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REVIEW

Prasugrel: Review of its Role in the Management of Arterial Coronary Thrombosis

Marek Postula[1,2] and Margaret M. Marczewski[3]

[1]1st Chair and Department of Cardiology, Central University Hospital, 1A Banacha St. 02-097 Warsaw, Poland. [2]Department of Experimental and Clinical Pharmacology, Medical University of Warsaw. [3]South Infirmary and Victoria University Hospital, Old Blackrock Road, Cork, Ireland.

Abstract: As aberrant platelet activation underlies intra-arterial thrombus formation, dual antiplatelet therapy- of aspirin and clopidogrel- has become a mainstay of treatment of acute coronary thrombosis. Two complementary yet independent mechanisms of blocking platelet activation and aggregation have proven to be clinically beneficial in preventing atherothrombotic complications, including myocardial infarction (MI), stroke, cardiovascular (CV) death, as well as stent-associated thrombosis. Nonetheless, the combination of aspirin and clopidogrel has its drawbacks, and recurrent atherothrombotic events occur in patients receiving this dual antiplatelet therapy. Of note is the phenomenon of so-called resistance, also known as hyporesponsiveness, to aspirin and/or clopidogrel, as this predisposes to recurrent cardiovascular events. Other limitations of clopidogrel include its modest level platelet inhibition, a wide variability in patient response and delayed onset of action. Prasugrel, which is a new member of the thienopyridine antiplatelet agents, is able to overcome these shortcomings of clopidogrel. It is 10 times more potent, has a rapid onset, and is not as influenced by drug interactions nor genetic polymorphisms of cytochrome enzymes; thus prasugrel results in a faster, higher and more consistent level of platelet inhibition. Clinically this translates into a reduction in thrombo-occlusive events, but also an increased bleeding risk. This paper reviews the available pharmacological and clinical data on prasugrel and clarifies the current place of prasugrel in the management of arterial coronary thrombosis.

Keywords: antiplatelet therapy, thienopyridine, $P2Y_{12}$ receptor, ADP receptor, prasugrel

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Introduction

Dual antiplatelet therapy, of aspirin with a thienopyridine, has become standard treatment for the prevention of ischemic events in patients with acute coronary syndromes (ACS) and the subset undergoing percutaneous coronary intervention (PCI). Clopidogrel has been the thienopyridine of choice in use, although the significant variability in patient response to the drug, its modest antiplatelet effect and delayed onset of action, have driven research for alternative options.[1–7] Prasugrel is a new addition to the thienopyridine class of antiplatelet agents, developed as a more potent option than clopidogrel in the treatment of arterial coronary thrombosis. By irreversibly inhibiting the platelet adenosine diphosphate (ADP) receptor, $P2Y_{12}$ subtype, both drugs prevent initial platelet activation and subsequent platelet aggregation, which are key steps in the pathophysiology of atherothrombotic diseases.[8] Prasugrel though, is more rapid and effective at inhibiting the ADP receptor, and there is evidence that this results in better prevention of thrombotic complications of ACS and PCI.[9,10] It also offers an alternative for patients with resistance to clopidogrel, who are at higher risk for ischemic complications.[11–14] Differences in metabolism from clopidogrel, allow prasugrel to achieve higher levels of its active metabolite, and not to be as influenced by genetic polymorphisms of cytochrome isoenzymes nor interactions with other drugs.[10,15–17] On the other hand, prasugrel's stronger inhibition of platelet function must be weighed against a higher risk of bleeding, particularly in certain vulnerable subgroups. Prasugrel brings new potential into the treatment of arterial coronary thrombosis, but warrants a closer look at its costs and benefits, to find an appropriate balance between efficacy and safety in clinical use.

Pharmacology

Prasugrel is a novel, third-generation oral thienopyridine that acts as a specific, irreversible antagonist of the platelet ADP $P2Y_{12}$ receptor. The thienopyridines are prodrugs requiring hepatic metabolism to their active form in order to exert their antiplatelet effect. The active metabolites bind irreversibly to the $P2Y_{12}$ purinregic receptor and inhibit ADP-induced platelet activation, plus subsequent aggregation, for the lifespan of the platelet. Although both clopidogrel and prasugrel require biotransformation, their differing metabolic pathways result in distinct pharmacologic profiles and clinically relevant differences (see Figure 1). A large portion of the administered dose of clopidogrel (85%) is metabolically inactivated by esterases, so only the remaining part (15%) can be converted into its active form through two cytochrome P450 (*CYP*)-dependent reactions.[18,19] In contrast, prasugrel is rapidly absorbed and metabolized, requiring

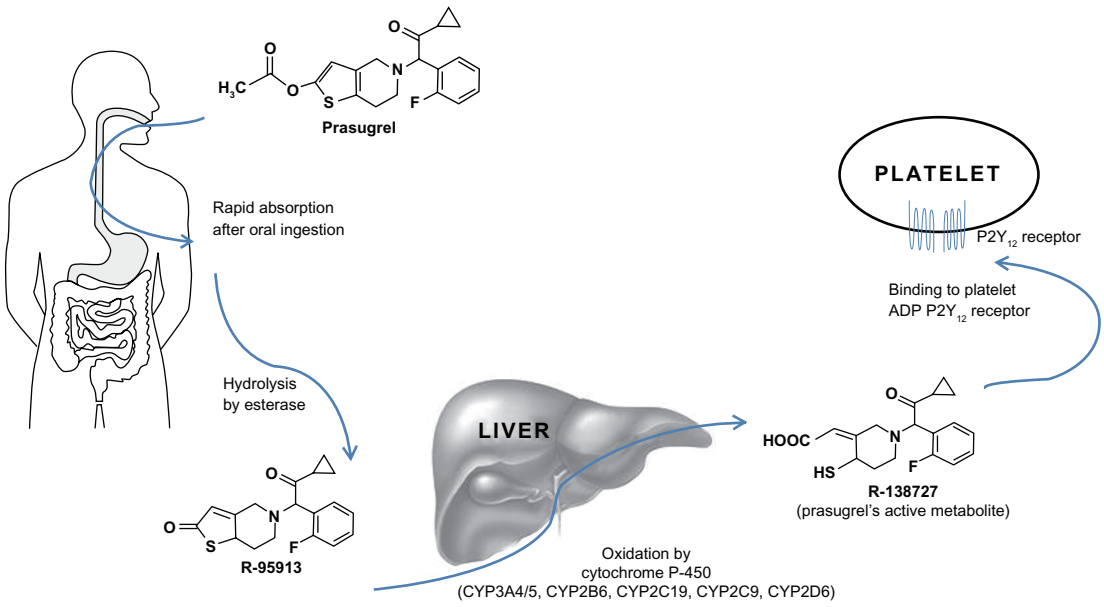

Figure 1. Metabolism of prasugrel and its mechanism of action.

Table 1. Comparison of clopidogrel and prasugrel with respect to pharmacologic properties and adverse effects.

Drug	Action	IPA to ADP	Route of administration	Metabolism	Time to peak effect	Offset of action	Adverse events, drawbacks
Clopidogrel 300 mg	IRR	~30%	Oral	Esterase inactivation, 2-step hepatic CYP-dependent activation	~4 hours	~5 days	Bleeding [major bleeding relative risk (95% CI) compared to placebo: 1.38 (1.13–1.67)],[1] interpatient variability
Prasugrel 60 mg	IRR	75%–80%	Oral	Esterase activation, 1-step CYP-dependent activation (liver or gut)	1–2 hours	~5 days	Bleeding [major bleeding relative risk (95% CI) compared to clopidogrel: 1.45 (1.15–1.83)][35]

Abbreviations: ADP, adenosine diphosphate; CYP, cytochrome P450; IPA, inhibition of platelet aggregation; IRR, irreversible.

only one *CYP*-dependent oxidative step to yield its active metabolite (R-138727).[20] This more efficient activation allows for a much quicker onset of action, a peak in concentration of the active metabolite 30 minutes after dosing, and more consistent and higher level platelet inhibition.[21,22] Thus prasugrel has approximately 10 times the potency of clopidogrel.[23] R-138727 is inactivated through S-methylation and 70% is excreted via renal mechanisms, with the mean elimination half-life of the active metabolite being 3.7 hours.[21,23]

The sequential cytochrome oxidation of clopidogrel involves *CYP3A4/5*, *CYP2C9*, *CYP1A2* in one step, and *CYP2B6* and *CYP2C19* in both steps.[19] Whereas the single oxidation in the formation of prasugrel's active metabolite could be mediated by any one of four CYP enzymes, mainly *CYP3A* and *CYP2B6*, with lesser contributions by *CYP2C9* and *CYP2C19*.[24] This choice of cytochrome involvement provides more flexibility and may explain why common polymorphisms of the metabolizing enzyme complex (cytochrome P450 2C19 isozyme, for example loss-of-function *CYP2C19* variants) barely interfere with the formation of prasugrel's active metabolite, even though they greatly affect clopidogrel.[16,25] The same reason could be behind interactions of other drugs with clopidogrel, whereas not with prasugrel.[26] For example, administration of proton pump inhibitors (PPIs) other than pantoprazole in patients after acute MI has been associated with a loss of clopidogrel's beneficial antiplatelet effect and an increased risk of reinfarction.[27] Also use of another common drug, atorvastatin, has been reported to interfere with clopidogrel activation,while not with prasugrel.[28,29] Whereas co-administration of potent *CYP3A* inhibitors such as ketoconazole, did not affect the overall exposure to prasugrel's active metabolite nor the associated pharmacodynamic response, which was not true with clopidogrel.[29] Rifampin, a *CYP3A4* inducer, and bupropion, a *CYP2B6* substrate, also did not result in clinically important drug interactions with prasugrel.[30] Thus aside from its favorable pharmacodynamics, prasugrel seems less susceptible than clopidogrel to interference of genetic polymorphisms (common functional CYP genetic variants) and drug-drug interactions.

Clinical Studies

Several randomized trials have evaluated the novel thienopyridine prasugrel (presented in Table 2), more are in progress or planned. **JUMBO-TIMI 26** (Joint Utilization of Medications to Block Platelets Optimally-Thrombolysis In Myocardial Infarction) was a phase 2, dose-ranging double-blind safety trial on 904 subjects that compared the bleeding risks of increasing prasugrel doses versus the standard ones of clopidogrel. Patients undergoing elective or urgent PCI with stents and receiving aspirin of 325 mg/day, were randomized

Table 2. Prasugrel: results of clinical trials.

Phase 2	JUMBO-TIMI 26[31]	904 patients for elective and urgent PCI	Dose ranging safety trial: prasugrel 40 mg LD + 7.5 mg MD, or 60 mg LD + 10 mg MD, or 60 mg LD + 15 mg MD, or clopidogrel 300 mg LD + 75 mg MD, on top of aspirin 325 mg daily; 30-day duration	Prasugrel 60 mg LD + 0 mg MD showed comparable TIMI major and minor bleeding to clopidogrel 300 mg LD + 75 mg MD; Trend towards decreased 30-day MACE
	PRINCIPLE-TIMI 44[32]	201 patients for elective PCI	Comparative pharmacodynamics: 60 mg LD +10 mg MD prasugrel vs. 600 mg LD + 150 mg MD clopidogrel; 30-day duration	Prasugrel demonstrated more rapid onset (<30 min) of higher IPA vs. clopidogrel both after LD and during maintenance phase
	SWAP[33]	139 patients with recent ACS	After 2 weeks of clopidogrel 75 mg daily, randomized to clopidogrel 75 mg MD, prasugrel 10 mg MD, or prasugrel 60 mg LD + 10 mg MD; treated for 13–15 days	Prasugrel with LD resulted in a rapid and sustained decrease in maximum platelet aggregation from 2 hours. Switching from clopidogrel to prasugrel MD was associated with reduced poor response rate, while prasugrel LD overcomes any poor response seen with clopidogrel
	ACAPULCO[34]	56 patients with UA/NSTEMI ACS	Crossover study: 900 mg LD of clopidogrel within 48 hours after UA/NSTEMI ACS symptoms, then either prasugrel 10 mg MD or clopidogrel 150 mg MD for 14 days then switch 14 days	Prasugrel MD significantly reduced the level of maximum platelet aggregation by 12.9% compared to the clopidogrel MD ($P < 0.001$)
	OPTIMUS-3[40,41]	35 CAD patients with t2DM	randomized to prasugrel 60 mg LD +10 mg MD or clopidogrel 600 mg LD + 150 mg MD for 1 week, with a 2 week washout period between study drugs	Significantly greater IPA with prasugrel was observed at 1 hr, 4 hr and 24 hr post LD and 7 days post-MD
Phase 3	TRITON-TIMI 38[35,49,50,54,55,57]	13,608 patients with ACS for PCI	randomized to 60 mg LD + 10 mg MD prasugrel or 300 mg LD + 75 mg MD clopidogrel, on top of aspirin; maximum duration 15 months	Superior efficacy for 60 mg LD + 10 mg MD prasugrel vs. 300 mg LD + 75 mg MD clopidogrel, with higher risk of bleeding

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; IPA, inhibition of platelet aggregation; LD, loading dose; MACE, major adverse cardiovascular events; MD, maintenance dose; MI, myocardial infarction; NSTEMI, non-ST elevation MI; PCI, percutaneous coronary intervention; STEMI, ST elevation MI; t2DM, type 2 diabetes mellitus; UA, unstable angina.

to either standard dosing with clopidogrel (loading dose [LD] 300 mg, maintenance dose [MD] 75 mg/d) or 1 of 3 prasugrel regimens (40 mg LD + 7.5 mg/d MD; 60 mg LD + 10 mg/d MD; 60 mg LD + 15 mg/d MD).[31] The LD was administered at the initiation of the PCI, and the MD was given subsequently for 30 days. The 30 day monitoring period showed prasugrel to have a comparable rate of TIMI (Thrombolysis In Myocardial Infarction) major bleeding (prasugrel 0.5% vs. clopidogrel 0.8%, $P = 0.54$), a more rapid onset of action and an insignificantly decreased rate of ischemic events. The primary end point (significant TIMI major or minor non-coronary artery bypass graft—related bleeding) was higher with prasugrel, but this did not achieve statistical significance (1.7% vs. 1.2%, $P = 0.59$). Of note, significantly lower rates of coronary target vessel thrombosis were seen in prasugrel-treated patients ($P < 0.024$).[31]

The subsequent phase 2 **PRINCPLE-TIMI 44** (Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction) trial included a 2 step crossover between prasugrel and high-dose clopidogrel after elective PCI. Its 201 patients were randomly assigned

to either prasugrel 60 mg or clopidogrel 600 mg 30 minutes before PCI, and then either to prasugrel 10 mg or clopidogrel 150 mg daily, with a crossover of therapy at 15 days. Its purpose was to provide information of the relative potency of prasugrel and clopidogrel on platelet function studies, as measured by ADP-stimulated inhibition of platelet aggregation (IPA). The IPA was shown to be significantly higher with prasugrel at all times, meaning after the loading dose (prasugrel mean IPA 74.8% ± 13.0% vs. clopidogrel 31.8% ± 21.2%, $P < 0.0001$), and in the course of the 28 day maintenance treatment (prasugrel mean IPA 61.3% ± 17.8% vs. clopidogrel 46.1% ± 21.3%, $P < 0.0001$), despite the use of the high-maintenance dose of clopidogrel.[32] Safety-wise, prasugrel was well-tolerated, with no TIMI major bleeding, 2 subjects (2%) experiencing a TIMI minor bleeding episode before the crossover, yet no subjects discontinuing therapy prematurely. Patients treated with prasugrel also had lower interpatient variability and fewer demonstrated hyporesponsiveness.[32] Thus PRINCIPLE-TIMI 44 presented data on the pharmacologic superiority of prasugrel, which provided rapid, high, consistent levels of inhibition of ADP-induced platelet aggregation, over higher-than-standard doses of clopidogrel.

Other smaller studies have investigated the pharmacodynamics of prasugrel versus clopidogrel. The SWitching Anti Platelet (**SWAP**) study on 100 patients with recent ACS investigated the effects of changing from the MD clopidogrel 75 mg/d to prasugrel of 10 mg/d, with or without a 60 mg LD. It showed such a switch to result in significantly lower platelet aggregation by one week, and in a subsequent analysis also significantly reduced the rate of thienopyridine poor responders.[33] Whereas the **ACAPULCO** study, another crossover study on 56 UA/NSTEMI (unstable angina/non-ST elevation MI) ACS patients, demonstrated prasugrel of 10 mg/d MD to provide greater platelet inhibition than clopidogrel both at 900 mg LD and 150 mg/d MD.[34]

After the favorable pharmacodynamic data on prasugrel, the phase 3 Trial to assess Improvement in Therapeutic Outcomes by optimizing platelet Inhibition with prasugrel Thrombolysis In Myocardial Infarction 38 (**TRITON-TIMI 38**), compared prasugrel to clopidogrel with respect to clinical outcomes. This was a larger scale clinical study of 13,608 moderate- to high- risk ACS patients scheduled for PCI, with a much longer duration of therapy (6 to 15 months, average duration 14.5 months). Patients were stratified according to presentation to those with moderate to high risk UA or NSTEMI (n = 10,074) and those with STEMI (ST-elevation MI) (n = 3,534), and on the background of aspirin, they were given either an intermediate dose of prasugrel (LD 60 mg, MD 10 mg/d) or clopidogrel LD 300 mg, MD 75 mg/d. The primary composite endpoint measured included death from cardiovascular (CV) causes, nonfatal MI, and nonfatal stroke, while the primary safety endpoints were TIMI life-threatening, major or minor bleeding not related to coronary artery bypass grafting (CABG).[35]

In the course of the 15 months' follow-up, prasugrel was consistently shown to be the more potent antiplatelet agent with a 19% relative risk reduction in the primary combined endpoint (clopidogrel 12.1% vs. prasugrel 9.9%, HR 0.81, $P < 0.001$), a trend shown to be significant since day 3 of treatment (clopidogrel 5.6% vs. prasugrel 4.7%, HR 0.82, $P = 0.01$), especially trumping clopidogrel with respect to preventing nonfatal MI events ($P < 0.001$). Looking at specific secondary endpoints, significant reductions were seen in the prasugrel group compared with the clopidogrel group in the rates of MI (9.5% vs. 7.3%, HR 0.76, 95% CI 0.67–0.85, $P < 0.001$), urgent target-vessel revascularization (3.7% vs. 2.5%, HR 0.66, 95% CI 0.54–0.81, $P < 0.001$), and stent thrombosis (2.4% vs. 1.1%, HR 0.48, 95% CI 0.36–0.64, $P < 0.001$), regardless of the stent type.[35]

At the same time, prasugrel showed a 30% greater relative risk of TIMI major bleeding (prasugrel 2.4% vs. clopidogrel 1.8%, HR 1.32, $P = 0.03$), including fatal hemorrhages (0.4% vs. 0.1%, $P = 0.002$).[35] There was also a significant difference in the discontinuation of treatment due to hemorrhagic adverse events (1.4% clopidogrel vs. 2.5% prasugrel, $P < 0.001$).[36] It is should also be noted that 0.1% of clopidogrel patients and 0.2% of prasugrel ones ($P = 0.03$) withdrew from the study because of colonic neoplasms.[35] Nonetheless, calculation of a net clinical benefit (as measured by the composite endpoint of death from any cause, nonfatal MI, nonfatal stroke, and non-CABG related nonfatal TIMI major bleed) was in favor of prasugrel in the overall trial population (prasugrel 12.2% vs. clopidogrel 13.9%, HR 0.87, $P = 0.004$).[35]

The benefits of prasugrel's potent antiplatelet action as well as its costs in bleeding risk, varied

according to specific subpopulations. The benefits of preventing ischemic events were most evident in **diabetics** (n = 3,146), who demonstrated a 30% relative risk reduction in the primary endpoint (clopidogrel 17.0% vs. prasugrel 12.2%, HR = 0.70, $P < 0.001$) without any differences in major bleedings.[35] **Elderly patients** (≥75 years of age) and **low-weight patients** (<60 kg) did not experience a net clinical benefit nor harm, while those with prior history of transient ischemic attack (TIA) or stroke experienced net clinical harm with prasugrel, exhibiting a significant trend toward major bleeding.[35] This will be further discussed in subsequent sections.

Several studies have or plan on examining the use of prasugrel versus clopidogrel in specific subgroups within the ACS population. **TRIGGER-PCI** is focusing on patients with high platelet reactivity on clopidogrel and after successful implantation of coronary drug-eluting stents. It has a 3-fold purpose: to assess the efficacy in decreasing adverse cardiovascular outcomes, the safety profile, and the inhibition of platelet activation.[37] The phase 3 **TRILOGY ACS** (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) is exploring the safety and efficacy of prasugrel in UA/NSTEMI patients who are to be medically managed without planned revascularization (i.e. without PCI).[38] It is presently recruiting participants and should be completed in October 2011. **ACCOAST** is also investigating the NSTEMI subgroup, but with respect to potential risks/benefits of pretreatment with prasugrel before scheduled PCI.[39] **OPTIMUS-3** (Third Optimizing Anti-Platelet Therapy in Diabetes MellitUS) compared platelet function under prasugrel versus high-dose clopidogrel treatment (600 mg LD, 150 mg/d MD) of drug-treated type 2 Diabetes Mellitus subjects with coronary artery disease (CAD).[40,41] Another study will investigate prasugrel in Asian subjects.[42] Taking that one step further, the genotype-guided **GeCCO** trial will focus on the ACS patients identified as *CYP2C19* extensive metabolizers and their response to prasugrel versus clopidogrel.[43]

Other trials are planned with specific purposes. As TRITON-TIMI 38 suggested benefits in 15 months of treatment, the phase 4 Dual Antiplatelet Therapy (**DAPT**) study will investigate the appropriate duration of dual antiplatelet therapy (12 vs. 30 months of aspirin plus a $P2Y_{12}$ antagonist- prasugrel or clopidogrel) in patients after PCI and stent implantation.[44] Another study will continue the exploration of drug-interactions with PPIs, as there have been reports of these drugs decreasing clopidogrel's effectiveness and being associated with poorer clinical outcomes.[26,27,45] The findings of this phase 2 observational study comparing prasugrel to clopidogrel could be very meaningful, as high risk ACS patients often require concomitant use of a PPI.

Safety

As with other antiplatelet agents, in evaluating prasugrel's efficacy, its safety profile- particularly the bleeding risk- must be taken into consideration. The **JUMBO-TIMI 26** study concluded prasugrel and clopidogrel to have comparable rates of significant bleeding as part of dual antiplatelet therapy with aspirin.[31] Yet this was on the basis of a mere 30 day follow-up, and the highest tested dose of prasugrel (LD 60 mg, MD 15 mg/d) did result in a higher rate of bleeding. Thus, in subsequent trials, an intermediate dose of prasugrel (LD 60 mg, MD 10 mg/d) was used. The **PRINCPLE-TIMI 44** also did not note any increase with prasugrel of TIMI major bleeding, but this could be due to its small number of patients and similarly short duration (30 days).[32]

As described above, the larger and longer **TRITON-TIMI 38** study did find a 30% increase in TIMI major bleeding events with prasugrel in the overall study population.[35] A *post hoc* subgroup analysis determined 3 subgroups of patients as particularly prone to serious bleeding: **the elderly** (age ≥ 75 years), **the underweight** (body mass < 60 kg) and **patients with a previous stroke or TIA**.[35] The latter subgroup, albeit small, was especially at risk of intracranial hemorrhage (2.3% vs. 0%, $P = 0.02$) and thus prasugrel would be best avoided. This is in stark contrast to clopidogrel, to which polyvascular disease patients manifest positive results.[46] Whereas patients with a history of cerebrovascular events demonstrated net harm with prasugrel, the other two vulnerable patient groups lacked net clinical benefit with the drug. In the underweight, a plausible mitigation strategy suggested by the TRITON researchers would be to use a lowered dosage of prasugrel (MD of 5 mg/d versus the usual 10 mg/d), although this has yet to be investigated in terms of safety and efficacy. While

patients 75 years of age or older in general should not be given prasugrel, unless they are at high risk because of diabetes or previous MI.[35]

The TRITON-TIMI 38 subjects were having planned PCI, but a small number (1%) underwent **CABG** surgery, because either PCI could not be performed or had been unsuccessful. Among this group, the rate of major bleeding with prasugrel was more than four times that of the clopidogrel group (13.4% vs. 3.2%, OR 4.73, $P < 0.001$).[35] Such straightforward results speak against the use of prasugrel in the initial management of patients with ACS, before the exact coronary anatomy is known and subsequent steps planned (medical treatment, PCI or cardiosurgery). This also raises questions about prasugrel's safety in patients undergoing other types of surgery and underscores the need to withdraw the drug a minimum of 1 week beforehand.

In the TRITON-TIMI 38 trial there was also an unexpected finding of excess newly-diagnosed **neoplasms** reported in the prasugrel study group (1.6% vs. 1.2% in the clopidogrel group). Although this had marginal statistical support, such a link would have profound implications, so the United States Food and Drug Administration (FDA) asked for further investigation.[35,47] Direct carcinogenicity of prasugrel was deemed unlikely, based upon negative findings of animal studies and the brief duration of TRITON. The FDA did then consider the possibility that prasugrel could stimulate existing tumors. Negative results of tumor-progression studies undertaken by the sponsor were enough to rule this out. Thus the FDA team supposed the cancer link could be a false positive finding but required the sponsors to collect further data on this post-approval.[47] Nonetheless this issue already prompted some to hypothesize about the possible link between antiplatelet agents and cancer.[48]

Efficacy

As with the more thorough and reliable safety data, the principle clinical evidence for prasugrel's effectiveness comes from the TRITON-TIMI 38 trial. The major findings of prasugrel's benefits have been presented above. Several subgroup analyses have been performed on this large data set, to better describe prasugrel's efficacy and to identify patients who best benefit from prasugrel. One revealed that the significant reductions in ischemic events with prasugrel treatment occurred early and were sustained, indicating a benefit in both the LD phase as well as the MD phase.[49] This long-term (15 month) improvement in clinical outcomes raises the issue of the appropriate duration for antiplatelet therapy after ACS. Another analysis showed in addition to preventing a larger number of first events (CV death, MI or stroke), prasugrel also prevented more subsequent events (clopidogrel 896 vs. prasugrel 701, RR for prasugrel 0.79%, $P < 0.001$).[50] Overall, both these analyses underscore the importance and benefit of continued therapy that achieves more-potent platelet inhibition, even after an initial event has occurred.

The ACS subpopulation with **diabetes mellitus** (DM), being at higher risk of recurrent atherothrombotic events, warranted a separate analysis. Diabetic patients have been shown to have enhanced platelet reactivity, and also a decreased response to treatment with clopidogrel.[51–53] Such a response could place these patients at greater risk of adverse cardiovascular events, therefore this high-risk patient subset might benefit from more intensive antiplatelet therapy.[14] Another look at the TRITON-TIMI 38 data with respect to diabetes status showed the reduction by prasugrel of the composite of CV death, MI and stroke noted in non-diabetic subjects (n = 10,462, 9.2% vs. 10.6%, $P = 0.02$), was even more significant in those with DM (n = 3,146, 12.2% vs. 17.0%, $P < 0.001$), especially those treated with insulin (n = 776, 14.3% vs. 22.2%, $P = 0.009$). Importantly, the reduction in ischemic events with prasugrel in DM patients was achieved without an increase in TIMI major bleeding (2.6% with clopidogrel vs. 2.5% with prasugrel, $P = 0.81$). In fact, diabetics were the subgroup to benefit the most from prasugrel in this study, having a 40% reduction rate in MIs with prasugrel therapy, and a marked decrease in stent thrombosis, as high as 69% in insulin-treated diabetics. This overall benefit could be represented as the number needed to treat (NNT) with prasugrel to prevent one primary endpoint event among patients with DM being 21, compared with a NNT of 71 among those without DM.[54] These clinical results were also substantiated through a pharmacodynamic study (OPTIMUS-3), which showed prasugrel (60 mg LD + 10 mg MD) to be associated with significantly greater inhibition of platelet function than clopidogrel (600 mg LD + 150 mg MD) in CAD patients with type 2 DM.[41]

An additional analysis was also performed on the **STEMI** subgroup of TRITON-TIMI 38. In this most serious subset of ACS patients (n = 3,534), the primary endpoint of CV death, nonfatal MI or nonfatal stroke was significantly reduced with prasugrel at 30 days (RRR = 32%, $P = 0.002$) as well as at 15 months (RRR = 21%, $P = 0.02$).[55] Over 15 months, prasugrel resulted in a 42% relative reduction in definite/probable stent thrombosis (1.6 vs. 2.8%, HR: 0.58, $P = 0.02$). Importantly, there was no difference observed between prasugrel and clopidogrel in the incidence of TIMI major non-CABG-related bleeding patients (2.4 vs. 2.1%, HR: 1.11, $P = 0.65$), life-threatening bleeding ($P = 0.75$) nor intracranial hemorrhage.[55]

Inadequate IPA has been identified as one of the predictors of stent thrombosis.[56] Hence in evaluating prasugrel's efficacy, one later analysis looked more in depth at **stent thrombosis** in TRITON-TIMI 38 patients. It considered the 95% of patients who received at least one coronary artery stent during the index hospitalization (n = 12,844), whether a drug-eluting stent (n = 5,743) or a bare-metal one (n = 6,461).[57] This analysis demonstrated that compared to the approved dose of clopidogrel, prasugrel reduced the rate of stent thrombosis by 52% ($P < 0.001$). Such a reduction was seen across all analyzed subgroups- of different age, sex, ACS presentation, diabetes status, glycoprotein IIb/IIIa use. Patients at higher risk for stent thrombosis, such as those with longer stents, bifurcation stents, impaired kidney function and diabetes, showed the greatest absolute benefits. The reductions by prasugrel were similar when the LD was administered before PCI (0.83% vs. 2.23%, $P = 0.002$) or after the procedure started (1.24% vs. 2.39%, $P < 0.0001$). Lastly, both early (<30 days: 1.56% vs. 0.64%, $P < 0.001$) and late (>30 days: 0.82% vs. 0.49%, $P = 0.035$) stent thrombosis was reduced by prasugrel, in ACS patients treated with either bare-metal or drug-eluting stents.[57] An analysis of patients at increased risk of stent thrombosis, such as diabetic and STEMI patients, found no increased bleeding risk with prasugrel.

All of the aforementioned analyses considered subgroups within TRITON-TIMI 38 in whom the beneficial effects of prasugrel were more evident than the bleeding risk. Yet in evaluating the efficacy of prasugrel over clopidogrel, it is important to note the dispute about the clopidogrel dose used in TRITON-TIMI 38. Many interventional cardiologists currently use a 600 mg LD of clopidogrel, twice the regimen used in TRITON, to significantly reduce the risk of periprocedural MI without an increased bleeding risk.[58] This may be a valid criticism, although clopidogrel is still registered for the 300 mg LD. The authors of TRITON retort that higher doses of clopidogrel used in the PRINCIPLE-TIMI 44 and ACAPULCO trials (600 mg and 900 mg LDs respectively) still provided inferior platelet inhibition to prasugrel.[32,55]

Patient Preference

The above clinical data demonstrate prasugrel to be especially beneficial in persons at high-risk of thrombo-occlusive events: diabetic patients, those with STEMI, as well as patients receiving stents during PCI. Another potential target group could be the ACS patients with reduced clopidogrel responsiveness. **Clopidogrel nonresponders** have been found in high proportions among patients undergoing elective PCI (24% with clopidgorel 300 mg, 11% with clopidogrel 600 mg) and those with acute MI.[59–62] Such a decreased responsiveness could be due to the presence of *CYP 2C19* reduced-function alleles. This genetic variant has been associated with an increased death rate from CV causes, MI, or stroke, and three-fold greater rate of stent thrombosis.[25,63] On the other hand, since these common polymorphisms of *CYP* enzymes do not affect prasugrel, this drug may be an effective alternative for clopidogrel non-responders.[16] The utility of prasugrel in various variants of *CYP 2C19* may be elucidated by the GeCCO trial that is still ongoing.[43]

Place in Therapy

Prasugrel was approved by the United States FDA on July 10, 2009, after 18 months of deliberations. Although many safety issues were tackled, in the end prasugrel was registered for the reduction of thrombotic cardiovascular events in ACS patients undergoing PCI. In assessing the costs and benefits of prasugrel, presented mainly in the TRITON-TIMI 38 trial, the FDA review team reasoned that the benefit of preventing irreversible tissue damage is generally worth the risk of transient and potentially-reversible bleeding events.[47] The bleeding events with serious con-

sequences, that would lead to irreversible harm (ex. intracranial hemorrhage), had been included in the primary end point, which was reduced by prasugrel. The FDA did require a boxed warning emphasizing the increased risk for patients 75 years of age or older and patients undergoing urgent CABG. In order to provide potential treatment for uncontrolled bleeding resulting from treatment with the drug, the manufacturer is also required to investigate the ability of platelet transfusion to reverse prasugrel-induced platelet inhibition.[47]

In the wake of FDA's approval of prasugrel, in October 2009 the United Kingdom's National Institute for Health and Clinical Excellence (NICE), issued its own guidelines. These recommend prasugrel in combination with aspirin in 3 specific but sizeable subgroups of ACS patients having PCI: those undergoing immediate primary PCI for STEMI, those who had stent thrombosis during clopidogrel treatment, as well as patients with DM.[64]

On the basis of FDA's approval, in mid-November 2009, the American College of Cardiology, the American Heart Association, and the Society for Cardiovascular Angiography and Interventions released updated joint guidelines for the use of prasugrel in STEMI and PCI (as summarized in Table 3). These guidelines do not explicitly endorse one thienopyridine over the other. They do allow for a 60 mg LD of prasugrel to be given in primary PCI, and in secondary PCI once the coronary anatomy is known. The MD of 10 mg can then be continued for 12 months or beyond 15 months if a drug-eluting stent is in place. The guidelines reiterate the need to stop prasugrel at least 7 days before CABG, that prasugrel should not be used in STEMI patients with a history of stroke and TIA, nor in patients ≥75 years old, unless they are high risk (diabetics, prior MI). Also mentioned is the need to lower the MD of prasugrel to 5 mg in patients weighing <60 kg. Overall, the guidelines leave the decision of which thienopyridine to use to physicians who may better evaluate the appropriate course of action for individual patients.[65]

Conclusions

Prudent use of antiplatelet therapy requires balancing the prevention of thrombo-occlusive events with increased bleeding risk. The newly approved prasugrel, being a more potent inhibitor of the $P2Y_{12}$ purinergic receptor, interferes both with pathological thrombus formation as well as the normal adaptive hemostatic response. Since it overcomes many of the limitations of clopidogrel- with less interpatient variability, stronger antiplatelet activity and faster onset of action- it has already found support for clinical use. The benefits of its potent and rapid action are most evident in patients at high risk of thrombo-occulsive events, i.e. diabetics, those undergoing PCI for STEMI, patients at risk of stent thrombosis or after one. Yet because the clinical data supporting the use of prasugrel originates mainly from one large trial (TRITON-TIMI 38), the drug has been approved for use in limited circumstances. Although some early studies are promising, the results of ongo-

Table 3. Antiplatelet therapy recommendations for patients with ST-elevation myocardial infarction (summary).

2009 AHA/ACC recommendations	Class
Prasugrel 60 mg should be given as soon as possible for primary PCI	IB
If the patient did not receive fibrinolytic therapy, either a loading dose of 300 to 600 mg of clopidogrel should be given or, once the coronary anatomy is known and PCI is planned, a loading dose of 60 mg of prasugrel should be given promptly and no later than 1 hour after the PCI	IB
In patients taking a thienopyridine in whom CABG the period of withdrawal should be at least 7 days in patients receiving prasugrel	IC
In patients receiving a stent (BMS or DES) during PCI for ACS, prasugrel 10 mg daily should be given for at least 12 months	IB
Continuation of prasugrel beyond 15 months may be considered in patients undergoing DES placement	IIbC
In STEMI patients with a prior history of stroke and transient ischemic attack for whom primary PCI is planned, prasugrel is not recommended as part of a dual-antiplatelet therapy regimen	IIIC

Abbreviations: ACS, acute coronary syndrome; BMS, bare metal stent; CABG, coronary artery bypass grafting; DES, drug-eluting stent; PCI, percutaneous coronary intervention.

ing trials are needed to support an expanded role of prasugrel in the medical management of ACS, in treating patients taking PPIs, or patients with genetic variants associated with clopidogrel nonresponsiveness. In the end, the choice of thienopyridine to be used should be left to the discretion of physicians, who based upon their own experience and knowledge of their patients, may select the most appropriate antiplatelet therapy for the prevention of arterial coronary thrombosis.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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