasma levels of metabolites of prasugrel were measured. Only 30 and 75 mg doses produced significant inhibition of platelet aggregation which was reduced to <40% at 24 h. No occurrence of adverse events have been reported.

The pharmacokinetics and pharmacodynamics of two different loading and maintenance doses regimens of prasugrel were studied in healthy volunteers. Thirty-two patients were allocated to either prasugrel 40 mg loading dose and 7.5 mg daily, prasugrel 60 mg load and 15 mg daily or placebo. Sixty milligrams dose did not produce any significant incremental inhibition over the 40 mg dose. Maintenance with both 15 and 7.5 mg significantly inhibited platelet activity in a dose-dependent manner after 20 days. The maximal concentration of inactive metabolites was detectable in the plasma 30 min after administration.

Matsushima et al. evaluated the pharmacokinetic and pharmacodynamic effects of two daily doses of prasugrel (2.5 or 10 mg) compared to placebo for 10 days. Only patients receiving the 10 mg dose of prasugrel achieved significant inhibition of adenosine-induced platelet aggregation and reached steady state by 2–4 days of therapy.

Similar findings were reported by Jakubowski et al. who enrolled 31 patients and compared the pharmacodynamic and pharmacokinetic effects of either placebo, prasugrel (5, 10 or 20 mg), or clopidogrel 75 for 10 days. Overall there was greater and more consistent inhibition of platelet aggregation in the 10 and 20 mg prasugrel treated patients compared to the 75 mg clopidogrel treated patients.
Brandy et al.\cite{31} randomized 68 healthy patients to either clopidogrel (loading dose 300 mg) or prasugrel (loading dose 60 mg). Administration of 60 mg of prasugrel resulted in more significant and consistent inhibition of ADP-induced platelet inhibition compared with clopidogrel.

As both clopidogrel and prasugrel rely on the CYP3A isoenzyme of the cytochrome p450 system to produce biologically active metabolites, Farid et al.\cite{32} compared the effects of inhibition of the cytochrome p450 CYP3A4 and CYP3A5 isoenzymes by ketoconazole on platelet activity after therapy with either clopidogrel or prasugrel. As a result, ketoconazole reduced the plasma concentration of the active metabolites of both compounds compared to baseline. However, such an effect was significantly higher for clopidogrel’s active metabolite compared with prasugrel thus suggesting that the generation of the active prasugrel metabolite can be compensable through other enzyme systems.\cite{32}

Similar findings were reported in a separate study which found that individuals with polymorphisms of CYP2C19 and CYP2C9 had lower inhibition of platelet aggregation when treated with clopidogrel.\cite{33}

In an open label study, Farid et al.\cite{34} assessed whether prasugrel affected the metabolism of bupropion (150 mg slow release formulation), which is converted to its active metabolite almost exclusively by CYP2B6. The study found that prasugrel co-administration with bupropion resulted in a weak inhibition of CYP2B6 compared to the prasugrel naive state.\cite{34}

Based on the prasugrel’s physicochemical structure, Small et al.\cite{35} hypothesized that an increase in gastric pH may reduce its solubility thus decreasing its absorption. They therefore co-administered the proton pump inhibitor lansoprazole. The study found that lansoprazole reduced the plasma concentration of the active prasugrel metabolite by 29%. This reduction in bioavailability, however, had no effect of inhibition of platelet aggregation. Conversely, lansoprazole had no effect on clopidogrel’s metabolite but attenuated its ability to inhibit platelet aggregation. Overall they concluded that no dose adjustment was necessary for patients talking prasugrel with the proton pump inhibitor lansoprazole.\cite{35}

Weerakkody et al.\cite{36,37} assessed the speed of effect on platelet inhibition by a 60 mg loading dose of prasugrel compared with a 300 mg loading dose of clopidogrel in healthy patients not on aspirin. Prasugrel treated patients had a more rapid and consistent inhibition of platelet aggregation compared with clopidogrel and all patients treated with 60 mg of prasugrel in this study were found to be ‘responders’.\cite{36,37}

Payne et al.\cite{38} compared prasugrel (loading dose/maintenance dose: 60 mg/10 mg) with two different regimes of clopidogrel (loading dose/maintenance dose: 300 mg/75 mg or 600 mg/75 mg). Sixty milligram of prasugrel induced more significant inhibition of platelet aggregation compared to both 300 and 600 mg of clopidogrel. Similarly, during the maintenance phase, prasugrel was more potent in suppressing platelet aggregation.\cite{38}

Taken together, these studies suggest that prasugrel, when used as a single antiplatelet agent, produces a more potent, rapid and consistent inhibition of platelets compared with current, clinically used doses of clopidogrel.

As thienopyridine agents are most commonly used clinically in combination with aspirin, Jackubowski et al.\cite{39} conducted a study on individuals taking 325 mg of aspirin. Healthy volunteers were administered prasugrel in one of four dosing regimes (loading dose/maintenance dose: 20 mg/5 mg, 30 mg/7.5 mg, 40 mg/10 mg or 60 mg/15 mg) or clopidogrel (loading dose/maintenance dose 300 mg/75 mg). Prasugrel additively inhibited platelet aggregation in a dose-dependent manner.

**Phase 2 studies**

Main features of Phase 2 studies are summarized in the Table 1. Consistent findings compared to Phase 1 data were reported in a study of 110 patients on aspirin, that were randomized to 28 days of either clopidogrel (loading dose/maintenance dose: 600 mg/75 mg) or prasugrel (loading dose/maintenance dose: 60 mg/10 mg). The study showed that prasugrel induced a quicker and more potent inhibition of ADP-induced platelet aggregation. The concentration of the active prasugrel metabolite was higher than the active clopidogrel metabolite suggesting that the observed differences in pharmacodynamic effects could be due to differences in metabolic efficiency generating the respective metabolites.\cite{40}

The prasugrel in comparison to clopidogrel for inhibition of platelet activation and aggregation-thrombolysis in myocardial infarction 44 (PRINCIPLE-TIMI 44) study compared prasugrel (loading dose/maintenance dose: 60 mg/10 mg) to high dose clopidogrel (loading dose/maintenance dose: 600 mg/150 mg) in aspirin treated patients undergoing PCI. Prasugrel produced more potent inhibition of ADP-induced platelet aggregation 6 h after administration of a 60 mg loading dose compared to 600 mg clopidogrel. Likewise maintenance therapy with a daily dose of 10 mg prasugrel produced more potent platelet inhibition than a daily
A dose of 150 mg clopidogrel after 14 days of treatment.41

The joint utilization of medications to block platelets optimally (JUMBO-TIMI 26) was a Phase 2 dose ranging and safety study which randomized 905 patients eligible for elective PCIs to one of four groups: low-dose prasugrel (40 mg loading dose, 7.5 mg daily maintenance dose), intermediate-dose prasugrel (60 mg loading dose, 10 mg daily maintenance dose), high-dose prasugrel (60 mg loading dose, 15 mg daily maintenance dose) or standard dose of clopidogrel (300 mg loading dose, 75 mg daily maintenance dose).42 All patients received concomitant 325 mg aspirin and the primary end-point of this study was clinically significant non-coronary artery bypass graft surgery related bleeding at 30 days. The study found that the overall major bleeding rates for clopidogrel and prasugrel were low (<1%) with no significant differences between the groups. Prasugrel treated patients had a lower incidence of major adverse cardiac events at the expense of more bleeding compared to clopidogrel treated patients and historical controls.43

Jernberg et al.44 sought to assess the effect of prasugrel (loading dose/maintenance dose: 40 mg/5 mg, 40 mg/7.5 mg, 60 mg/10 mg, 60 mg/15 mg) or clopidogrel (loading dose/maintenance dose: 300 mg/75 mg) on inhibition of platelet activity (IPA) in patients with stable coronary artery disease on chronic aspirin therapy. IPA was assessed using turbidometric platelet aggregation following ADP stimulation. Both the 40 and 60 mg loading doses of prasugrel produced a greater IPA at 4 h compared to a 300 mg loading dose of clopidogrel. Similarly maintenance with both doses of prasugrel (10 and 15 mg) achieved a more significant IPA compared to 75 mg of clopidogrel at 28 days. Importantly at 28 days there were no ‘non-responders’ in the prasugrel treated group in comparison to 45% in the clopidogrel cohort.44

These studies suggested that prasugrel in combination of aspirin produces a more rapid, consistent and potent inhibition of platelet function compared with clopidogrel in combination with aspirin or either separately. Furthermore there was no evidence to suggest any significantly different increase in bleeding rates or adverse events in prasugrel treated patients.

### Phase 3 studies

The large Phase 3 trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction (TRITON-TIMI) 38 trial45 was then...
conducted to assess whether the superior antiplatelet profile or prasugrel would provide a clinically significant benefit over clopidogrel. The double-blinded study randomized 13,608 patients with acute coronary syndromes to aspirin and prasugrel (60 mg loading dose, 10 mg daily maintenance dose) or aspirin and clopidogrel (300 mg loading dose, 75 mg daily maintenance dose). The primary end-point of the study, a composite of cardiovascular death, myocardial infarction or stroke, was significantly reduced in the prasugrel group, driven largely by reductions in the rate of non-fatal myocardial infarction. There was no reduction in mortality. There was, however, a significant increase in bleeding complications in the prasugrel group. Patients who benefited most from prasugrel treatment over clopidogrel treatment were those with diabetes mellitus, myocardial infarction and lesions requiring the placement of a long stent or bifurcation stenting. Conversely those who did not benefit included elderly patients, those with a low body weight (<60 kg) and those with a previous history of stroke or transient ischemic attacks.46

There has been much discussion about the implications of the TRITON-TIMI 38 study in the literature. The underlying mechanisms of acute coronary syndromes necessitate an intensive antiplatelet therapies. Therefore the challenge for physicians is to identify those who have most to gain and those most at risk from it.

In a recently published sub-study which included 12,844 patients who had at least one coronary stent implanted, significant reductions in ischaemic coronary events including reduced stent thrombosis was seen in patients treated with prasugrel (60 mg loading dose, 10 mg daily maintenance dose) compared to clopidogrel (300 mg loading dose, 75 mg daily maintenance dose) in both bare metal stent and drug eluting stent treated patients. Overall for every 1000 patients treated, prasugrel prevented 12 episodes of stent thrombosis and 15 ischaemic cardiovascular events at the expense of five major bleeds in comparison to clopidogrel.46

An important consideration in interpreting the superiority of prasugrel’s anti-ischaemic effect in the TRITON-TIMI 38 study is that the clopidogrel arm received a 300 mg loading dose which takes longer to achieve sufficient platelet inhibition compared to the 600 mg dose.47 Furthermore, patients were not loaded with clopidogrel prior to angiography but only when a decision to proceed with PCI was made, and the timing of initial clopidogrel administration prior to stent implantation remains unclear. Whether the clinical differences seen in the TRITON-TIMI 38 study would still occur if the latter clopidogrel regimen was used is uncertain although, as discussed earlier, pharmacodynamic evaluation in the PRINCIPLE-TIMI 44 trial,38 showed that prasugrel was more potent than high dose clopidogrel in suppressing ADP-induced platelet aggregation.

In a TRITON-TIMI 38 sub study, authors analysed clinical end points within the first 3 days and from 3 days to the rest of the follow-up showing that both the loading and the maintenance dose of prasugrel were superior to clopidogrel for the reduction of ischemic events.48 Importantly they reported that the excess of bleeding was present only during the maintenance dose. Recently, it has been shown that Prasugrel is able to provide a net benefit over clopidogrel in particular in patients with diabetes mellitus, i.e. a reduction of ischemic events was not counterbalanced by an increased risk of major bleeds.49

Prasugrel showed superiority over clopidogrel even in the setting of ST elevation myocardial infarction with an durable benefit up to 15 months.50

On a pharmacodynamic/pharmacologic basis such superiority might be explained by the absence of any interaction of the common functional cytochrome p450 genetic variants with drug metabolite levels and inhibition of platelet aggregation.51

We performed an exploratory meta-analysis pooling data from Phases 2 and 3 trials in order to assess the risk of major and minor bleeding when prasugrel is administered instead of clopidogrel. In Phase 2 studies, where different doses of prasugrel have been administered, we considered the highest. The administration of prasugrel instead of clopidogrel conferred a higher risk of major bleeding [OR 1.33 (1.05–1.68), P=0.02], as well as minor bleedings [OR of 2.02 (1.21–3.37), P=0.01] (Figure 2).

**Which role for prasugrel?**

In summary, prasugrel showed to be more rapid acting, potent and consistent in its antiplatelet activity compared to clopidogrel. It is rapidly absorbed and efficiently converted by the liver into its active metabolite which exerts antiplatelet effects by irreversibly binding to and inhibiting the G-protein linked P2Y12 class of ADP receptors. When administered in combination with aspirin to patients with acute coronary syndromes, once the decision of performing PCI has been taken, it reduced both ischemic coronary events and the incidence of coronary stent thrombosis compared with the current best practice regimen of aspirin and clopidogrel. This beneficial effect is partly offset by excess major bleeding, so that its practical implementation...
requires careful selection of those patients who are likely to benefit according to their risk/benefit profile.

Given the widespread use of drug eluting stents, which necessitates reliable and effective antiplatelet therapy to reduce the risk of stent thrombosis, prasugrel has made a timely entry into the cardiovascular therapeutic arena. There are basically two main issues.

First, prasugrel has been tested against clopidogrel in patients unselected with regard to clopidogrel responsiveness, however, its use might be mostly adequate in those patient acknowledged as ‘non-responders’ following platelet function testing. Of note, the approach of systematically assess the platelet function after dual antiplatelet therapy would imply a wider adoption of such tools and need further assessment of the exact timing of such tests, particularly in scenarios where the prompt administration of a thienopyridine is mandatory such as in the case of acute coronary syndromes.

From a practical point of view, a major issue would be the choice of the ‘gold-standard’ technique and the definition of a ‘cut-off’ in order to clearly define the condition of ‘non-responder’. However, it is conceivable that a single cut-off could oversimplify the platelet physiology in response to clopidogrel and therefore the presence of different ‘level of responsiveness’ might better depict the clinical scenario although possibly adding further complexity.

The historical ‘gold standard’ test is light transmittance aggregometry (turbidimetric) (LTA), which is based on the stimulation of platelet–platelet aggregation in platelet-rich plasma after stimulation with various agonists. Light transmittance aggregometry has been the most widely used technique to monitor the effects of antiplatelet agents, including aspirin, clopidogrel, other P2Y12 inhibitors and platelet glycoprotein IIb/IIIa inhibitors. Despite potential disadvantages such as the immediate processing, variable reproducibility, large required sample volumes, LTA has been the most widely investigated method to predict clinical outcomes. This method should be considered, according to the state of art, the one to be implemented in routine platelet testing.
However, recent data seem to question the clinical utility of the LTA even though these data assessed the clinical significance of the test in a different setting, i.e. proton pump inhibitor-thienopyridines interaction.53

Secondly, in order to thoughtfully direct the implementation of prasugrel it is necessary to define the inherent risk of bleeding. Several predictive models and scores have been proposed, including the CRUSADE bleeding risk score,54 the GRACE55 score, the REPLACE-2 risk score56 and more recently a score from the US National Cardiovascular Data Registry.57 Overall consistency among these scores has to be acknowledged with regard to the included variables however, the REPLACE-2 score has been developed and presented according to both clinical and procedural variables in patients undergoing PCI via the femoral approach treated with aspirin and clopidogrel (300 mg) thus it has a good overall applicability. Briefly, age, female gender, the use of intra aortic balloon pump, IIb/IIa, glomerular filtration rate, anaemia (defined as haematocrit <39 and 36% in men and women, respectively), and the use of low molecular-weight heparin <48 h before PCI have been included in the predictive model. The risk of bleeding has been then distinguished in very low (score 0), low (score 2–6), moderate (score 7–9) and high (score ≥ 10) which means a risk of 1, 1.5, 2.6 and 5.4%, respectively.56 Major exclusion criteria of the REPLACE-2 trial were acute myocardial infarction (MI), intervention on left main coronary artery, serum creatinine 4.0 mg/dl or dependence on dialysis, significant haemorrhagic risk (active internal bleeding or bleeding diathesis, surgery, trauma or gastrointestinal or genitourinary tract bleeding within six weeks), intracranial neoplasm or vascular malformation, prior intracranial bleeding and thrombocytopenia.57

The UK’s National Institute for Health and Clinical Excellence (NICE) acknowledged these issues related to prasugrel implementation in its provisional recommendations.58 Precisely, according to NICE guidelines, prasugrel in combination with aspirin has to be considered an option: (i) during primary PCI, (ii) when a definite stent thrombosis occurred during clopidogrel therapy and (iii) in diabetic patients. Moreover, beyond these conditions, in those patients receiving prasugrel following an acute coronary syndrome, the choice of continuing with the same drug is left to clinician discretion. As usual, NICE guidelines also dictate the way the drug is going to be reimbursed and they will definitely affect other countries in the European Union. This ‘restricted’ recommendation is mainly based on the fact that the TRITON-TIMI 38 trial45 did not tested prasugrel against preloaded clopidogrel that is currently standard practice. In patients admitted with ST elevation MI, there is not enough time for clopidogrel preloading to reach the steady-state effect therefore the indication sounds. The indication in those having a definite stent thrombosis is interesting because NICE guidelines clearly address the issue of clopidogrel non-responsiveness which is one of the main factors involved. As for diabetic patients, data from TRITON were robust enough to show a clear superiority of prasugrel over clopidogrel, and diabetes is another strong predictor of stent thrombosis.

Avenues for future research

Recently, it has been showed that a further 900 mg loading dose of clopidogrel in patients already on clopidogrel and undergoing a new cardiac catheterization might provide a better inhibition of residual platelet aggregation.59 In this specific setting, the comparison of prasugrel with such a further clopidogrel loading would be of clear interest.

Moreover, prasugrel administration might be successful in those patients requiring dual antiplatelet therapy with contraindication or intolerance to aspirin. The absence of concomitant aspirin administration might counterbalance the increased risk of bleeding due to prasugrel itself compared to clopidogrel. However, such a hypothesis requires objective data.

Under a practical perspective, the POPULAR study, comparing eight assays, showed that only LTA using 5 and 20 μm/l ADP and the Accumetrics Verify Now P2Y12 analyser could predict the composite of death, MI, stent thrombosis and stroke in patients undergoing PCI with stent implantation. This study fuelled great debate at the latest AHA meeting as, while presenting the survival curves, authors missed to show the same data after adjustment for confounders (age, diabetes, renal failure and so on), which provoked several doubts. After the recent presentation at the European Society of Cardiology congress of the PLATO trial results, Ticagrelor is expected to be part of the cardiovascular arena by the next year. It will be of great interest to compare those new agents.

Conclusion

Clopidogrel still plays a pivotal role among the cardiovascular drugs, however, time for newer and more effective agents has come. Future researches aiming at the best balance of ischemic protection
and bleeding risk will probably find the drug worth of its heritage.

Conflict of interest: None declared.

References


