

Oral antiplatelet therapy in diabetes mellitus and the role of prasugrel: an overview

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Abstract: Diabetics have a prothrombotic state that includes increased platelet reactivity. This contributes to the less favorable clinical outcomes observed in diabetics experiencing acute coronary syndromes as well as stable coronary artery disease. Many diabetics are relatively resistant to or have insufficient response to several antithrombotic agents. In the setting of percutaneous coronary intervention, hyporesponsiveness to clopidogrel is particularly common among diabetics. Several strategies have been examined to further enhance the benefits of oral antiplatelet therapy in diabetics. These include increasing the dose of clopidogrel, triple antiplatelet therapy with cilostazol, and new agents such as prasugrel. The large TRITON TIMI 38 randomized trial compared clopidogrel to prasugrel in the setting of percutaneous coronary intervention for acute coronary syndromes. The diabetic subgroup (n = 3146) experienced considerable incremental benefit with a 4.8% reduction in cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke at 15-month follow-up with prasugrel treatment. Among diabetics on insulin this combined endpoint was reduced by 7.9% at 15 months. Major bleeding was not increased in the diabetic subgroup. This confirms the general hypothesis that more potent oral antiplatelet therapy can partially overcome the prothrombotic milieu and safely improve important clinical outcomes in diabetics.

Keywords: percutaneous coronary intervention, acute coronary syndromes, diabetes mellitus, prasugrel, antithrombotic agents

Scope of the problem

The prevalence of diabetes mellitus in individuals with coronary artery disease is estimated to be 14.8% in developed countries. Among those presenting with acute coronary syndromes or undergoing percutaneous coronary intervention (PCI), the prevalence of diabetes mellitus is estimated at 30% and 26%, respectively.^{1,2} Similarly, the prevalence of diabetes mellitus among patients undergoing coronary artery bypass graft surgery in the United States between 1990 to 2000 was estimated at 30% in the Society for Thoracic Surgeons registry.³

Often aptly referred to as the “diabetes disadvantage,” diabetics have inferior outcomes compared to non-diabetics across the spectrum of cardiovascular presentations and procedures. For example, after adjusting for other baseline and treatment differences in the pooled Thrombolysis In Myocardial Infarction (TIMI) trials from 1997 to 2006, diabetes independently and significantly conferred a 78% increased risk of 30-day mortality in unstable angina (UA)/non-ST-segment myocardial infarction (NSTEMI) patients and a 40% increased 30-day mortality in those with STEMI. At 1 year, the excess mortality risk independently attributed to

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diabetes was 65% and 22%, respectively for UA/NSTEMI and STEMI.⁴ In the PCI arena, multiple reports have noted significantly higher rates of stent thrombosis among diabetics, even after adjusting for vessel diameter and implanted stent length. In the large multicenter EVASTENT registry of largely on-label sirolimus eluting stent use, the rate of drug-eluting stent thrombosis was 4.3% among diabetics (vs 3.0% in nondiabetics) with multivessel disease and 3.2% (vs 1.7% in nondiabetics) with single vessel disease at 1-year follow-up.⁵ Among diabetics, insulin-requiring diabetes was an additional independent risk factor for stent thrombosis.

Vascular pathophysiology in diabetes mellitus

In addition to a greater burden of atherosclerotic disease and more co-morbidities, diabetics have a prothrombotic state. Multiple factors have been either demonstrated or hypothesized to have a causative role in the etiology of this greater thrombotic risk. These include endothelial dysfunction, impaired coagulation function, depressed fibrinolysis, and impaired platelet function.^{6–8}

The endothelium of diabetics has increased “stickiness”, likely from greater expression of adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1), decreased nitric oxide (NO) generation, and increased interaction between the endothelium and inflammatory leukocytes.⁹ Greater oxidative stress in diabetes results in induction of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), a rapid response transcription factor that regulates the inflammatory immune response to numerous noxious stimuli.¹⁰ Decreased NO elaboration and increased production of the potent vasoconstrictor endothelin-1 (ET-1) impair normal vasodilatation.^{11,12} These mechanisms likely

account for the impaired endothelium-dependent dilation of the brachial artery observed in diabetics.^{13,14}

Diabetics have been documented to have higher levels of fibrinogen, von Willebrand factor (vWF), factor VII, factor VIII, and thrombin generation.^{15,16} Counter regulatory levels of antithrombin III and sulfated heparins are also lower. Similarly, diabetics have been documented to have lower levels of tissue plasminogen activator (t-PA) as well as elevated plasma levels of plasminogen activator inhibitor-1 (PAI-1) and α -2 antiplasmin, likely accounting for the observation of relatively impaired endogenous fibrinolysis.^{17–19}

Platelet dysfunction in diabetics leads to hyper-responsiveness to platelet agonists and subsequent increases in pathological platelet activation and aggregation (Table 1).^{8,20} In a study of 257 diabetics with coronary artery disease (CAD) compared to 565 nondiabetics with CAD, Serebruany et al measured significantly higher baseline aggregatory response to the agonists adenosine diphosphate (ADP) and collagen by light transmittance aggregometry, the Ultegra Rapid Platelet Function Analyzer, and the Siemens PFA-100 analyzer.²¹ Diabetics have greater expression of platelet and endothelial cell adhesion molecules such as platelet endothelial cell adhesion molecule-1 (PECAM-1) and VCAM-1.²² Diabetics have higher levels of GP IIb/IIIa antigen and activity. Diabetics have more vitronectin receptors and intact epitope of the protease-activated receptor-1 (PAR-1) thrombin receptor. Diabetics have higher plasma levels of the soluble 100-kD P-selectin fragment and P-selectin upregulation and expression on platelets, indicating a higher baseline state of platelet activation.^{23,24} Soluble CD40 ligand levels are also elevated in diabetics. Activated platelets express and release CD40 ligand which induces endothelial cells to secrete chemokines and to express adhesion molecules that recruit leukocytes, causing inflammation of the vessel wall.²⁵

Table 1 Platelet abnormalities seen in diabetics⁸

- Increased thromboxane A2 production
- Increased platelet activation due to increased surface adhesion molecules expression (CD31, CD62P, CD63) vitronectin receptors and intact epitope of the PAR-1 thrombin receptor
- Increased expression of platelet and endothelial cell adhesion molecules (PECAM-1 and VCAM)
- Increased expression of platelet surface receptors (P-selectin, GP Ib, GP IIb/IIIa)
- Increased platelet mediated thrombin generation
- Increased platelet hypersensitivity to agonists (ADP, collagen, thrombin, platelet activating factor)
- Decreased platelet sensitivity to PGI2 and nitric oxide
- Reduced endothelial synthesis of PGI2 and nitric oxide
- Accelerated thrombopoiesis or platelet turnover resulting in generation of fresh and hyper reactive platelets
- Increase production of proinflammatory and proatherogenic cytokines and chemokines (platelet factor 4, interleukin 1 β , CD40 L)
- Abnormal platelet calcium and magnesium homeostasis resulting in platelet hyperactivity, hyperaggregability, and adhesiveness

Accelerated platelet turnover may also occur in diabetics with vascular disease.²⁶ These new platelets entering the circulation may diminish the effectiveness of some agents such as aspirin.

Reading almost like a laundry list, the diabetic's vascular pathophysiology is admittedly complex and not fully elucidated. While all the precise inter-relationships and their relative importance are uncertain, the distribution of numerous important parameters of endothelial and thrombotic function and control in diabetics is dissimilar to the nondiabetic norm. From a clinical perspective, the multifactorial nature of this dysregulation helps explain the less optimal outcomes (diabetes disadvantage) we observe in our practices. It also emphasizes that the outcomes in diabetics, as demonstrated in TRITON TIMI 38 with prasugrel, are more contingent upon optimal antiplatelet and antithrombin therapy.

Given this prothrombotic state and increased baseline risk, randomized trials and meta-analyses have generally documented greater absolute benefit from both oral and parenteral antiplatelet therapy in diabetic patients with acute coronary syndromes compared to nondiabetics. Our currently available oral agents with significant antiplatelet activity are aspirin, ticlopidine, clopidogrel, and cilostazol. Prasugrel, a potent third-generation thienopyridine, has recently been added to our therapeutic options. The additional agents ticagrelor, elinogrel, and cangrelor as well as oral thrombin receptor antagonists will likely be approved for non-experimental use in the coming years. A brief review of the efficacy and limitations of existing agents delineates the need for more consistently effective agents.

Aspirin for primary and secondary prevention in diabetics

Aspirin irreversibly inhibits the COX₁ enzyme needed for the production of TXA₂ thus reducing platelet aggregation. Aspirin has not been proven to be beneficial for primary prevention of cardiovascular events in diabetics without other risk factors (perhaps because of inadequately powered trials).^{27,28} In contrast, the role of oral antiplatelet therapy for secondary prevention in diabetics with a history of atherothrombotic events is firmly established. The antiplatelet trialists collaborative individual patient data meta-analysis demonstrated a reduction of 38 ± 12 (SD) events per 1000 high-risk diabetics (history of myocardial infarction [MI], UA, cerebrovascular accident [CVA], or transient ischemic attack [TIA]) treated with an antiplatelet agent, mostly aspirin ($P < 0.002$).²⁹

Clopidogrel for secondary prevention in diabetes

Inhibiting the platelet P2Y₁₂ receptor also reduces platelet activation and aggregation. In the CAPRIE trial that compared the second-generation thienopyridine clopidogrel to aspirin therapy in patients with recent ischemic stroke, recent MI, or established peripheral arterial disease, clopidogrel reduced the 1-year ischemic events compared to aspirin from 12.7% to 11.8% ($P = 0.096$) and from 17.7% to 15.6% in a subgroup of 3866 patients with diabetes mellitus ($P = 0.042$).^{30,31} In the PLUTO diabetes trial, 1 month treatment with aspirin and clopidogrel provided greater platelet inhibition as measured by various platelet function tests compared with treatment with aspirin alone.³² In the landmark CURE trial, acute coronary syndrome patients without ST elevation were randomized to clopidogrel vs placebo superimposed on background aspirin therapy. 2849 of the 12,562 patients enrolled in CURE were diabetic. The diabetic subgroup had a 1-year event rate (cardiovascular death, MI, CVA) of 14.2% with dual antiplatelet therapy compared to 16.75% with aspirin monotherapy.³³ Although this reduction in events in the diabetic subgroup alone did not quite reach statistical significance, the point estimate of benefit was greater among diabetics than nondiabetics. The absolute 1% increase in major bleeding to 3.7% with dual antiplatelet therapy vs 2.7% with aspirin alone (relative risk [RR] 1.38, 95% CI 1.13 to 1.67, $P = 0.001$) should be assumed to apply to the diabetic subgroup as well.

In all, 7 large scale trials have evaluated dual antiplatelet therapy with clopidogrel and aspirin vs monotherapy with either clopidogrel or aspirin alone. Mostly secondary prevention trials except for the multiple-risk-factor group in CHARISMA, the clinical indications have ranged from acute coronary syndromes (ACS) to peripheral vascular and cerebrovascular diseases. A substantial portion of the enrolled patients were diabetic. Where reported, the outcomes for diabetics vs nondiabetics by treatment strategy are outlined in Table 2.

Glycoprotein inhibitor use in diabetics

Although not directly inhibiting platelet activation, the familiar glycoprotein IIb/IIIa receptor antagonists like abciximab, eptifibatide, and tirofiban markedly reduce platelet aggregation by preventing cross-linking between activated platelets. Blocking the IIb/IIIa receptors prevents binding to vWF and fibrin. A meta-analysis of the randomized trials of IIb/IIIa agents vs placebo in non-STE ACS demonstrated

Table 2 Summary of randomized controlled trials of therapy with aspirin and Plavix®

Trial	Design	Patient population	Follow up	Therapy	Results
CURE ³³	ACS ^a	12562 pts (DM + 22.8%) (DM + 22.4%)	9 mo	Placebo Id, placebo Plavix load, Plavix ASA was given to both groups	Mi, stroke or CV death 11.4% ($P < 0.001$); 16.7% ^c (DM+); 9.9% (DM-) 9.3%; 14.2% ^c (DM+); 7.9% (DM-)
PCI-CURE ⁷²	ACS ^a + PCI	2658 pts (DM + 19%) (DM + 19%)	8 mo	Placebo Id, ADP antagonist ^b , placebo Plavix Id, ADP antagonist ^b , Plavix ASA was given to both groups	CV death, MI 8% ($P = 0.047$); 16.5% ^c (DM+); 11.7% (DM-) 6%; 12.9% ^c (DM+); 7.9% (DM-)
CREDO ⁷³	PCI (elective or high likelihood)	2116 pts (DM + 25.4%) (DM + 27.5%)	12 mo	Placebo Id, Plavix (28 d), Placebo (29 d–12 mo) Plavix Id, Plavix (28 d), Plavix (29 d–12 mo) ASA was given to both groups	Death, MI or stroke 11.5% ($P = 0.02$) RRR = 26.9% 8.5%
COMMIT ⁷⁴	Suspected acute MI	45852 pts DM not defined	28 d	Placebo + ASA (162 mg) Plavix + ASA (162 mg)	Death, reinfarction, stroke 10.1% ($P = 0.002$) 9.2%
CHARISMA ⁷⁵	Cardiovascular disease or multiple risk factors	15603 pts (DM + 41.7%) (DM + 42.3%)	28 mo	ASA _(75–162 mg) + Placebo ASA _(75–162 mg) + Plavix	CV death, MI or stroke 7.3% ^c overall; 7.9% CV+ ($P = 0.046$) 6.8% ^c overall; 6.9% CV+ no difference by DM for overall
CHARISMA subanalysis ⁷⁶	Prior MI, ischemic stroke, or symptomatic PAD	9478 pts (DM + 31.3%) (DM + 30.8%)		ASA _(75–162 mg) + Placebo ASA _(75–162 mg) + Plavix	CV death, MI, or stroke 8.8% ($P = 0.01$) 7.3%
CARESS ⁷⁷	Symptomatic ≥50% carotid stenosis	107 pts (DM + 32.1%) (DM + 31.4%)	7 d	Placebo + ASA Plavix load, Plavix (7 d) + ASA	Microembolic signals 72.7% ($P = 0.005$) 43.8%
MATCH ⁷⁸	Ischemic stroke or TIA + at least 1 vascular risk factor	7599 pts (DM + 68%) (DM + 68%)	18 mo	Plavix + Placebo Plavix + ASA _(75 mg)	Vascular death, MI, ischemic stroke, rehospitalization 16.8% ^c (DM+); 16.5% (DM-) 15.1% ^c (DM+); 17.0 (DM-)-th groups

^aNon-STEMI ACS; ^bPretreatment with Plavix® or placebo plus aspirin for 10 days prior PCI. Post PCI > 80% of patients in both groups received either Plavix® or ticlopidine for 4 weeks and then placebo or Plavix® for 8 months; ^c $P = ns$ or confidence interval crosses zero (for subgroup analysis).

Abbreviations: ADP, adenosine diphosphate; ASA, aspirin; ACS, acute coronary syndromes; d, days; DM, diabetes mellitus; Id, load; PCI, percutaneous coronary intervention; MI, myocardial infarction; mo, months; PAD, peripheral artery disease; RRR, relative risk; TIA, transient ischemic attack.

a 30-day mortality reduction from 6.2% with placebo to 4.6% with IIb/IIIa agents at 30 days in the 6458 diabetes patients enrolled in PRISM, PRISM-PLUS, PARAGON A, PARAGON B, PURSUIT, and GUSTO IV (odds ratio [OR] 0.74, 95% CI 0.59 to 0.92, $P = 0.007$). Among the 23,072 nondiabetes patients 30-day mortality was 3.0% in both IIb/IIIa and placebo groups. Among the 1279 diabetics undergoing PCI, 30-day mortality was 1.2% with IIb/IIIa therapy and 4.0% with placebo (OR = 0.30; 95% CI 0.14 to 0.69, $P = 0.002$).³⁴ Broadly applied, these current treatments have almost certainly significantly improved the outcomes of diabetics suffering ACS. The clinical results in diabetics of powerfully inhibiting platelet aggregation with parenteral glycoprotein IIb/IIIa receptor antagonists may provide a foretaste of the potential incremental efficacy results that may be expected with more potent oral agents than aspirin and clopidogrel.

Resistance to antiplatelet therapy in diabetes

While diabetics are at higher baseline risk and thus potentially have more to gain from effective therapies, diabetics also have relatively less intrinsic response to many current antithrombotic agents. This likely reflects the diabetic's prothrombotic milieu described above. Diabetics have been documented to have less antiplatelet response to both aspirin and clopidogrel as well as less antithrombotic response to the indirect thrombin inhibitors enoxaperin and unfractionated heparin.³⁵

Examining platelet inhibition as measured by light transmittance aggregometry (LTA) with 20 μ M ADP at 24 hours after a 300 mg clopidogrel load, Angiolillo demonstrated that 38% of diabetics had <10% platelet inhibition compared to 8% of nondiabetics.³⁶ Similarly, another 6% of diabetics were low (10% to 29% inhibition) responders. In total, 44% of diabetic were non- or low-responders compared to 22% of nondiabetics. In the maintenance phase with 75 mg of clopidogrel daily, mean in vitro platelet inhibition to 20 μ M or 6 μ M of ADP was also significantly lower in diabetics than nondiabetics. Among similar patients with CAD, Serebraunyt et al have demonstrated that diabetics have less response to aspirin and clopidogrel as measured by several different assays of platelet function.²¹

Low platelet inhibitory response as measured by multiple assays has now been definitively linked to increased risk of clinical events such as stent thrombosis. A meta-analysis of 20 studies in 2930 patients using LTA, VerifyNow®, PFA-100, thromboelastogram, and vasodilator stimulated

phosphoprotein phosphorylation index (VASP-P Index) demonstrates a summary OR of 3.85 (95% CI 3.08 to 4.80) for adverse clinical ischemic events among patients with low response to aspirin.³⁷ Low response to clopidogrel has now also been linked to increased events. In a study of 173 type 2 diabetics with CAD, Angiolillo and others observed a 37.8% rate of major adverse cardiovascular events at 2 years follow-up in low responders to clopidogrel compared to 13.2%, $P < 0.001$, in the more robust responders.³⁸ A large ($n = 1608$) study from Munich in unselected patients undergoing PCI using the multiplate analyzer conclusively demonstrated that patients in the lowest quintile of platelet response to clopidogrel are at increased risk of stent thrombosis. The 30-day definite stent thrombosis rate in the lowest quintile of response was 2.2% compared to 0.2% in the other four "normal responding" quintiles ($P = 0.0001$). The combined death and stent thrombosis rates were 3.1% and 0.6%, respectively. There was a nonsignificant trend to increased bleeding in the quintile with the greatest platelet response.³⁹ In a randomized trial comparing proceeding to PCI after 600 mg clopidogrel load vs one or more reloads if platelet response was subtherapeutic as measured by the VASP index, Bonello et al demonstrated a lower clinical event rate with platelet function assay guided clopidogrel therapy.⁴⁰

The GRAVITAS trial failed to show a clinically significant benefit to increasing the maintenance dose of clopidogrel to 150 mg daily in low responders to the loading dose as measured by the VerifyNow® assay. Rather than disproving the concept of platelet functional test guided therapy, GRAVITAS suggests simply doubling the maintenance dose is an inadequate therapy for most clopidogrel low responders⁴²

Hyporesponsiveness to antithrombins: implications for oral antiplatelet therapy in diabetics

In addition to higher baseline risk and low response to antiplatelet therapy, relative hyporesponsiveness of diabetics to indirect thrombin inhibitors also may contribute to the observations in the ExTRACT TIMI 25 study.⁴¹ Diabetics suffering a STEMI had substantially higher 30-day mortality than non-diabetics with either enoxaperin or unfractionated heparin. Diabetics assigned to enoxaperin, however, had lower 30-day mortality than with unfractionated heparin ($P = 0.039$). This implies that more effective thrombin inhibition, whether due to an intrinsically more active agent or simply an agent permitting a greater proportion of the treated to rapidly achieve therapeutic effect, is particularly salutary in diabetics. Given that thrombin is the most potent

in vivo activator of platelets, perhaps additional approaches to overcome thrombin would include more effective antiplatelet therapy in the forms of greater P2Y₁₂ and/or PAR1 thrombin receptor inhibition. By reducing the impact of any activated thrombin that escapes anti-thrombin therapy, more potent antiplatelet agents help mitigate any shortcomings of the antithrombin agents in diabetics.⁴³

Given the pivotal thrombin-platelet activation interaction in thrombosis, the ACUITY trial provides some insight into the particular importance of adequate inhibition of this thrombotic axis in diabetics.⁴⁴ The direct thrombin inhibitor bivalirudin has the mechanistic advantage of more powerful inhibition of clot-bound thrombin compared to unfractionated heparin and low-molecular-weight heparin. In patients presenting with UA/NSTEMI/ACS receiving background aspirin therapy and clopidogrel treatment timed at the discretion of the investigator's local practice pattern, the ACUITY randomized trial tested the strategies of bivalirudin monotherapy vs unfractionated heparin (UFH) or enoxaperin coupled with routine IIb/IIIa receptor antagonist administration in patients with UA/NSTEMI/ACS. In the diabetic subgroup (n = 2585), numerically fewer ischemic outcomes were observed at 30 days with bivalirudin monotherapy, 7.8%, compared to 8.8% with the strategy of indirect thrombin inhibitors (UFH or enoxaperin) combined with routine intravenous IIb/IIIa inhibitor. While this difference was not statistically significant ($P = 0.39$), it is mechanistically interesting that more potent antithrombin therapy alone performed equally well to IIb/IIIa receptor inhibition for ischemic outcomes in diabetics. Hence, more effective inhibition of the key *in vivo* platelet agonist thrombin is of great utility in diabetics. Noncoronary artery bypass grafting (CABG) related major bleeding was substantially lower with the direct thrombin inhibitor (bivalirudin) strategy at 3.7% vs 7.1% with UFH or enoxaperin with routine IIb/IIIa therapy ($P = 0.0002$). Hence, the net clinical outcome combining composite ischemic events and major bleeding was superior ($P = 0.02$) for bivalirudin (10.8%) vs indirect thrombin inhibitor with routine IIb/IIIa (13.7%) in the setting of an early invasive strategy to manage non-ST elevation ACS in diabetics. This result for a direct thrombin inhibitor compared to routine IIb/IIIa therapy is particularly impressive given the variability of administration of dual oral antiplatelet therapy in this carefully double-blinded trial. While background aspirin therapy was near universal, the timing and dosing of clopidogrel was consistent with routine practice. Hence, many patients received clopidogrel on the table only once the anatomy was defined or after PCI.⁴⁵ Given this understandable

reluctance to pre-treat with clopidogrel until the anatomy is defined and ascertained to be nonsurgical, a more rapidly effective and consistently therapeutic agent than clopidogrel without excess bleeding would be desirable.

Given that many diabetics are low responders to clopidogrel, the ACUITY diabetic subgroup data generate the promising hypothesis that a P2Y₁₂ receptor antagonist such as prasugrel with more rapid, potent, and consistent platelet inhibition may further enhance the ischemic benefit of the bivalirudin monotherapy strategy in diabetics. Hopefully, this would remain without increased "bleeding penalty" as observed in the diabetic subgroup of TRITON TIMI-38 with prasugrel (n = 3146). The non-CABG TIMI major bleeding rate at 450 days was similarly low at 2.5% with the more potent agent prasugrel as clopidogrel at 2.6% despite their combined use with unfractionated heparin, enoxaperin, and IIb/IIIa use in 53%. Perhaps the major bleeding rates would be even lower with bivalirudin than the indirect thrombin inhibitors as observed in the Bivalirudin Angioplasty Trial and lower than indirect thrombin inhibitors combined with IIb/IIIa therapy as observed in REPLACE2, ACUITY, and HORIZONS-AMI.⁴⁶⁻⁴⁹

Prasugrel's more potent antiplatelet effects

TIMI 44 examined the effect of prasugrel on platelet function compared to clopidogrel in 201 patients undergoing elective cardiac catheterization for possible PCI.⁵⁰ Of the patients in TIMI 44, 30.8% were diabetic. In a randomized, double-blind, cross-over design, patients received either a 600 mg loading dose of clopidogrel or 60 mg of prasugrel. The primary endpoint was inhibition of platelet aggregation to 20 μ M ADP at 6 hours after the loading dose. This was $74.8\% \pm 13.0\%$ with prasugrel and $31.8\% \pm 21.1\%$ with clopidogrel ($P < 0.0001$) (Figure 1). As early as 30 minutes after the loading dose, inhibition of platelet aggregation (IPA) was $30.8\% \pm 29.0\%$ with prasugrel and only $4.9\% \pm 13.0\%$ with clopidogrel ($P < 0.0001$). At the other timepoints of 2 and 18 to 24 hours, the degree of platelet inhibition remained markedly different favoring prasugrel. Similar results were observed with the VASP platelet reactivity index. A VASP platelet reactivity index of $<50\%$ is generally considered therapeutic and has been associated with a very low probability of ischemic complications surrounding PCI.

Among the 112 patients that proceeded to PCI, a maintenance dose of 10 mg of prasugrel was compared to 150 mg of clopidogrel. Again the endpoint at 14 days was IPA

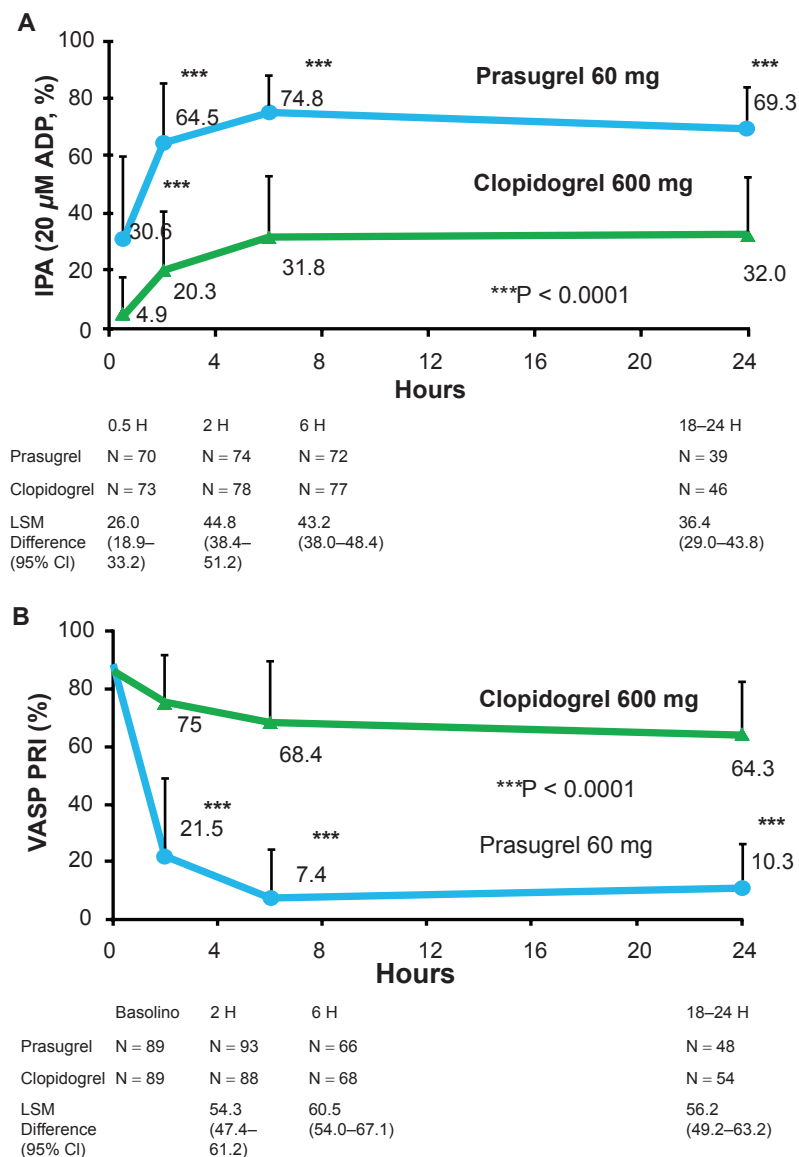


Figure 1 Inhibition of platelet aggregation (IPA) with 600 mg loading dose of clopidogrel vs 60 mg of prasugrel in TIMI-44. **(A)** As measured by 20 μ M adenosine diphosphate (ADP) with light transmittance aggregometry and **(B)** with the vasodilator stimulated phosphoprotein index (VASP)-platelet reactivity index %. Copyright © 2007. Wolters Kluwer Health. All rights reserved. Reproduced with permission from Wiviott SD, Trenk D, Frelinger AL, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation*. 2007;116(25):2923–2932.⁵⁰

to 20 μ M ADP. IPA was $61.3\% \pm 17.8\%$ with prasugrel and $46.1\% \pm 21.3\%$ with clopidogrel ($P < 0.0001$). (Figure 2) At day 15, the patients in the maintenance phase were crossed over to the other agent and platelet function was reassessed at 29 days. This demonstrated essentially reversal of the degree of platelet inhibition between the crossed over groups. The former prasugrel group's IPA dropped to $46.8\% \pm 13.2\%$ on clopidogrel. The former clopidogrel group's IPA increased to $60.8\% \pm 15.9\%$ with prasugrel ($P < 0.0001$). TIMI 44 conclusively demonstrated a more rapid, potent, and consistent platelet inhibition with 60 mg loading dose

and 10 mg maintenance dose of prasugrel compared with a 600 mg loading dose and 150 mg maintenance dose of clopidogrel. In addition to the primary endpoint of IPA to 20 μ M ADP, TIMI 44 documented qualitatively and quantitatively similar results with other platelet function tests and agonist concentrations. These included maximal platelet aggregation with light transmittance aggregometry at 5 μ M ADP, VASP index, and the VerifyNow[®] point-of-care P2Y₁₂ assay.

Both thienopyridines are prodrugs whose active metabolites irreversibly inhibit the P2Y₁₂ receptor. These

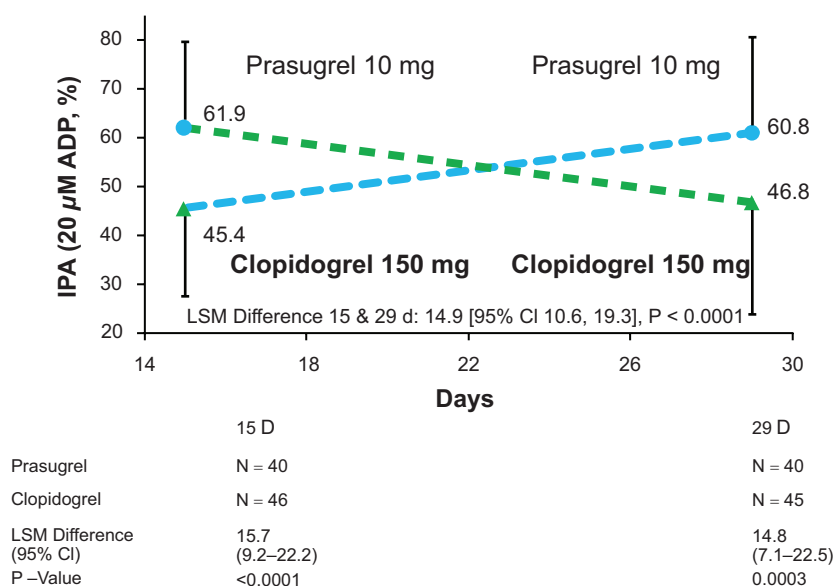


Figure 2 Inhibition of platelet aggregation (IPA) to 150 mg maintenance dose of clopidogrel vs 10 mg of prasugrel in TIMI-44. As measured by 20 μ M adenosine diphosphate (ADP) with light transmittance aggregometry. Copyright © 2007. Wolters Kluwer Health. All rights reserved. Reproduced with permission from Wiviott SD, Trenk D, Frelinger AL, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation*. 2007;116(25):2923–2932.⁵⁰

active metabolites bind covalently with disulfide bonds to cysteine residues of the platelet P2Y₁₂ receptor inhibiting its interaction with stimulatory ADP. This irreversible binding then inhibits platelets for the remainder of their 7- to 10-day lifespan. The in vivo platelet function and clinical differences between prasugrel and clopidogrel arise from differences in the efficiency of generation of their active metabolites. Once generated, the active metabolites have similar intrinsic potencies to inhibit ADP interaction with the P2Y₁₂ receptor.⁵¹

Once orally administered and absorbed, esterases convert approximately 85% of the administered clopidogrel molecules to an inactive metabolite (Figure 3). The remainder of the prodrug is biotransformed into its active metabolite by two cytochrome P-450 (CYP) dependent oxidative steps. CYP polymorphisms affect the efficiency of these conversions and the ultimate degree of platelet inhibition. In particular the CYP2C19*2 allele has been demonstrated to have reduced area under the plasma concentration–time curve for the active metabolite

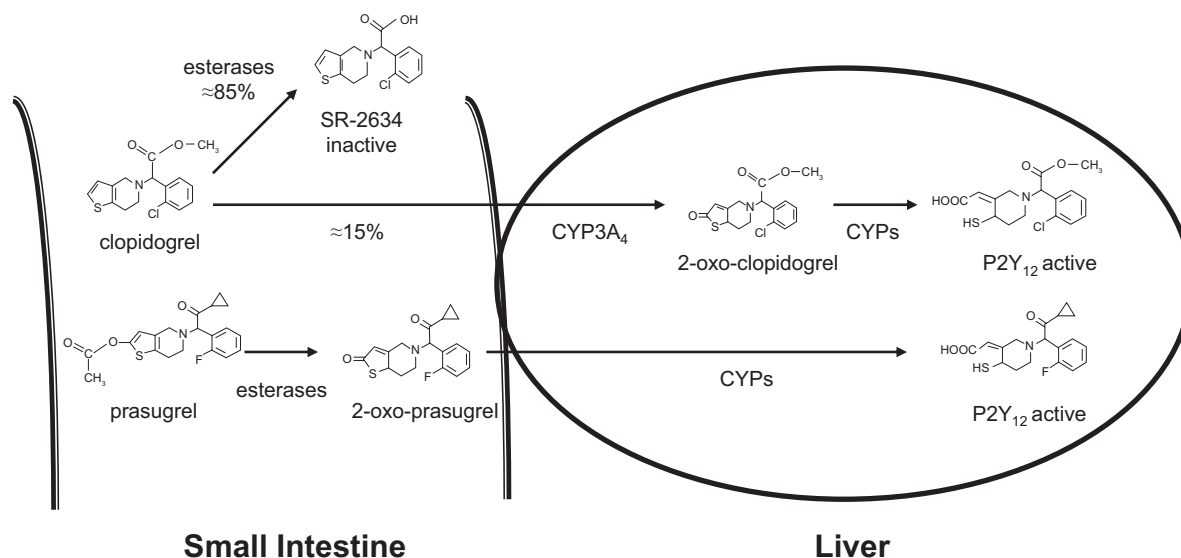


Figure 3 Metabolic pathways for biotransformation of thienopyridines to active metabolites.

of clopidogrel as well as significantly lower reduction in maximal platelet aggregation.^{52,53} Approximately 30% of Whites, 40% of Blacks, and 55% of East Asians carry at least 1 copy of the CYP2C19 reduced-function allele. In the TRITON TIMI-38 study, patients with a reduced-function CYP2C19 allele randomized to clopidogrel experienced a 53% higher rate of cardiovascular death, nonfatal MI, or

stroke compared to noncarriers (12.1% vs 8.0%, HR 1.53, 95% CI 1.07 to 2.19, $P = .01$). The HR for stent thrombosis was 3.09 with stent thrombosis rate of 2.6% for carriers vs 0.8% for noncarriers, $P = 0.02$, at 450 days, albeit most events occurred early in the first 30 days (Figure 4).

In addition to important genetic variations in the efficiency of enzymatic metabolism required to biotransform

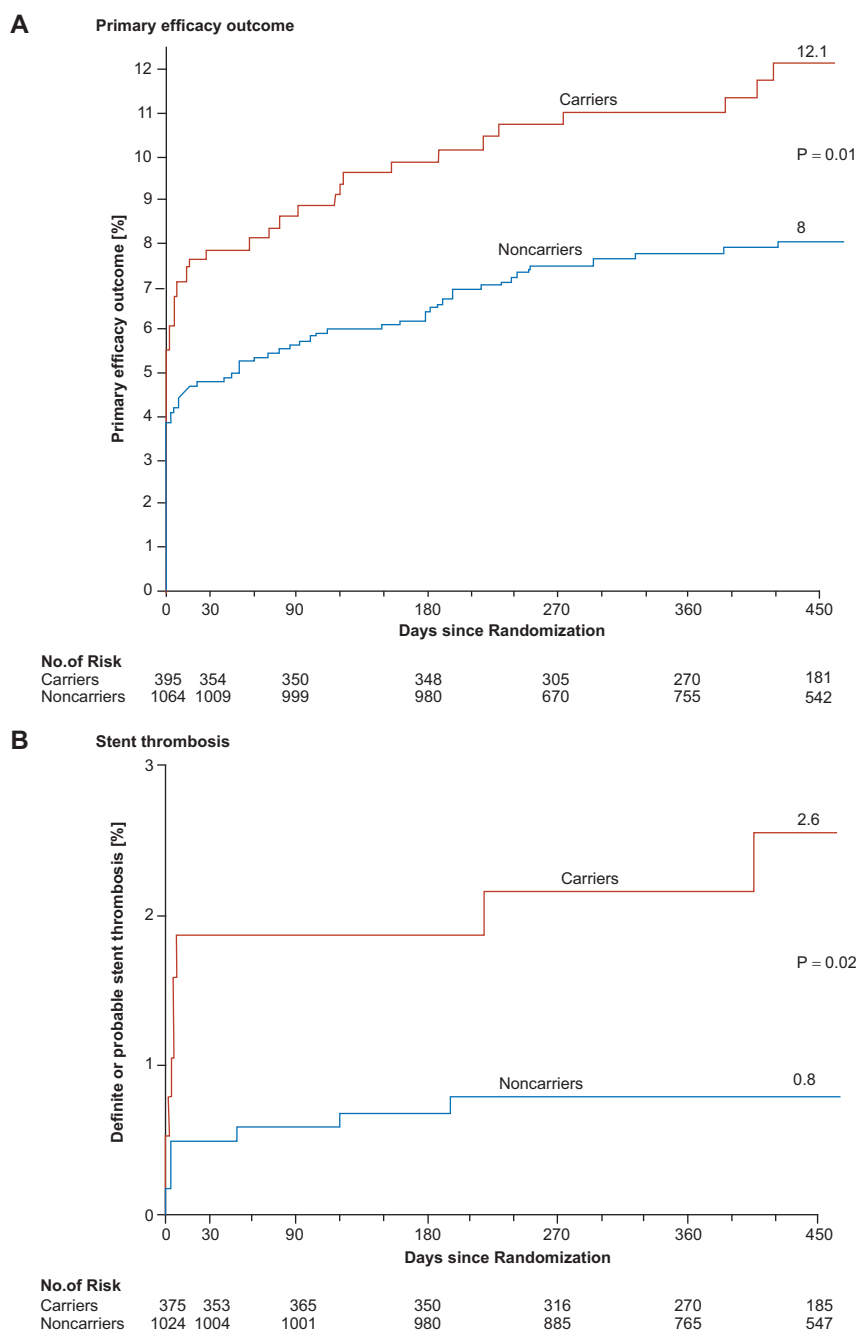


Figure 4 Kaplan-Meier curves depicting (A) the rate of death, myocardial infarction, or stroke for carriers of the CYP2C19 reduced-function allele vs noncarriers and (B) the rate of stent thrombosis among carriers vs noncarriers of a CYP2C19 reduced-function allele after percutaneous intervention in TRITON-TIMI 38. Copyright © 2009. Massachusetts Medical Society. All rights reserved. Reproduced with permission from Mega JL, Close SL, Wiwatt SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med.* 2009;360(4):354–362.⁵²

clopidogrel to its active metabolite, there may be clinically important drug–drug interactions that may also reduce the ultimate concentration of the active metabolite. Some proton pump inhibitors, for instance, further reduce plasma concentrations of the active metabolite required for effective P2Y₁₂ receptor inhibition. Retrospective studies in Canadian and Veterans Affairs databases have now drawn an association between co-administration of some proton pump inhibitors and higher post-PCI ischemic event rates.^{54,55}

Prasugrel on the other hand rapidly undergoes biotransformation. It is quickly hydrolyzed by carboxylesterases to a thiolactone (2-oxo-prasugrel (R-95913)) and then converted to its active metabolite (R-138727 with cleaved heterocyclic 5-member ring) by multiple cytochrome P450 isoenzymes. This biotransformation appears to be consistent, rapid, and efficient in all patients tested to date.⁵⁶ Wallentin et al have demonstrated a much larger area under the curve of active metabolite for a loading dose of 60 mg of prasugrel compared to 600 mg of clopidogrel with correspondingly much lower residual platelet reactivity in the prasugrel-treated patients.⁵⁷ Similarly, Brandt et al in a cross-over design, have demonstrated in healthy volunteers that the nonresponders to a 300 mg clopidogrel loading dose all respond to a 60 mg load of prasugrel as measured by turbidometric aggregometry.⁵⁸

Prasugrel's clinical effectiveness in diabetics

The clinic implications of these differences in the pharmacokinetics and pharmacodynamics of prasugrel vs clopidogrel have been evaluated in the landmark TRITON-TIMI 38 study. (58) STEMI (2900) and NSTEMI/ACS (10,000) patients undergoing an invasive strategy were randomized to clopidogrel 300 mg load with 75 mg maintenance vs prasugrel 60 mg load and 10 mg maintenance. A significant 19% reduction in cardiovascular death, MI, and stroke was observed with prasugrel at 450 days (9.9%) compared to clopidogrel (12.1%), $P = 0.0004$. Non-CABG TIMI major bleeding increased 32% from 1.8% with clopidogrel to 2.4% with prasugrel, $P = 0.03$. Combining these endpoints, the majority of patient subgroups had better outcomes with prasugrel. Exceptions were patients weighing <60 kg and patients >75 years old, where the outcomes were equal. Patients with prior TIA or CVA did worse with prasugrel.

TRITON-TIMI 38 included 3146 diabetics.⁶⁰ Perhaps because of their higher baseline risk and prothrombotic state, the diabetic subgroup reaped particular benefit from the more potent agent. At 450 days follow-up, there was a 30% significant

reduction (HR 0.70) in cardiovascular death, MI, and stroke with prasugrel at 12.2% compared to 17.0% with clopidogrel, $P < 0.001$ (Figure 5). Most of this difference occurred in the first 30 days but there continued to be increasing separation of the event curves over the next 420 days. For every 21 diabetic patients treated with prasugrel instead of clopidogrel, one major ischemic event was prevented. No difference was observed in non-CABG TIMI major bleeding with a rate of 2.5% with prasugrel and 2.6% with clopidogrel (Figure 5, panel D). The combination of TIMI major or minor bleeding was numerically higher with prasugrel at 5.3% vs 4.3% but not significantly different, $P = 0.13$.

Whereas nondiabetics experienced a 14% reduction in the composite ischemic event rate with prasugrel compared to clopidogrel, this reduction was 26% in diabetics not requiring insulin, and 37% in those treated with insulin. Enhanced outcomes in diabetics with a more potent inhibitor of platelet activation and aggregation fits given the mechanisms of the diabetic prothrombotic state. From a practice standpoint, the precautions for increased bleeding risk from the overall trial (history of TIA/CVA, age ≥ 75 , or body weight < 60 kg) should be considered to apply to the diabetic subgroup since no significant interaction ($P = 0.29$) was observed between treatment and diabetes status for major hemorrhage. Ultimately, the dosing of prasugrel may need to be individualized.

Large retrospective analyses have generally not identified diabetes mellitus as a prominent, independent risk factor for bleeding surrounding PCI. For example, the ACC-National Cardiovascular Data Registry CathPCI Registry bleeding prediction model examining 302,152 patients did not find that diabetics had a significantly elevated risk of bleeding. Diabetes was also not an independent predictor of bleeding. In the TRILOGY trial, a 5 mg dose of prasugrel will be prospectively tested in high bleeding risk patients.⁶¹

Prasugrel will be an important new addition to our armamentarium of antiplatelet agents in clinical cardiovascular practice for many subsets of patients, particularly diabetics. While TRITON-TIMI 38 supports the use of prasugrel in most patients presenting with an acute coronary syndrome undergoing PCI, there will likely remain a significant role for both established and other new antiplatelet agents. These are expected to include the oral nonthienopyridine P2Y₁₂ receptor antagonist ticagrelor (AZD-6140), the intravenous rapidly reversible modified adenosine triphosphate analogue cangrelor that antagonizes ADP-induced activation of the P2Y₁₂ receptor, the oral or intravenous agent elinogrel, and oral PAR-1 thrombin receptor antagonists such as SCH530348 and E5555.

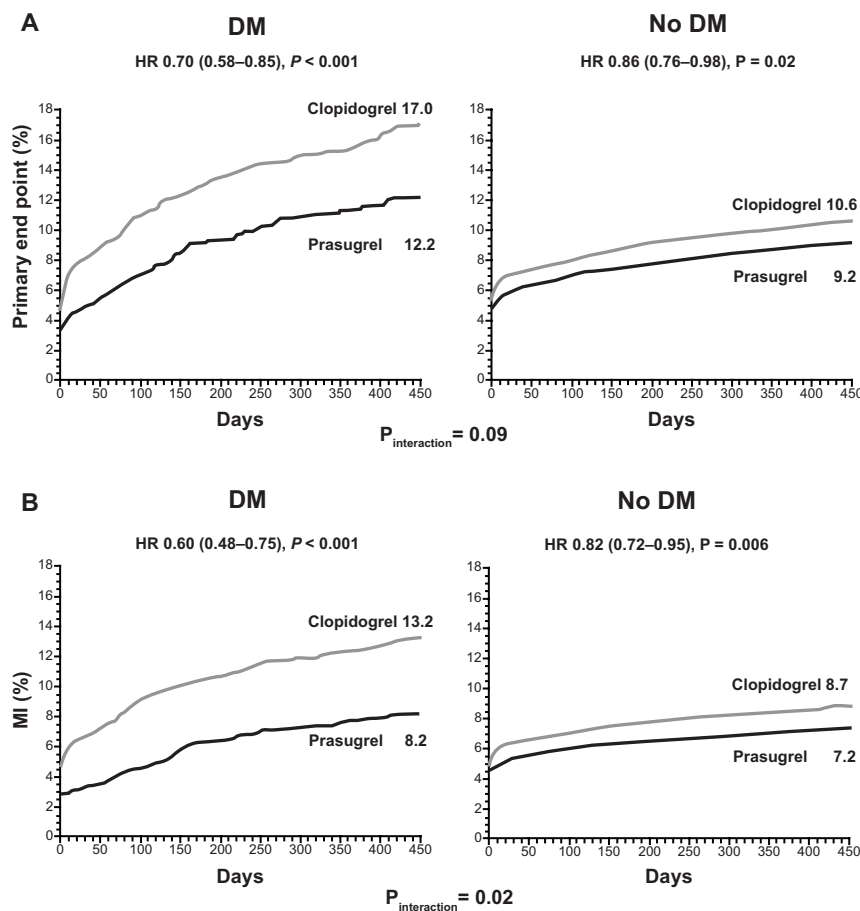


Figure 5 Kaplan-Meier curves for outcomes **A)** composite cardiovascular endpoint, **B)** for myocardial infarction (MI), **C)** for definite stent thrombosis, **D)** for TIMI major bleeding not related to coronary artery bypass grafting, and **E)** net benefit with clopidogrel vs prasugrel in TRITON-TIMI 38 stratified by diabetes (DM) or no diabetes. Copyright © 2008. Wolters Kluwer Health. All rights reserved. Reproduced with permission from Wiviott SD, Braunwald E, Angiolillo DJ, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. *Circulation*. 2008;118(16):1626-1636.⁴⁰

Alternative regimens to consider in diabetics

In routine clinical practice there will likely remain a necessity for alternative regimens to prasugrel particularly in the identified subgroups in TRITON-TIMI 38. Specifically weight < 60 kg, and age ≥ 75 patients (17% of the study population) had no incremental benefit from prasugrel. Patients with a history of prior TIA or CVA (another 4% of the study population) did worse with prasugrel than clopidogrel. Since prasugrel was not superior to clopidogrel in these subgroups, this naturally raised the question of whether clopidogrel is superior to placebo in these same subgroups. The CURE investigators have re-examined these subgroups identified in TRITON-TIMI 38. In the CURE trial, these subgroups did better with dual antiplatelet therapy in the form of clopidogrel and aspirin than placebo and aspirin.

In addition to these subgroups identified in TRITON, there will certainly be other high-bleeding risk patients identified

in routine practice. They will likely need dose reductions of prasugrel or alternative regimens, particularly for chronic maintenance therapy. Other real world constraints such as the commonly encountered economic constraint with clopidogrel will probably also dictate alternative regimens. When the exclusive patent on Plavix[®] expires, generic clopidogrel may be the only economically feasible agent for many patients, particularly those with documented therapeutic response on functional testing.

Strategies we and others have employed in our practices for high-risk patients have included maintenance doses of 150 mg of clopidogrel (albeit GRAVITAS now suggests this may be insufficient) and/or triple antiplatelet therapy with clopidogrel, aspirin, and cilostazol. High-risk patients have been identified based on both clinical and angiographic characteristics. Diabetics, high body mass index patients, those previously treated with brachytherapy, and hyporesponders as measured by platelet function assays should be

considered for more intensive therapy.^{62,63} In patients with a prior history of stent thrombosis and intravascular ultrasound confirmation of adequate deployment of the initial stent as well as compliance with dual antiplatelet therapy, certainly more aggressive and platelet function assay guided antiplatelet therapy seems advisable. Anatomic indications in our practice for higher doses of clopidogrel, platelet function assays, or triple antiplatelet therapy have been bifurcational stenting, multivessel stenting, long overlapping stents, small diameter vessels, unprotected left main stenting, and last patent vessel/graft anatomies.

A 600 mg loading dose of clopidogrel is no longer controversial given a meta-analysis of the 10 randomized trials evaluating this issue.⁶⁴ Lotrointe et al demonstrate an OR of cardiac death or nonfatal myocardial infarction of 0.54 (95% CI 0.32 to 0.90) with a 600 mg load compared to 300 mg. There was no significant increase in bleeding. In addition to TIMI-44, other data is evolving to support a higher maintenance dose of clopidogrel in some subsets including diabetics. The Optimal Antiplatelet Therapy in Diabetes Mellitus study (OPTIMUS) evaluated the functional impact of an 150 mg maintenance dose of clopidogrel in diabetics.^{65,66} Diabetics were randomized to a 75 or 150 mg maintenance dose of clopidogrel. Platelet aggregation was significantly reduced with the higher dose. However, 60% of the diabetics on the 150 mg regimen remained in the suboptimal response range. The efficacy and safety of this higher maintenance dose has been prospectively evaluated (GRAVITAS). The

lack of significant clinical response to 150 mg maintenance dose confirms that this remains an insufficient therapy in many clopidogrel hyporesponders.

Recent data confirms the utility of triple antiplatelet therapy (aspirin, clopidogrel, and cilostazol) in some patients including diabetics. The Optimal Antiplatelet Therapy in Diabetes Mellitus 2 study (OPTIMUS-2) demonstrates enhanced platelet inhibition when cilostazol is added to aspirin and clopidogrel therapy.⁶⁷ Lee et al have demonstrated reduced stent thrombosis and improved clinical outcomes with triple antiplatelet therapy in the DECLARE-Long study.⁶⁸ A randomized trial in 1212 patients with ACS, randomly assigned patients to standard dual-antiplatelet treatment (aspirin and clopidogrel) or triple-antiplatelet therapy with the addition of a 6-month course of cilostazol after successful PCI. The primary endpoint was a composite of cardiac death, nonfatal MI, stroke, or target vessel revascularization (TVR) at 1 year. Triple-antiplatelet treatment was associated with a significantly lower incidence of the primary end points (10.3% vs 15.1%; $P = 0.011$). The need for TVR was similar between both regimens (7.9% vs 10.7%; $P = 0.10$). Female patients and clinically or angiographically high-risk patients benefited more from the triple-antiplatelet treatment. There were no significant differences in major or minor bleeding between the 2 regimens.⁶⁸ The Cilostazol after Drug-Eluting Stent in diabetics trial (CIDES) randomized 280 diabetics to either cilostazol and aspirin or clopidogrel and aspirin after an initial month of triple therapy.

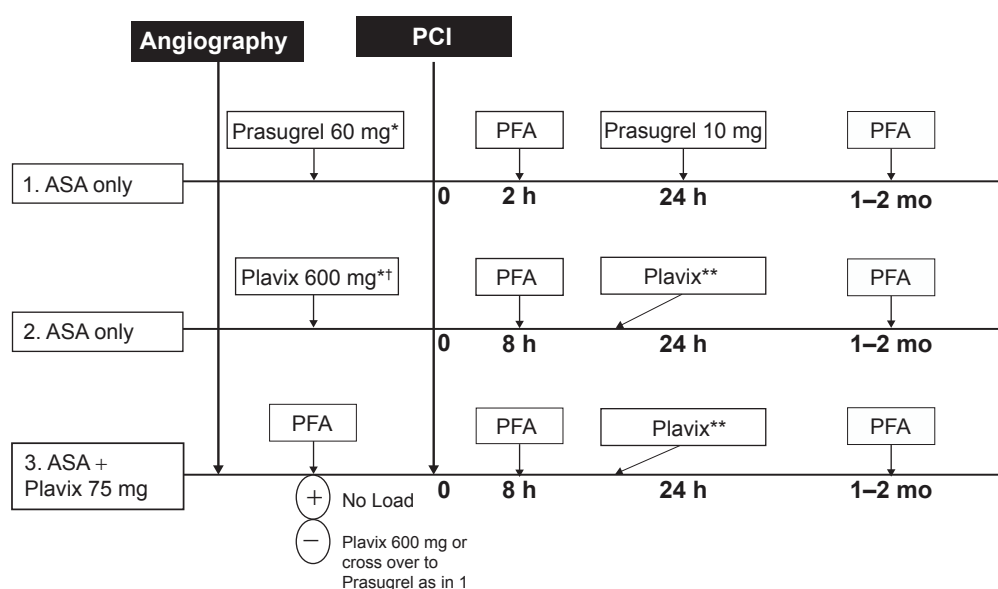


Figure 6 Proposed strategy for platelet function testing and individualized therapy.

*Can also be given pre Angiography.

†Also perform PFA if plavix pre-treatment >2 hours prior to PCI.

**Tailored plavix therapy based on PFA (75 mg qd, 75 mg bid, or 150 mg qd, and/or add cilostazol or switch to prasugrel or ticagrelor).

There was 1 stent thrombosis in each group by 7 months follow-up. The rate of angiographic restenosis (stent plus 5-mm borders) was 9 (8.0%) in the cilostazol group and 20 (16.1%) in the clopidogrel group, $p = 0.041$.⁷⁰

At present, our antiplatelet therapy strategies are largely based upon overall and subgroup findings in large trials. Individual patient tailored therapy based on platelet function assays (PFAs) and perhaps genotyping will likely become the future standard of care as prospective trials evaluate these strategies including their incremental cost-effectiveness. A flow chart depicting the timing of PFA testing with adjustments in therapy outlines our proposed practice with the addition of prasugrel (Figure 6). Until prospective validation of these approaches in RCTs, as with all medical practice, we will need to base treatment decisions on the applicable main and subgroup results of trials without individualized PFA evaluations.⁷¹ Potent new agents like prasugrel may obviate the need for platelet function assays to assess efficacy but may still be beneficial to predict safety. As always, supplementing these data with astute clinical judgment and patient-specific risk prediction instruments will undoubtedly further optimize individual patient outcomes.

Disclosures

The authors declare no conflicts of interest.

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