CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will differentiate the pharmacology, effectiveness, and uses of the thienopyridine drugs

LAWRENCE D. LAZAR, MD
Department of Cardiovascular Medicine, Cleveland Clinic

A. MICHAEL LINCOFF, MD
Professor of Medicine; Vice Chairman, Department of Cardiovascular Medicine; Director, Center for Clinical Research, Lerner Research Institute; Director, Cleveland Clinic Coordinating Center for Clinical Research, Department of Cardiovascular Medicine, Cleveland Clinic

Prasugrel for acute coronary syndromes: Faster, more potent, but higher bleeding risk

ABSTRACT

Prasugrel (Effient) has been approved for reducing the risk of thrombotic complications in patients with acute coronary syndromes who are to undergo percutaneous coronary intervention. In a large clinical trial (N Engl J Med 2007; 357:2001–2005), prasugrel was superior to clopidogrel (Plavix), another drug of its class, in this situation. However, bleeding complications were more frequent with prasugrel, and so this drug should be avoided in patients at higher risk of bleeding.

KEY POINTS

The thienopyridines—ticlopidine (Ticlid), clopidogrel (Plavix), and now prasugrel—reduce the risk of death from and serious complications of acute coronary syndromes by inhibiting platelet aggregation.

Compared with clopidogrel, prasugrel is more potent, faster in onset, and more consistent in inhibiting platelets.

Prasugrel should be avoided in patients at higher risk of bleeding, including those with a history of stroke or transient ischemic attack, those age 75 or older, or those who weigh less than 60 kg.

doi:10.3949/ccjm.76a.09116

PRASUGREL (Effient) is more potent and consistent in its effects than clopidogrel (Plavix), thus preventing more thrombotic events—but at a price of more bleeding. Therefore, the drugs must be appropriately selected for the individual patient.

Over the last 9 years, the thienopyridines—ticlopidine (Ticlid), clopidogrel, and now prasugrel—have become essential tools for treating acute coronary syndromes.

The usual underlying mechanism of acute coronary syndromes is thrombosis, caused by rupture of atherosclerotic plaque.[1] Accordingly, antithrombotic agents—aspirin, heparin, low-molecular-weight heparin, glycoprotein IIb/IIIa inhibitors, the direct thrombin inhibitor bivalirudin (Angiomax), and thienopyridines—have all been shown to reduce the risk of major adverse cardiac outcomes in this setting.

In this article, we review the pharmacology and evidence of effectiveness of the thienopyridine drugs, focusing on prasugrel, the latest thienopyridine to be approved by the US Food and Drug Administration (FDA).

THIENOPYRIDINES INHIBIT PLATELET ACTIVATION AND AGGREGATION

Thienopyridines are prodrugs that require conversion by hepatic cytochrome P450 enzymes. The active metabolites bind irreversibly to platelet P2Y12 receptors. Consequently, they permanently block signalling mediated by platelet adenosine diphosphate-P2Y12 receptors, thereby inhibiting glycoprotein IIb/IIIa receptor activation and platelet aggregation.

Aspirin, in contrast, inhibits platelets by blocking the thromboxane-mediated pathway. Therefore, the combination of aspirin plus a thienopyridine has an additive effect.[2]

The effect of thienopyridines on platelets is irreversible. Therefore, although the half-life of prasugrel's active metabolite is 3.7 hours, its inhibitory effects last for 96 hours, essentially the time for half the body's circulating platelets to be replaced.

TICLOPIDINE, THE FIRST THIENOPYRIDINE

Ticlopidine was the first thienopyridine to be approved by the FDA. Its initial studies in unstable angina were small, their designs did not call for patients to concurrently receive aspirin, and all they showed was that ticlopidine was about as beneficial as aspirin. Consequently, the studies had little impact on clinical practice.[3]

In a pivotal trial,[4] patients who received coronary stents were randomized to afterward receive either the combination of ticlopidine plus aspirin or anticoagulation therapy with heparin, phenprocoumon (a coumarin derivative available in Europe), and aspirin. At 30 days, an ischemic complication (death, myocardial infarction [MI], repeat intervention) had occurred in 6.2% of the anticoagulation therapy group vs 1.6% of the ticlopidine group, a risk reduction of 75%. Rates of stent occlusion, MI, and revascularization were 80% to 85% lower in the ticlodipine group. This study paved the way for widespread use of thienopyridines.

Ticlopidine's use was limited, however, by a 2.4% incidence of serious granulocytopenia and rare cases of thrombocytopenic purpura.

Clopidogrel and prasugrel are prodrugs that require conversion by P450 enzymes

BENEFIT OF CLOPIDOGREL

Although prasugrel is the focus of this review, the trials of prasugrel all compared its efficacy with that of clopidogrel. Furthermore, many patients should still receive clopidogrel and not prasugrel, so it is important to be familiar with the evidence of clopidogrel's benefit.

Once approved for clinical use, clopidogrel was substituted for ticlopidine in patients undergoing coronary stenting on the basis of studies showing it to be at least as effective as ticlopidine and more tolerable. A series of trials of clopidogrel were done in patients across a spectrum of risk groups, from those at high risk of coronary heart disease to those presenting with ST-elevation MI. The time of pretreatment in the studies ranged from 3 hours to 6 days before percutaneous coronary intervention, and the duration of treatment following intervention ranged from 30 days to 1 year.

Clopidogrel in non-ST-elevation acute coronary syndromes

The CURE trial[2] (Clopidogrel in Unstable Angina to Prevent Recurrent Events), published in 2001, established clopidogrel as a therapy for unstable ischemic syndromes, whether treated medically or with revascularization. In that trial, 12,562 patients with acute coronary syndromes without ST elevation (ie, unstable angina or non-ST-elevation MI), as defined by electrocardiographic changes or positive cardiac markers, were randomized to receive clopidogrel (a 300-mg loading dose followed by 75-mg maintenance doses) or placebo for a mean duration of 9 months. All patients also received aspirin 75 mg to 325 mg daily.

The composite outcome of death from cardiovascular causes, nonfatal MI, or stroke occurred in 20% fewer patients treated with clopidogrel than with placebo (9.3% vs 11.4%). The benefit was similar in patients undergoing revascularization compared with those treated medically.

Although there were significantly more cases of major bleeding in the clopidogrel group than in the placebo group (3.7% vs 2.7%), the number of episodes of life-threatening bleeding or hemorrhagic strokes was the same.

PCI-CURE[5] was a substudy of the CURE trial in patients who underwent a percutaneous coronary intervention. Patients were pretreated with clopidogrel or placebo for a mean of 6 days before the procedure. Afterward, they all received clopidogrel plus aspirin in an unblinded fashion for 2 to 4 weeks, and then the randomized study drug was resumed for a mean of 8 months.

Significantly fewer adverse events occurred in the clopidogrel group as tallied at

the time of the intervention, 1 month later, and 8 months later.

Clopidogrel in ST-elevation acute MI

The CLARITY-TIMI 28 trial[6] (Clopidogrel as Adjunctive Reperfusion Therapy—Thrombolysis in Myocardial Infarction 28) showed that adding clopidogrel (a 300-mg loading dose, then 75 mg daily) to aspirin benefitted patients with ST-elevation MI receiving fibrinolytic therapy. At 30 days, cardiovascular death, recurrent MI, or urgent revascularization had occurred in 11.6% of the clopidogrel group vs 14.1% of the placebo group, a statistically significant difference. The rates of major or minor bleeding were no higher in the clopidogrel group than in the placebo group, an especially remarkable finding in patients receiving thrombolytic therapy.

PCI-CLARITY.[7] About half of the patients in the CLARITY trial ultimately underwent a percutaneous coronary intervention after fibrinolytic therapy, with results reported as the PCI-CLARITY substudy. Like those in PCI-CURE, these patients were randomized to receive pretreatment with either clopidogrel or placebo before the procedure, in this study for a median of 3 days. Both groups received clopidogrel afterward. At 30 days from randomization, the outcome of cardiovascular death, MI, or stroke had occurred in 7.5% of the clopidogrel group compared with 12.0% of the placebo group, which was statistically significant, without any significant excess in the rates of major or minor bleeding.

COMMIT[8] (the Clopidogrel and Metoprolol in Myocardial Infarction Trial) also showed clopidogrel to be beneficial in patients with acute MI. This trial included more than 45,000 patients in China with acute MI, 93% of whom had ST-segment elevation. In contrast to CLARITY, in COMMIT barely more than half of the patients received fibrinolysis, fewer than 5% proceeded to percutaneous interventions, and no loading dose was given: patients in the clopidogrel group received 75 mg/day from the outset.

At 15 days, the incidence of death, reinfarction, or stroke was 9.2% with clopidogrel compared with 10.1% with placebo, a small but statistically significant difference. Again, the rate of major bleeding was not significantly higher, either overall or in patients over age 70.

Of note, patients over age 75 were excluded from CLARITY, and as mentioned, no loading dose was used in COMMIT. Thus, for patients receiving fibrinolysis who are over age 75, there is no evidence to support the safety of a loading dose, and clopidogrel should be started at 75 mg daily.

Clopidogrel in elective percutaneous coronary intervention

The CREDO trial[9] (Clopidogrel for the Reduction of Events During Observation) was in patients referred for elective percutaneous coronary intervention. Three to 24 hours before the procedure, the patients received either a 300-mg loading dose of clopidogrel or placebo; afterward, all patients received clopidogrel 75 mg/day for 28 days. All patients also received aspirin.

A clopidogrel loading dose 3 to 24 hours before the intervention did not produce a statistically significant reduction in ischemic events, although a post hoc subgroup analysis suggested that patients who received the loading dose between 6 and 24 hours before did benefit, with a relative risk reduction of 38.6% in the composite end point ($P = .051$).

Clopidogrel is beneficial in a spectrum of coronary disease

After 28 days, the patients who had received the clopidogrel loading dose were continued on clopidogrel, while those in the placebo group were switched back to placebo. At 1 year, the investigators found a significantly lower rate of the composite end point with the prolonged course of clopidogrel (8.5% vs 11.5%).

In summary, these studies found clopidogrel to be beneficial in a broad spectrum of coronary diseases. Subgroup analyses suggest that pretreatment before percutaneous coronary intervention provides additional benefit, particularly if clopidogrel is given at least 6 hours in advance (the time necessary for clopidogrel to cause substantial platelet inhibition).

SOME PATIENTS RESPOND LESS TO CLOPIDOGREL

The level of platelet inhibition induced by clopidogrel varies. In different studies, the frequency of clopidogrel "nonresponsiveness"

ranged from 5% to 56% of patients, depending on which test and which cutoff values were used. The distribution of responses to clopidogrel is wide and fits a normal gaussian curve.[10]

A large fraction of the population carries a gene that may account for some of the interpatient variation in platelet inhibition with clopidogrel. Carriers of a reduced-function CYP2C19 allele—approximately 30% of people in one study—have significantly lower levels of the active metabolite of clopidogrel, less platelet inhibition from clopidogrel therapy, and a 53% higher rate of death from cardiovascular causes, MI, or stroke.[11]

PRASUGREL, THE NEWEST THIENOPYRIDINE

Prasugrel, FDA-approved in July 2009 for the treatment of acute coronary syndromes, is given in an oral loading dose of 60 mg followed by an oral maintenance dose of 10 mg daily.

Pharmacology of prasugrel vs clopidogrel

Platelet inhibition by clopidogrel varies widely, in part due to genetic polymorphisms

As noted previously, the thienopyridines are prodrugs that require hepatic conversion to exert antiplatelet effects.

Metabolism. Prasugrel's hepatic activation involves a single step, in contrast to the multiple-step process required for activation of clopidogrel. Clopidogrel is primarily hydrolyzed by intestinal and plasma esterases to an inactive terminal metabolite, with the residual unhydrolized drug undergoing a two-step metabolism that depends on cytochrome P450 enzymes. Prasugrel is also extensively hydrolyzed by these esterases, but the intermediate product is then metabolized in a single step to the active sulfhydryl compound, mainly by CYP3A4 and CYP2B6.

Thus, about 80% of an orally absorbed dose of prasugrel is converted to active drug, compared with only 10% to 20% of absorbed clopidogrel.

Time to peak effect. With clopidogrel, maximal inhibition of platelet aggregation occurs 3 to 5 days after starting therapy with 75 mg daily without a loading dose, but within 4 to 6 hours if a loading dose of 300 to 600 mg is given. In contrast, a prasugrel loading dose produces more than 80% of its platelet inhibitory effects by 30 minutes, and peak activity is observed within 4 hours.[12] The platelet inhibition induced by prasugrel at 30 minutes after administration is comparable to the peak effect of clopidogrel at 6 hours.[13]

Dose-response. Prasugrel's inhibition of platelet aggregation is dose-related.

Prasugrel is about 10 times more potent than clopidogrel and 100 times more potent than ticlopidine. Thus, treatment with 5 mg of prasugrel results in inhibition of platelet activity (distributed in a gaussian curve) very similar to that produced by 75 mg of clopidogrel. On the other hand, even a maintenance dose of 150 mg of clopidogrel inhibits platelet activity to a lesser degree than 10 mg of prasugrel (46% vs 61%),[14] so clopidogrel appears to reach a plateau of platelet inhibition that prasugrel can overcome.

At the approved dose of prasugrel, inhibition of platelet aggregation is significantly greater and there are fewer "nonresponders" than with clopidogrel.

Interactions. Drugs that inhibit CYP3A4 do not inhibit the efficacy of prasugrel, but they can inhibit that of clopidogrel. Some commonly used drugs that have this effect are the statins (eg, atorvastain [Lipitor]) and the macrolide antibiotics (eg, erythromycin). Furthermore, whereas proton pump inhibitors have been shown to diminish the effect of clopidogrel by reducing the formation of its active metabolite, no such effect has been noted with prasugrel.

Prasugrel in phase 2 trials: Finding the optimal dosage

A phase 2 trial compared three prasugrel regimens (loading dose/daily maintenance dose of 40 mg/7.5 mg, 60 mg/10 mg, and 60 mg/15 mg) and standard clopidogrel therapy (300 mg/75 mg) in patients undergoing elective or urgent percutaneous coronary intervention.[15] No significant difference in outcomes was seen in the groups receiving the three prasugrel regimens. However, more "minimal bleeding events" (defined by the criteria of the TIMI trial[16]) occurred with high-dose prasugrel than with lower-dose prasugrel or with clopidogrel, leading to use of the intermediate-dose prasugrel regimen (60-mg loading dose, 10-mg daily maintenance) for later trials.

Another phase 2 trial randomized 201 patients undergoing elective percutaneous coronary intervention to receive prasugrel 60 mg/10 mg or clopidogrel 600 mg/150 mg.[14] In all patients, the loading dose was given about 1 hour before cardiac catheterization. As soon as 30 minutes after the loading dose, platelet inhibition was superior with prasugrel (31% vs 5% inhibition of platelet aggregation), and it remained significantly higher at 6 hours (75% vs 32%) and during the maintenance phase (61% vs 46%).

Phase 3 trial of prasugrel vs clopidogrel: TRITON-TIMI 38

Only one large phase 3 trial of prasugrel has been completed: TRITON-TIMI 38 (the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction),[17] which enrolled adults with moderate-risk to high-risk acute coronary syndromes scheduled to undergo a percutaneous coronary intervention. In this trial, 10,074 patients were enrolled who had moderate- to high-risk unstable angina or non-ST-elevation MI, and 3,534 patients were enrolled who had ST-elevation MI.

Patients were randomized to receive prasugrel (a 60-mg loading dose, then 10 mg daily) or clopidogrel (a 300-mg loading dose, then 75 mg daily) and were treated for 6 to 15 months. All patients also received aspirin.

The primary end point, a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke, occurred in significantly fewer patients treated with prasugrel than with clopidogrel (9.9% vs 12.1%, $P < .001$) (TABLE 1). Most of the benefit was due to fewer nonfatal MIs during the follow-up period (7.4% vs 9.7%, $P < .001$). Additionally, the prasugrel group had a significantly lower rate of stent thrombosis compared with the clopidogrel group (1.1% vs 2.4%; $P < .001$).

These benefits came at a price of more bleeding. Of those patients who did not undergo coronary artery bypass grafting, more experienced bleeding in the prasugrel group than in the clopidogrel group (2.4% vs 1.8%, $P = .03$), including a higher rate of life-threatening bleeding (1.4% vs 0.89%, $P = .01$) and fatal bleeding (0.4% vs 0.1%, $P = .002$). More patients discontinued prasugrel because of hemorrhage (2.5% vs 1.4%, $P < .001$). In patients who proceeded to coronary artery bypass grafting, the rate of major bleeding was more than four times higher in those who received prasugrel than in those who received clopidogrel (13.4% vs 3.2%, $P < .001$).

A higher rate of adverse events related to colon cancer was also noted in patients treated with prasugrel, although the authors suggest this may have resulted from the stronger antiplatelet effects of prasugrel bringing more tumors to medical attention due to bleeding.

Overall death rates did not differ significantly between the treatment groups.

In a post hoc analysis,[18] prasugrel was superior to clopidogrel in preventing ischemic events both during the first 3 days following randomization (the "loading phase") and for the remainder of the trial (the "maintenance phase"). Whereas bleeding risk was similar with the two drugs during the loading phase, prasugrel was subsequently associated with more bleeding during the maintenance phase.

Certain patient subgroups had no net benefit or even suffered harm from prasugrel compared with clopidogrel.[17] Patients with previous stroke or transient ischemic attack had net harm from prasugrel (hazard ratio 1.54, $P = .04$) and showed a strong trend toward a greater rate of major bleeding ($P = .06$). Patients age 75 and older and those weighing less than 60 kg had no net benefit from prasugrel.

Prasugrel is as effective at 30 minutes as clopidogrel is at 4 to 6 hours

Cost of prasugrel

Prasugrel is currently priced at 18% more than clopidogrel, with average wholesale prices per pill of $6.65 for prasugrel 10 mg compared with $5.63 for clopidogrel 75 mg. (Prasugrel 10-mg pills cost $6.33 at drugstore.com or $7.60 at CVS; clopidogrel 75-mg pills cost $5.33 at drugstore.com or $6.43 at CVS.) The patent on clopidogrel expires in November 2011, after which the price differential is expected to become significantly greater.

TICAGRELOR, A REVERSIBLE ORAL AGENT

Ticagrelor, the first reversible oral P2Y12 receptor antagonist, is an alternative to thienopyridine therapy for acute coronary syndromes.

Ticagrelor is quickly absorbed, does not

TABLE 1

TRITON-TIMI 38: Greater efficacy but more bleeding with prasugrel vs clopidogrel

END POINT	PRASUGREL	CLOPIDOGREL	*P* VALUE
Efficacy end points [a]			
Primary end point (nonfatal MI, death from cardiovascular causes, or nonfatal stroke)	9.9%	12.1%	< .001
Nonfatal MI	7.3%	9.5%	< .001
Death from cardiovascular causes	2.1%	2.4%	.31
Nonfatal stroke	1.0%	1.0%	.93
Stent thrombosis [b]	1.1%	2.4%	< .001
Death from any cause	3.0%	3.2%	.64
Bleeding complications [a]			
Non-CABG-related TIMI major bleeding [c]	2.4%	1.8%	.03
Life-threatening bleeding	1.4%	0.9%	.01
Major or minor TIMI bleeding [c]	5.0%	3.8%	.002
Bleeding requiring transfusions	4.0%	3.0%	< .001
CABG-related TIMI major bleeding [d]	13.4%	3.2%	< .001

TRITON-TIMI 38: The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38; CABG: coronary artery bypass grafting. Percentages are Kaplan-Meier estimates of the rate of the end point at 15 months. .

[a] Efficacy end points are based on the intention-to-treat population (prasugrel N = 6,813, clopidogrel N = 6,795), while complication numbers are for patients who received at least one dose of the study drug (prasugrel N = 6,741, clopidogrel N = 6,716) and for end points occurring within 7 days after the study drug was discontinued or occurring within a longer period if the end point was believed by the local investigator to be related to the use of the study drug.

[b] Stent thrombosis was defined as definite or probable thrombosis, according to the Academic Research Consortium; the numbers of patients at risk were all patients whose index procedure included at least one intracoronary stent: 6,422 patients in each of the two treatment groups.

[c] TIMI major bleeding is defined as a drop in hemoglobin concentration of 5 g/dL or more, intracranial hemorrhage, or cardiac tamponnade. Minor bleeding is a drop in hemoglobin of 3 to 4.9 g/dL.

[d] For major bleeding related to CABG, the total number of patients were all patients who had received at least one dose of prasugrel or clopidogrel before undergoing CABG: 179 and 189, respectively.

ADAPTED FROM WIVIOTT SD, BRAUNWALD E, MCCABE CH, ET AL. PRASUGREL VERSUS CLOPIDOGREL IN PATIENTS WITH ACUTE CORONARY SYNDROMES. N ENGL J MED 2007; 357:2001–2015. WITH PERMISSION FROM THE MASSACHUSETTS MEDICAL SOCIETY.

Prasugrel dosage: A 60-mg loading dose, then 10 mg/day

require metabolic activation, and has a rapid antiplatelet effect and offset of effect, which closely follow drug-exposure levels. In a large randomized controlled trial in patients with acute coronary syndromes with or without ST-segment elevation, treatment with ticagrelor compared with clopidogrel resulted in a significant reduction in death from vascular causes, MI, or stroke (9.8% vs 11.7%).[19]

Given its reversible effect on platelet inhibition, ticagrelor may be preferred in patients whose coronary anatomy is unknown and

for whom coronary artery bypass grafting is deemed probable. It is still undergoing trials and is not yet approved.

TAKE-HOME POINTS

Prasugrel is more potent, more rapid in onset, and more consistent in inhibiting platelet aggregation than clopidogrel. A large clinical trial[17] found prasugrel to be superior to clopidogrel for patients with moderate- to high-risk acute coronary syndromes with high probability of undergoing a percutaneous coronary intervention.

Who should receive prasugrel, and how?

Prasugrel should be given after angiography to patients with non-ST-elevation acute coronary syndromes or at presentation to patients with ST-elevation MI. When used for planned percutaneous coronary intervention, prasugrel should be given at least 30 minutes before the intervention, as was done in phase 2 trials (although its routine use in this situation is not recommended—see below).

It is given in a one-time loading dose of 60 mg by mouth and then maintained with 10 mg by mouth once daily for at least 1 year. (At least 9 months of treatment with a thienopyridine is indicated for patients with acute coronary syndromes who are medically treated, and at least 1 year is indicated following urgent or elective percutaneous coronary intervention, including balloon angioplasty and placement of a bare-metal or drug-eluting stent.)

Who should not receive prasugrel?

For now, prasugrel should be avoided in favor of clopidogrel in patients at higher risk of bleeding. It is clearly contraindicated in patients with prior transient ischemic attack or stroke, for whom the risk of serious bleeding seems to be prohibitive. It should generally be avoided in patients age 75 and older, although it might be considered in those at particularly high risk of stent thrombosis, such as those with diabetes or prior MI. In patients weighing less than 60 kg, the package insert advises a reduced dose (5 mg), although clinical evidence for this practice is lacking.

As yet, we have no data assuring that prasugrel is safe to use in combination with fibrinolytic agents, so patients on thrombolytic therapy for acute MI should continue to receive clopidogrel starting immediately after lysis. Furthermore, in patients who proceeded to coronary artery bypass grafting, the rate of major bleeding was more than four times higher in the prasugrel group than in the clopidogrel group in the TRITON-TIMI 38 trial.[17] No thienopyridine should be given to patients likely to proceed to coronary artery bypass grafting.

Only clopidogrel has evidence supporting its use as an alternative to aspirin for patients with atherosclerotic disease who cannot tolerate aspirin. Neither drug has evidence for use for primary prevention.

Other areas of uncertainty

Prior to angiography. Indications for prasugrel are currently limited by the narrow scope of the trial data. TRITON-TIMI 38,[17] the only large trial completed to date, randomized patients to receive prasugrel only after their coronary anatomy was known, except for ST-elevation MI patients. It is unknown whether the benefits of prasugrel will outweigh the higher risk of bleeding in patients with acute coronary syndromes who do not proceed to percutaneous coronary interventions.

Prasugrel is contraindicated in patients with prior TIA or stroke

A clinical trial is currently under way comparing prasugrel with clopidogrel in 10,000 patients with acute coronary syndromes who will be medically managed without planned revascularization: A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome Subjects (TRILOGY ACS), ClinicalTrials.gov Identifier: NCT00699998. The trial has an estimated completion date of March 2011.

In cases of non-ST-elevation acute coronary syndrome, it is reasonable to wait to give a thienopyridine until after the coronary anatomy has been defined, if angiography will be completed soon after presentation. For example, a 1-hour delay before giving prasugrel still delivers antiplatelet therapy more quickly than giving clopidogrel on presentation. If longer delays are expected before angiography, however, the patient should be

given a loading dose of clopidogrel "up front," in accordance with guidelines published by the American College of Cardiology, American Heart Association, and European Society of Cardiology,[20] which recommend starting a thienopyridine early during hospitalization based on trial data with clopidogrel.

Patients undergoing elective percutaneous coronary intervention are at lower risk of stent thrombosis and other ischemic complications, so it is possible that the benefits of prasugrel would not outweigh the risks in these patients. Thus, prasugrel cannot yet be recommended for routine elective percutaneous coronary intervention except in individual cases in which the interventionalist feels that the patient may be at higher risk of thrombosis.

REFERENCES

1. **Yeghiazarians Y, Braunstein JB, Askari A, Stone PH**. Unstable angina pectoris. N Engl J Med 2000; 342:101–114.
2. **Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators**. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345:494–502.
3. **Balsano F, Rizzon P, Violi F, et al**. Antiplatelet treatment with ticlopidine in unstable angina. A controlled multicenter clinical trial. The Studio della Ticlopidina nell'Angina Instabile Group. Circulation 1990; 82:17–26.
4. **Schömig A, Neumann FJ, Kastrati A, et al**. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996; 334:1084–1089.
5. **Mehta SR, Yusuf S, Peters RJG, et al; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial (CURE) Investigators**. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001; 358:527–533.
6. **Sabatine MS, Cannon CP, Gibson CM, et al; CLARITY-TIMI 28 Investigators**. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005; 352:1179–1189.
7. **Sabatine MS, Cannon CP, Gibson CM, et al; Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI) 28 Investigators**. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. JAMA 2005: 294:1224–1232.
8. **Chen ZM, Jiang LX, Chen YP, et al; COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group**. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005; 366:1607–1621.
9. **Steinhubl SR, Berger PB, Mann JT 3rd, et al; CREDO Investigators**. Clopidogrel for the reduction of events during observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002; 288:2411–2420.
10. **Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Bhatt DL, Topol EJ**. Variability in platelet responsiveness to clopidogrel among 544 individuals. J Am Coll Cardiol 2005; 45:246–251.
11. **Mega JL, Close SL, Wiviott SD, et al**. Cytochrome P-450 polymorphisms and response to clopidogrel. N Engl J Med 2009; 360:354–362.
12. **Helft G, Osende JI, Worthley SG, et al**. Acute antithrombotic effect of a front-loaded regimen of clopidogrel in patients with atherosclerosis on aspirin. Arterioscler Thromb Vasc Biol 2000; 20:2316–2321.
13. **Weerakkody GJ, Jakubowski JA, Brandt JT, et al**. Comparison of speed of onset of platelet inhibition after loading doses of clopidogrel versus prasugrel in healthy volunteers and correlation with responder status. Am J Cardiol 2007; 100:331–336.
14. **Wiviott SD, Trenk D, Frelinger AL, et al; PRINCIPLE-TIMI 44 Investigators**. 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; 116:2923–2932.
15. **Wiviott SD, Antman EM, Winters KJ, et al; JUMBO-TIMI 26 Investigators**. Randomized comparison of prasugrel (CS-747, LY640315), a novel thienopyridine P2Y12 antagonist, with clopidogrel in percutaneous coronary intervention: results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 Trial. Circulation 2005; 111:3366–3373.
16. **Bovill EG, Terrin ML, Stump DC, et al**. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II Trial. Ann Intern Med 1991; 115:256–265.
17. **Wiviott SD, Braunwald E, McCabe CH, et al; TRITON-TIMI 38 Investigators**. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007; 357:2001–2015.
18. **Antman EM, Wiviott SD, Murphy SA, et al**. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. J Am Coll Cardiol 2008; 51:2028–2033.
19. **Wallentin L, Becker RC, Budaj A, et al; PLATO Investigators, Freij A, Thorsén M**. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009; 361:1045–1057.
20. **Braunwald E, Antman EM, Beasley JW, et al**. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non–ST-segment elevation myocardial infarction—summary article*1: A report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2002; 40:1366–1374.

***ADDRESS**: Lawrence D. Lazar, MD, Department of Cardiovascular Medicine, Cleveland Clinic, J2-3, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail lazarl@ccf.org.*