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Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

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ABSTRACT

BACKGROUND

Dual-antiplatelet therapy with aspirin and a thienopyridine is a cornerstone of treatment to prevent thrombotic complications of acute coronary syndromes and percutaneous coronary intervention.

METHODS

To compare prasugrel, a new thienopyridine, with clopidogrel, we randomly assigned 13,608 patients with moderate-to-high-risk acute coronary syndromes with scheduled percutaneous coronary intervention to receive prasugrel (a 60-mg loading dose and a 10-mg daily maintenance dose) or clopidogrel (a 300-mg loading dose and a 75-mg daily maintenance dose), for 6 to 15 months. The primary efficacy end point was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The key safety end point was major bleeding.

RESULTS

The primary efficacy end point occurred in 12.1% of patients receiving clopidogrel and 9.9% of patients receiving prasugrel (hazard ratio for prasugrel vs. clopidogrel, 0.81; 95% confidence interval [CI], 0.73 to 0.90; $P < 0.001$). We also found significant reductions in the prasugrel group in the rates of myocardial infarction (9.7% for clopidogrel vs. 7.4% for prasugrel; $P < 0.001$), urgent target-vessel revascularization (3.7% vs. 2.5%; $P < 0.001$), and stent thrombosis (2.4% vs. 1.1%; $P < 0.001$). Major bleeding was observed in 2.4% of patients receiving prasugrel and in 1.8% of patients receiving clopidogrel (hazard ratio, 1.32; 95% CI, 1.03 to 1.68; $P = 0.03$). Also greater in the prasugrel group was the rate of life-threatening bleeding (1.4% vs. 0.9%; $P = 0.01$), including nonfatal bleeding (1.1% vs. 0.9%; hazard ratio, 1.25; $P = 0.23$) and fatal bleeding (0.4% vs. 0.1%; $P = 0.002$).

CONCLUSIONS

In patients with acute coronary syndromes with scheduled percutaneous coronary intervention, prasugrel therapy was associated with significantly reduced rates of ischemic events, including stent thrombosis, but with an increased risk of major bleeding, including fatal bleeding. Overall mortality did not differ significantly between treatment groups. (ClinicalTrials.gov number, NCT00097591.)

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THE SHORT-TERM AND LONG-TERM BENEFITS of dual-antiplatelet therapy with aspirin and clopidogrel have been established for patients with acute coronary syndromes¹⁻³ and those undergoing percutaneous coronary intervention (PCI).^{4,5} Despite these benefits, many patients continue to have recurrent atherothrombotic events while receiving standard dual antiplatelet therapy.¹ In addition, important limitations of clopidogrel remain, such as only a modest antiplatelet effect, with substantial interpatient variability^{6,7} and a delayed onset of action.⁵ Small clinical studies have suggested that patients with a reduced pharmacologic response to clopidogrel may be at increased risk for adverse clinical events, including myocardial infarction and coronary-stent thrombosis.⁸⁻¹¹

Prasugrel — a novel thienopyridine — is a prodrug that, like clopidogrel, requires conversion to an active metabolite before binding to the platelet P2Y₁₂ receptor to confer antiplatelet activity.¹² At the currently studied doses, prasugrel inhibits adenosine diphosphate–induced platelet aggregation more rapidly, more consistently, and to a greater extent than do standard and higher doses of clopidogrel in healthy volunteers¹³ and in patients with coronary artery disease,^{14,15} including those undergoing PCI.¹⁶ Phase 2 testing of prasugrel, as compared with clopidogrel, in patients undergoing elective or urgent PCI showed a trend toward fewer ischemic events, with an acceptable safety profile.¹⁷ Thus, we designed the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38, a phase 3 trial involving patients with acute coronary syndromes with scheduled PCI, comparing a regimen of prasugrel with the standard-dose regimen of clopidogrel approved by the Food and Drug Administration.¹⁸ Although our trial was designed to compare regimens of prasugrel and clopidogrel, it also tests the hypothesis that the use of an agent producing a higher level of inhibition of adenosine diphosphate–induced platelet aggregation and a less-variable response than standard-dose clopidogrel reduces ischemic events.

METHODS

TRITON–TIMI 38 was designed as a collaboration between the TIMI Study Group, the sponsors — Daiichi Sankyo and Eli Lilly — and a steering committee of investigators (see the Appendix).

Quintiles Corporation provided data- and site-management services. All key prespecified and exploratory analyses were performed by the TIMI Study Group, using an independent copy of the complete database. The academic authors wrote all drafts of the manuscript and vouch for the veracity and completeness of its content. The database was locked on September 22, 2007; the analyses reported herein were completed on October 26, 2007.

STUDY POPULATION

We enrolled 13,608 patients with acute coronary syndromes (representative of the entire spectrum of those syndromes) with scheduled PCI. Patients were randomly assigned to the clopidogrel group or the prasugrel group in two strata: 10,074 patients with moderate-to-high-risk unstable angina or non–ST-elevation myocardial infarction and 3534 patients with ST-elevation myocardial infarction. The inclusion criteria for patients with unstable angina or non–ST-elevation myocardial infarction were ischemic symptoms lasting 10 minutes or more and occurring within 72 hours before randomization, a TIMI risk score¹⁹ of 3 or more, and either ST-segment deviation of 1 mm or more or elevated levels of a cardiac biomarker of necrosis. Patients with ST-elevation myocardial infarction could be enrolled within 12 hours after the onset of symptoms if primary PCI was planned or within 14 days after receiving medical treatment for ST-elevation myocardial infarction.¹⁸

Full exclusion criteria have been published previously.¹⁸ Key exclusion criteria included an increased risk of bleeding, anemia, thrombocytopenia, a history of pathologic intracranial findings, or the use of any thienopyridine within 5 days before enrollment.¹⁸ The protocol was approved by the institutional review boards associated with all participating centers, and written informed consent was provided by all patients.

STUDY PROTOCOL

A loading dose of study medication (60 mg of prasugrel or 300 mg of clopidogrel) was administered, in a double-blind manner, anytime between randomization and 1 hour after leaving the cardiac catheterization laboratory. Since the protocol was designed as a trial of patients with acute coronary syndromes who were undergoing PCI, the coronary anatomy had to be known to be suitable for PCI before randomization in all patients with unstable angina or non–ST-elevation myocardial infarction, or in those enrolled after medical treat-

ment for ST-elevation myocardial infarction. If the coronary anatomy was previously known or primary PCI for ST-elevation myocardial infarction was planned, pretreatment with the study drug was permitted for up to 24 hours before PCI. Randomization was to occur before PCI was performed, and the study drug was to be administered as soon as possible after randomization.

The choice of vessels treated, devices used, and adjunctive medication administered to support PCI was left to the discretion of the treating physician. After PCI, patients received maintenance doses of either prasugrel (10 mg) or clopidogrel (75 mg) daily. Use of aspirin was required, and a daily dose of 75 to 162 mg was recommended. Study visits were conducted at hospital discharge, at 30 days, at 90 days, and at 3-month intervals thereafter, for a total of 6 to 15 months.¹⁸

END POINTS

The primary efficacy end point was a composite of the rate of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke during the follow-up period. Key secondary end points at 30 and 90 days were the primary composite end point and a composite of death from cardiovascular causes, nonfatal myocardial infarction, or urgent target-vessel revascularization. Key secondary end points for the entire follow-up period were stent thrombosis and a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or rehospitalization due to a cardiac ischemic event. Additional prespecified analyses included an analysis of the rates of the primary end point from randomization to day 3 and a landmark analysis of those data from day 3 to the end of the study. Key safety end points were TIMI major bleeding not related to coronary-artery bypass grafting (CABG), non-CABG-related TIMI life-threatening bleeding, and TIMI major or minor bleeding, as previously defined.¹⁸ Stent thrombosis was defined as definite or probable stent thrombosis according to the Academic Research Consortium.²⁰ All components of the primary, secondary, and key safety end points were adjudicated by members of an independent clinical events committee that was unaware of the group assignments.

STATISTICAL ANALYSIS

Efficacy comparisons were performed on the basis of the time to the first event, according to the intention-to-treat principle. Safety analyses were

carried out on data from patients who received at least one dose of the study drug. The Gehan–Wilcoxon test was used to compare the treatment groups with regard to the primary efficacy end point¹⁸; the log-rank test was used in a prespecified sensitivity analysis for the primary end point and in all analyses of key secondary and safety end points. Because of the substantial overlap between the cohort of patients with unstable angina or non-ST-elevation myocardial infarction and the overall population of patients with acute coronary syndromes, and to preserve the statistical power to detect a difference between the two treatment groups, we used a closed testing procedure. The primary efficacy end point was analyzed in the cohort with unstable angina or non-ST-elevation myocardial infarction first, and only if there was a statistically significant difference between the treatment groups was this end point analyzed in the overall cohort.¹⁸ Rates of the end points are expressed as Kaplan–Meier estimates at 15 months and were compared with the use of hazard ratios and two-sided 95% confidence intervals. An independent data monitoring committee monitored the safety and efficacy of the study drugs. P values of less than 0.05 were considered to indicate statistical significance.

We calculated that a total of 875 primary end points would be required for the study to have a 90% power to detect a 20% reduction in the relative risk of the primary end point among patients with unstable angina or non-ST-elevation myocardial infarction receiving prasugrel, as compared with clopidogrel. It was estimated that 9500 patients with unstable angina or non-ST-elevation myocardial infarction would need to be enrolled to achieve this number of end points.¹⁸ A prespecified assessment conducted when 650 patients had had a primary end point found a slightly lower-than-expected aggregate rate of the end point, which led us to increase the number of patients in the cohort with unstable angina or non-ST-elevation myocardial infarction to approximately 10,100.¹⁸

RESULTS

We randomly assigned 13,608 patients (10,074 with unstable angina or non-ST-elevation myocardial infarction and 3534 with ST-elevation myocardial infarction), from 707 sites in 30 countries, to a treatment group between November 2004 and January 2007. The baseline characteristics were sim-

ilar to those in contemporary studies of patients with acute coronary syndromes who were undergoing PCI and were well matched between the treatment groups (Table 1). The median duration of therapy was 14.5 months. A total of 14 patients (0.1%) were lost to follow-up.

Nearly all patients (99%) had PCI at the time of randomization, 94% received at least one intracoronary stent, and 47% received at least one drug-eluting stent. The study drug was administered before the first coronary guidewire was placed in 25% of patients, after the first coronary guidewire was placed and during the PCI or within 1 hour after PCI in 74%, and more than 1 hour after PCI in 1%.

EFFICACY END POINTS

The rate of the primary efficacy end point was significantly reduced in favor of prasugrel among the patients with unstable angina or non-ST-elevation myocardial infarction (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.93; $P=0.002$); therefore, as prespecified, the analysis was also performed in the overall cohort of patients with acute coronary syndromes. A significant benefit of prasugrel was also observed in the ST-elevation myocardial infarction cohort alone (hazard ratio, 0.79; 95% CI, 0.65 to 0.97; $P=0.02$), and there was no significant interaction between treatment group and enrollment stratum (unstable angina or non-ST-elevation myocardial infarction vs. ST-elevation myocardial infarction).

In the overall cohort, a total of 781 patients (12.1%) in the clopidogrel group had the primary end point, as compared with 643 patients (9.9%) in the prasugrel group (hazard ratio, 0.81; 95% CI, 0.73 to 0.90; $P<0.001$) (Table 2 and Fig. 1A), supporting the primary hypothesis of superior efficacy. A significant reduction in the primary end point was seen in the prasugrel group by the first prespecified time point, 3 days (5.6% in the clopidogrel group vs. 4.7% in the prasugrel group; hazard ratio, 0.82; 95% CI, 0.71 to 0.96; $P=0.01$) (Fig. 1B), and persisted throughout the follow-up period. From 3 days to the end of the study, the primary end point had occurred in 6.9% of patients receiving clopidogrel and in 5.6% of patients receiving prasugrel (hazard ratio, 0.80; 95% CI, 0.70 to 0.93; $P=0.003$) (Fig. 1C). The difference between the treatment groups with regard to the rate of the primary end point was largely related to a significant reduction in myocardial infarction

in the prasugrel group (9.7% in the clopidogrel group vs. 7.4% in the prasugrel group; hazard ratio, 0.76; 95% CI, 0.67 to 0.85; $P<0.001$). The rate of myocardial infarction with subsequent death from cardiovascular causes (including arrhythmia, congestive heart failure, shock, and sudden or unwitnessed death) was also reduced in the prasugrel group (0.7% in the clopidogrel group vs. 0.4% in the prasugrel group; hazard ratio, 0.58; 95% CI, 0.36 to 0.93; $P=0.02$). There was no significant difference between the two treatment groups in the rate of stroke or of death from cardiovascular causes not preceded by recurrent myocardial infarction.

Prasugrel showed superior efficacy in major prespecified subgroups (Fig. 2), without significant interactions between the characteristics of the patients and the treatment group. A benefit with prasugrel with regard to the primary end point was found both with the use of glycoprotein IIb/IIIa-receptor antagonists during the index hospitalization (hazard ratio for prasugrel vs. clopidogrel, 0.79; 95% CI, 0.69 to 0.91; $P<0.001$) or without such use (hazard ratio, 0.84; 95% CI, 0.72 to 0.99; $P=0.03$). The benefit tended to be greater among the 3146 patients with diabetes (17.0% of whom had the primary end point in the clopidogrel group, vs. 12.2% in the prasugrel group; hazard ratio, 0.70; 95% CI, 0.58 to 0.85; $P<0.001$) than among the 10,462 patients without diabetes (10.6% of whom had the primary end point in the clopidogrel group, vs. 9.2% in the prasugrel group; hazard ratio, 0.86; 95% CI, 0.76 to 0.98; $P=0.02$). There was no significant interaction between treatment effect and diabetes status ($P=0.09$) or the timing of the study-drug administration ($P=0.40$).

Similar significant reductions were seen for prasugrel in the overall cohort with regard to the prespecified secondary end point of death from cardiovascular causes, nonfatal myocardial infarction, or urgent target-vessel revascularization at 30 days (hazard ratio, 0.78; 95% CI, 0.69 to 0.89; $P<0.001$) and at 90 days (hazard ratio, 0.79; 95% CI, 0.70 to 0.90; $P<0.001$). A significant reduction in the rate of urgent target-vessel revascularization alone was also found in the prasugrel group by the end of the follow-up period (hazard ratio, 0.66; 95% CI, 0.54 to 0.81; $P<0.001$) (Table 2). A reduction in favor of prasugrel was also seen by the end of the follow-up period for the end point of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or rehos-

pitalization for ischemia (hazard ratio, 0.84; 95% CI, 0.76 to 0.92; $P < 0.001$) (Table 2). The rate of definite or probable stent thrombosis, as defined by the Academic Research Consortium, was significantly reduced in the prasugrel group as compared with the clopidogrel group, with 68 patients (1.1%) and 142 patients (2.4%), respectively, having at least one occurrence (hazard ratio, 0.48; 95% CI, 0.36 to 0.64; $P < 0.001$). The significant reduction in the rate of stent thrombosis was also found among patients receiving prasugrel in combination with bare-metal stents alone (hazard ratio, 0.52; 95% CI, 0.35 to 0.77; $P < 0.001$) and among those receiving prasugrel in combination with at least one drug-eluting stent (hazard ratio, 0.43; 95% CI, 0.28 to 0.66; $P < 0.001$).

SAFETY END POINTS

Among patients treated with prasugrel, 146 (2.4%) had at least one TIMI major hemorrhage that was not related to CABG, as compared with 111 patients (1.8%) treated with clopidogrel (hazard ratio, 1.32; 95% CI, 1.03 to 1.68; $P = 0.03$) (Table 3). This excess of TIMI major bleeding included a higher rate of life-threatening bleeding in the prasugrel group (1.4%, vs. 0.9% in the clopidogrel group; hazard ratio, 1.52; 95% CI, 1.08 to 2.13; $P = 0.01$) at the end of the study, as well as from the time of randomization to day 3 (0.4% vs. 0.3%; hazard ratio, 1.38; 95% CI, 0.79 to 2.41; $P = 0.26$) and from day 3 to the end of the study (1.0% vs. 0.6%; hazard ratio, 1.60; 95% CI, 1.05 to 2.44; $P = 0.03$). Fatal TIMI major bleeding occurred in significantly more patients treated with prasugrel (0.4%) than those treated with clopidogrel (0.1%) ($P = 0.002$) (Table 3), and more patients in the prasugrel group had nonfatal life-threatening bleeding (1.1%, vs. 0.9% in the clopidogrel group; hazard ratio, 1.25; 95% CI, 0.87 to 1.81; $P = 0.23$). A higher rate of TIMI major bleeding related to instrumentation and a significantly higher rate of spontaneous TIMI major bleeding were seen in the prasugrel group than in the clopidogrel group (Table 3). Intracranial hemorrhage was reported in 19 patients (0.3%) receiving prasugrel and 17 patients (0.3%) receiving clopidogrel ($P = 0.74$). The combination of non-CABG-related TIMI major or minor hemorrhage was more frequent among patients receiving prasugrel than among those receiving clopidogrel (hazard ratio, 1.31; 95% CI, 1.11 to 1.56; $P = 0.002$) (Table 3).

Few patients underwent CABG; among them,

the rate of TIMI major bleeding was also greater with prasugrel than with clopidogrel (Table 3). More patients treated with prasugrel (2.5%, vs. 1.4% of patients treated with clopidogrel; $P < 0.001$) discontinued the study drug owing to adverse events related to hemorrhage.

When the rates of certain efficacy and bleeding end points — death from any cause, nonfatal myocardial infarction, nonfatal stroke, and TIMI major hemorrhage — were included in a prespecified analysis of net clinical benefit, the findings favored prasugrel (13.9% of patients in the clopidogrel group vs. 12.2% in the prasugrel group; hazard ratio, 0.87; 95% CI, 0.79 to 0.95; $P = 0.004$). Death from cardiovascular causes (including death related to intracranial hemorrhage or to bleeding related to a cardiovascular procedure) or fatal hemorrhage occurred in 151 patients (2.4%) receiving clopidogrel and in 142 patients (2.2%) receiving prasugrel (hazard ratio, 0.94; 95% CI, 0.75 to 1.18; $P = 0.59$).

As a result of the discordance between the efficacy results (lower rates of ischemic end points in the prasugrel group than in the clopidogrel group) and the safety results (higher rates of bleeding end points with prasugrel than with clopidogrel) during the entire follow-up period, we performed a series of post hoc exploratory analyses to identify the subgroups of patients who did not have a favorable net clinical benefit (defined as the rate of death from any cause, nonfatal myocardial infarction, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleeding) from the use of prasugrel or who had net harm. There were three specific groups of interest; patients who had a previous stroke or transient ischemic attack had net harm from prasugrel (hazard ratio, 1.54; 95% CI, 1.02 to 2.32; $P = 0.04$), patients 75 years of age or older had no net benefit from prasugrel (hazard ratio, 0.99; 95% CI, 0.81 to 1.21; $P = 0.92$), and patients weighing less than 60 kg had no net benefit from prasugrel (hazard ratio, 1.03; 95% CI, 0.69 to 1.53; $P = 0.89$). In both treatment groups, patients with at least one of these three risk factors had higher rates of bleeding than those without them (Table 4). Patients with a history of cerebrovascular events had no evidence of a clinical benefit from prasugrel (as compared with clopidogrel), as evaluated by the primary efficacy end point, and had a strong trend toward a greater rate of TIMI major bleeding ($P = 0.06$), including intracranial hemor-

Characteristic	Prasugrel (N=6813)	Clopidogrel (N=6795)
Unstable angina or NSTEMI (%)	74	74
STEMI (%)	26	26
Age		
Median (yr)	61	61
25th percentile, 75th percentile (yr)	53, 69	53, 70
≥75 yr (%)	13	13
Female sex (%)	25	27
BMI†		
Median	28	28
25th percentile, 75th percentile	25, 31	25, 31
White race (%)‡	92	93
Region of enrollment (%)		
North America	32	32
Western Europe	26	26
Eastern Europe	24	25
Middle East, Africa, or Asia–Pacific region	14	14
South America	4	4
Medical history (%)		
Hypertension	64	64
Hypercholesterolemia	56	56
Diabetes mellitus	23	23
Tobacco use	38	38
Previous MI	18	18
Previous CABG	8	7
Creatinine clearance <60 ml/min (%)§	11	12
Index procedure (%)		
PCI	99	99
CABG	1	1
Stent	94	95
Bare-metal stent only	48	47
≥1 Drug-eluting stent	47	47
Multivessel PCI	14	14
Antithrombin use to support PCI (%)		
Heparin	66	65
LMWH	9	8
Bivalirudin	3	3
Other or multiple therapies	22	23
Glycoprotein IIb/IIIa–receptor antagonist use during index hospitalization (%)	54	55
Timing of study-drug administration (%)¶		
Before PCI	26	25
During PCI	73	74
After PCI	1	1

Table 1. (Continued.)

Characteristic	Prasugrel (N = 6813)	Clopidogrel (N = 6795)
Pharmacotherapy during index hospitalization (%)		
ACE inhibitor or ARB	76	75
Beta-blocker	88	88
Statin	92	92
Calcium-channel blocker	18	17
Aspirin	99	99

* Patients could have had more than one type of medical history, undergone more than one type of index procedure, or received more than one type of pharmacotherapy during index hospitalization. The percentage of female patients and the percentage of patients who received an angiotensin-converting-enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) differed significantly between the prasugrel group and the clopidogrel group ($P=0.02$ and $P=0.03$, respectively). NSTEMI denotes non-ST-elevation myocardial infarction (MI), STEMI ST-elevation MI, CABG coronary-artery bypass grafting, PCI percutaneous coronary intervention, and LMWH low-molecular-weight heparin. Beta-blocker is defined as β -adrenergic-receptor antagonist, and statin is defined as hydroxymethylglutaryl-coenzyme A reductase inhibitor.

† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

‡ Race was self-reported.

§ Creatinine clearance was estimated with the use of the Cockcroft-Gault formula.

¶ Administration of the study drug before PCI occurred before the first coronary guidewire was placed during the index PCI; administration during PCI occurred after the first coronary guidewire was placed or within 1 hour after the patient was taken from the cardiac catheterization laboratory; and administration after PCI occurred more than 1 hour after the patient was taken from the cardiac catheterization laboratory.

rhage in six patients (2.3%) in the prasugrel group, as compared with none in the clopidogrel group ($P=0.02$). As a result, there was a significant interaction between a history of cerebrovascular events and the degree of net clinical benefit of prasugrel as compared with clopidogrel (Table 4), indicating a significant harm from prasugrel among patients with a history of cerebrovascular events (518 patients), as compared with a significant benefit from prasugrel among patients without such a history (13,090 patients). There was also a significant interaction between the presence or absence of any of these three risk factors and the degree of net clinical benefit for prasugrel as compared with clopidogrel ($P=0.006$), though no significant harm was evident. Among patients without any of these three risk factors, there was greater efficacy with prasugrel (hazard ratio, 0.74; 95% CI, 0.66 to 0.84; $P<0.001$), no significant difference in the rate of major bleeding in the prasugrel group and the clopidogrel group (hazard ratio, 1.24; 95% CI, 0.91 to 1.69; $P=0.17$), and a substantially favorable net clinical benefit for the use of prasugrel (Table 4).

The rate of serious adverse events not related to hemorrhage was similar in the prasugrel group and the clopidogrel group (occurring in 22.5% and 22.8% of patients, respectively; $P=0.52$). The study

drug was discontinued owing to adverse events not related to hemorrhage in 4.7% of patients treated with prasugrel and in 5.0% of patients treated with clopidogrel ($P=0.37$). The adverse events reported included severe thrombocytopenia in 17 patients in the prasugrel group (0.3%) and 18 patients in the clopidogrel group (0.3%) ($P=0.86$); neutropenia in 2 patients ($<0.1\%$) and 10 patients (0.2%) ($P=0.02$), respectively; and colonic neoplasms in 13 patients (0.2%) and 4 patients (0.1%) ($P=0.03$). Known gastrointestinal bleeding preceded the diagnosis of colonic neoplasms in nine patients (seven in the prasugrel group and two in the clopidogrel group).

DISCUSSION

The risk of myocardial ischemic events in patients with acute coronary syndromes has been shown to be reduced by means of platelet inhibition with the use of aspirin²¹ and, even more effectively as compared with the use of aspirin alone, dual-antiplatelet therapy with aspirin and ticlopidine or clopidogrel, two inhibitors of the P2Y₁₂ adenosine-diphosphate receptor.^{1-3,5} Our results show that the treatment of patients with acute coronary syndromes, across the full spectrum of such syndromes, with prasugrel (a 60-mg loading dose,

Table 2. Major Efficacy End Points in the Overall Cohort at 15 Months.*

End Point	Prasugrel (N = 6813) <i>no. of patients (%)</i>	Clopidogrel (N = 6795) <i>no. of patients (%)</i>	Hazard Ratio for Prasugrel (95% CI)	P Value†
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary end point)	643 (9.9)	781 (12.1)	0.81 (0.73–0.90)	<0.001
Death from cardiovascular causes	133 (2.1)	150 (2.4)	0.89 (0.70–1.12)	0.31
Nonfatal MI	475 (7.3)	620 (9.5)	0.76 (0.67–0.85)	<0.001
Nonfatal stroke	61 (1.0)	60 (1.0)	1.02 (0.71–1.45)	0.93
Death from any cause	188 (3.0)	197 (3.2)	0.95 (0.78–1.16)	0.64
Death from cardiovascular causes, nonfatal MI, or urgent target-vessel revascularization	652 (10.0)	798 (12.3)	0.81 (0.73–0.89)	<0.001
Death from any cause, nonfatal MI, or nonfatal stroke	692 (10.7)	822 (12.7)	0.83 (0.75–0.92)	<0.001
Urgent target-vessel revascularization	156 (2.5)	233 (3.7)	0.66 (0.54–0.81)	<0.001
Death from cardiovascular causes, nonfatal MI, nonfatal stroke, or rehospitalization for ischemia	797 (12.3)	938 (14.6)	0.84 (0.76–0.92)	<0.001
Stent thrombosis‡	68 (1.1)	142 (2.4)	0.48 (0.36–0.64)	<0.001

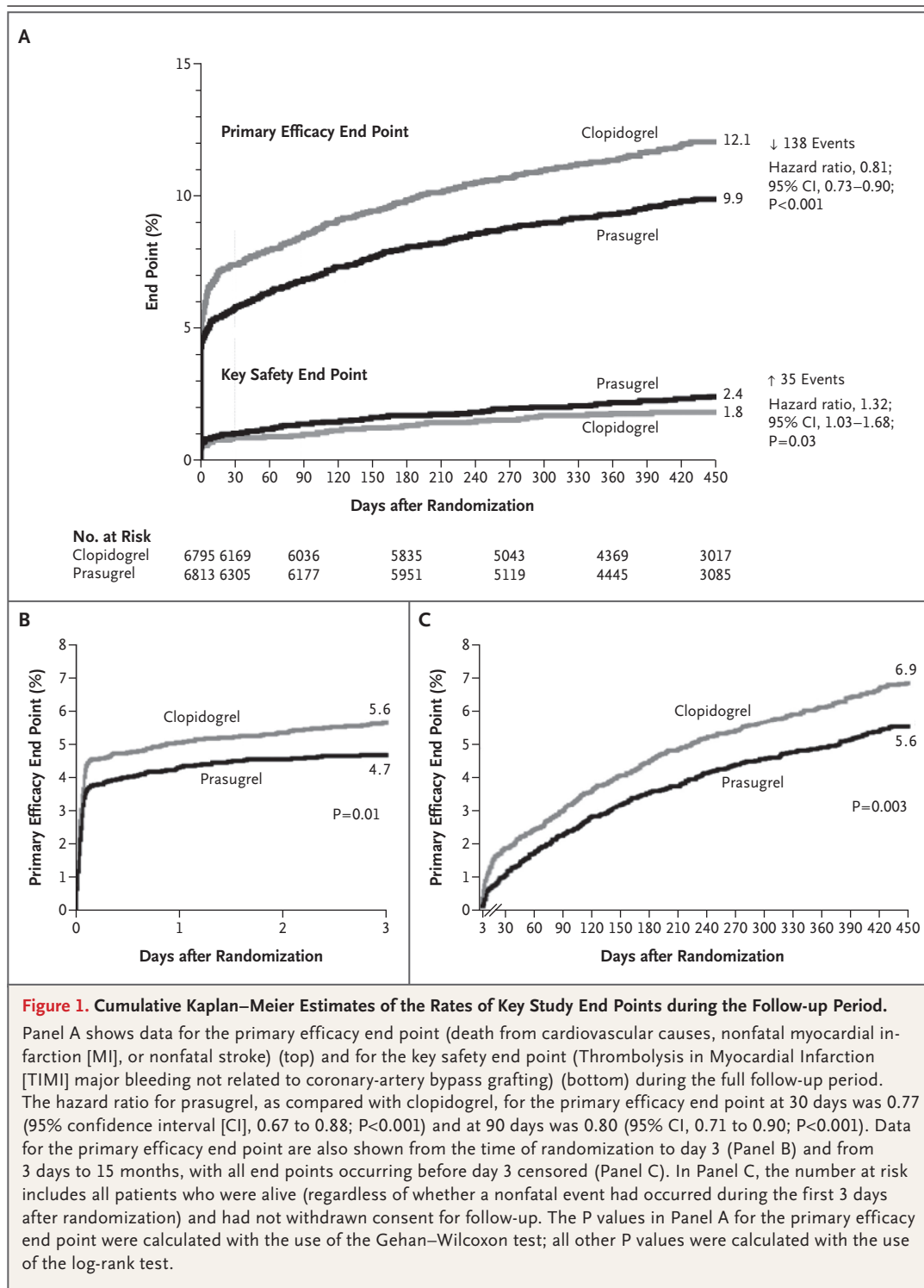
* The percentages are Kaplan–Meier estimates of the rate of the end point at 15 months. Patients could have had more than one type of end point. Death from cardiovascular causes and fatal bleeding (Table 3) are not mutually exclusive, since intracranial hemorrhage and death after cardiovascular procedures that were complicated by fatal bleeding were included in both end points. MI denotes myocardial infarction.

† P values were calculated with the use of the log-rank test. The prespecified analysis for the primary end point used the Gehan–Wilcoxon test, for which the P value was less than 0.001.

‡ 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: 6422 patients in each of the two treatment groups.

followed by a 10-mg maintenance dose), as compared with clopidogrel at the standard, approved dose, resulted in a significant 2.2% absolute reduction and a 19% relative reduction in the rate of the primary efficacy end point (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). The rates of ischemic events were also reduced in the prasugrel group, with a 2.3% absolute reduction and a 24% relative reduction for myocardial infarction, a 1.2% absolute reduction and a 34% relative reduction for urgent target-vessel revascularization, and a 1.3% absolute reduction and a 52% relative reduction for stent thrombosis, a rare but potentially devastating clinical event. Our study was not powered to detect a reduction in the rate of death from cardiovascular causes, and no significant benefit was seen for prasugrel over clopidogrel. However, a 0.3% absolute reduction and a 42% relative reduction were found for recurrent myocardial infarction followed by death from cardiovascular causes.

The reduction in the rate of ischemic events by means of antiplatelet agents, including both oral agents (aspirin and clopidogrel)^{1,21} and intravenous agents (glycoprotein IIb/IIIa-receptor antagonists),^{22–24} has uniformly been accompanied by an increase in bleeding. The Antithrombotic Trialists' Collaboration reported a proportional increase in the odds of major bleeding of 60% with the use of antiplatelet agents (largely aspirin), as compared with placebo.²¹ In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, therapy with clopidogrel plus aspirin, as compared with aspirin alone, was associated with a 38% increase in the odds of major bleeding.¹ The reduction in ischemic events we observed with prasugrel as compared with standard-dose clopidogrel was, as expected, associated with a significant increase in the rate of bleeding. The relative rate of TIMI major hemorrhage was increased by 32% with prasugrel (Table 3). There was an increase in the rate of life-threatening bleeding with prasugrel, including a significant increase in fatal



major hemorrhage. Bleeding episodes, including major or life-threatening hemorrhage, were more frequent in the prasugrel group than in the clopidogrel group, both near the time of PCI and after

PCI. Though few patients underwent CABG, major bleeding occurred at a higher rate among those receiving prasugrel than among those receiving clopidogrel. This finding suggests that, with a

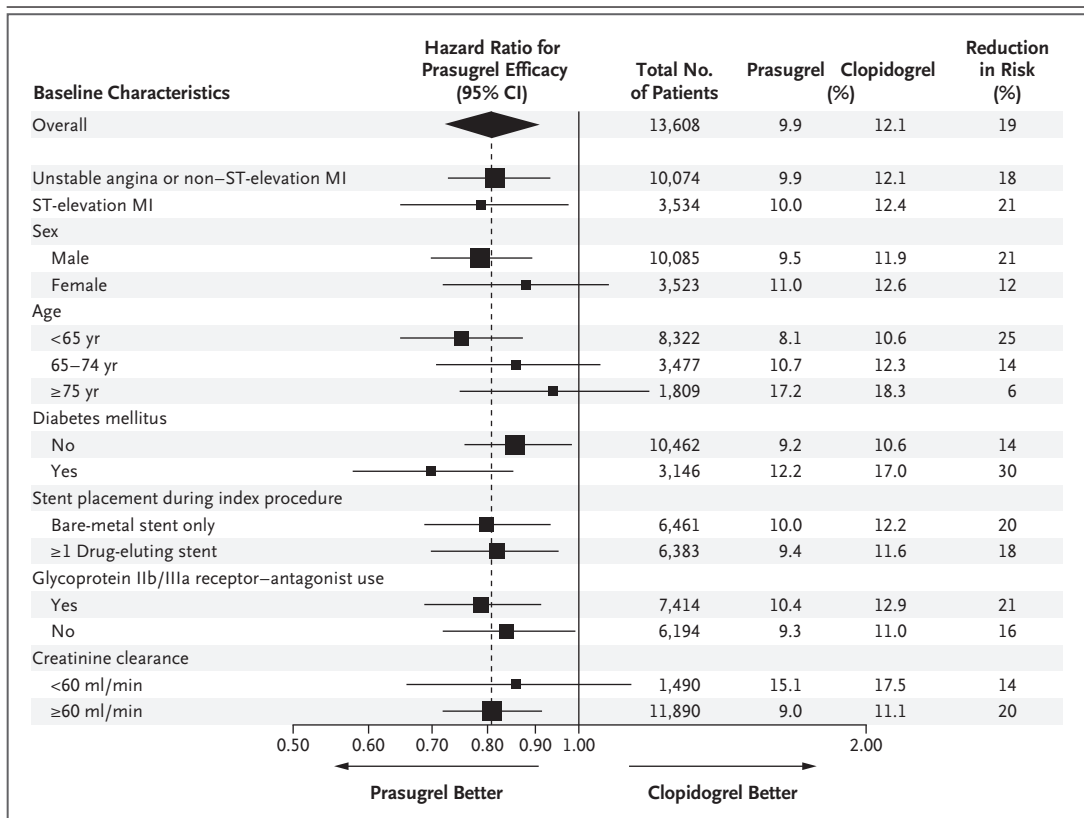


Figure 2. Hazard Ratios and Rates of the Primary End Point, According to Selected Subgroups of Study Patients.

The primary end point was defined as death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal stroke. The percentages are Kaplan–Meier estimates of the rate of the end point at 15 months. For each subgroup, the size of the square is proportional to the number of patients in the subgroups and represents the point estimate of the treatment effect. The overall treatment effect of prasugrel as compared with clopidogrel is represented by the diamond, and the dashed vertical line represents the corresponding overall point estimate. None of the P values for interactions were significant. Glycoprotein IIb/IIIa–receptor antagonist use was that during the index hospitalization.

strategy of more potent platelet inhibition, greater attention to the discontinuation of therapy before surgery may be needed.²⁵

Although the results of post hoc subgroup analyses should be considered exploratory, we identified three subgroups of interest that had less clinical efficacy and greater absolute levels of bleeding than the overall cohort, resulting in less net clinical benefit or in clinical harm. These included patients with a history of stroke or transient ischemic attack before enrollment, the elderly (age ≥75 years), and those with a body weight of less than 60 kg, risk factors that have been previously identified as being associated with an increased risk of adverse outcomes from the use of antiplatelet or antithrombotic agents.^{26,27} Patients who had had a cerebrovascular event before en-

rollment in our trial had numerically worse clinical outcomes, as measured in terms of the primary end point, and more frequent bleeding (including intracranial bleeding) than did those without such a history. In previous studies of patients with stroke,²⁸ dual-antiplatelet therapy has been associated with an increased risk of adverse outcomes, particularly intracranial bleeding, as compared with single-antiplatelet therapy. We therefore believe that our findings regarding prasugrel among patients with a history of cerebrovascular events add to the concerns about the risk of intensive inhibition of platelet aggregation in this population. Among the elderly and among patients with a body weight of less than 60 kg in whom neither net benefit nor net harm was observed, it would be expected that increased levels

Table 3. Thrombolysis in Myocardial Infarction (TIMI) Bleeding End Points in the Overall Cohort at 15 Months.*

End Point	Prasugrel (N=6741) <i>no. of patients (%)</i>	Clopidogrel (N=6716) <i>no. of patients (%)</i>	Hazard Ratio for Prasugrel (95% CI)	P Value
Non-CABG-related TIMI major bleeding (key safety end point)	146 (2.4)	111 (1.8)	1.32 (1.03–1.68)	0.03
Related to instrumentation	45 (0.7)	38 (0.6)	1.18 (0.77–1.82)	0.45
Spontaneous	92 (1.6)	61 (1.1)	1.51 (1.09–2.08)	0.01
Related to trauma	9 (0.2)	12 (0.2)	0.75 (0.32–1.78)	0.51
Life-threatening†	85 (1.4)	56 (0.9)	1.52 (1.08–2.13)	0.01
Related to instrumentation	28 (0.5)	18 (0.3)	1.55 (0.86–2.81)	0.14
Spontaneous	50 (0.9)	28 (0.5)	1.78 (1.12–2.83)	0.01
Related to trauma	7 (0.1)	10 (0.2)	0.70 (0.27–1.84)	0.47
Fatal‡	21 (0.4)	5 (0.1)	4.19 (1.58–11.11)	0.002
Nonfatal	64 (1.1)	51 (0.9)	1.25 (0.87–1.81)	0.23
Intracranial	19 (0.3)	17 (0.3)	1.12 (0.58–2.15)	0.74
Major or minor TIMI bleeding	303 (5.0)	231 (3.8)	1.31 (1.11–1.56)	0.002
Bleeding requiring transfusion§	244 (4.0)	182 (3.0)	1.34 (1.11–1.63)	<0.001
CABG-related TIMI major bleeding¶	24 (13.4)	6 (3.2)	4.73 (1.90–11.82)	<0.001

* The data shown are for patients who received at least one dose of the study drug 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. Percentages are Kaplan–Meier estimates of the rate of the end point at 15 months. Patients could have had more than one type of end point. CABG denotes coronary-artery bypass grafting.

† The most frequent sites of life-threatening bleeding were gastrointestinal sites, intracranial sites, the puncture site, and retroperitoneal sites.

‡ One patient in the clopidogrel group had a fatal gastrointestinal hemorrhage while receiving the study medication, but hemoglobin testing was not performed and, therefore, the criteria for TIMI major bleeding (including life-threatening and fatal bleeding) could not be applied and the data do not appear in this table.

§ Transfusion was defined as any transfusion of whole blood or packed red cells.

¶ 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. The ratio is the odds ratio, rather than the hazard ratio, and was evaluated with the use of the Cochran–Mantel–Haenszel test.

of the active metabolite of prasugrel may have led to an increased risk of bleeding, owing to altered disposition of the drug or smaller body size. In contrast, a large majority of patients without any of these risk factors had a significant net clinical benefit with the prasugrel regimen studied, as compared with the clopidogrel regimen (hazard ratio, 0.80; 95% CI, 0.71 to 0.89; $P < 0.001$). Additional work to define populations with an increased risk of bleeding, in association with oral regimens yielding high degrees of inhibition of platelet aggregation, is likely to be helpful in guiding therapy.

In addition to the results of our key prespecified safety analyses, we noted a higher rate of adverse events related to colonic cancer in the prasugrel group than in the clopidogrel group. Though

we cannot fully rule out either a possible causative effect or the play of chance, this imbalance may have resulted from the more potent antiplatelet effect of prasugrel bringing more events to medical attention, a phenomenon seen with other anticoagulant agents, including warfarin.^{29,30}

Treatment with prasugrel at the dosage used in our trial has been shown to generate higher and more consistent levels of active metabolite than treatment with approved doses of clopidogrel.¹³ This results in higher levels of mean inhibition of platelet aggregation, lower interpatient variability in such inhibition, and fewer patients considered to have poor responsiveness or hyporesponsiveness when platelet function is assessed in the laboratory.¹³ Considerable research has focused on the presence and clinical meaning of hyporesponsive-

Table 4. The Balance of Efficacy and Safety in Selected Subgroups.*

End Point	Prasugrel <i>no. of patients/total no. (%)</i>	Clopidogrel	Hazard Ratio for Prasugrel (95% CI)	P Value	P Value for Interaction†
History of stroke or TIA					
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary efficacy end point)	47/262 (19.1)	35/256 (14.4)	1.37 (0.89–2.13)	0.15	
Non-CABG-related TIMI major bleeding	14/257 (5.0)	6/252 (2.9)	2.46 (0.94–6.42)	0.06	
Death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleeding	57/262 (23.0)	39/256 (16.0)	1.54 (1.02–2.32)	0.04	
No history of stroke or TIA					
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary efficacy end point)	596/6551 (9.5)	746/6539 (12.0)	0.79 (0.71–0.88)	<0.001	0.02
Non-CABG-related TIMI major bleeding	132/6484 (2.3)	105/6464 (1.8)	1.26 (0.97–1.62)	0.08	0.22
Death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleeding	727/6551 (11.8)	854/6539 (13.8)	0.84 (0.76–0.93)	<0.001	0.006
Age ≥75 yr, body weight <60 kg, or history of stroke or TIA					
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary efficacy end point)	198/1320 (16.1)	199/1347 (16.0)	1.02 (0.84–1.24)	0.83	
Non-CABG-related TIMI major bleeding	52/1305 (4.3)	38/1328 (3.3)	1.42 (0.93–2.15)	0.10	
Death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleeding	249/1320 (20.2)	239/1347 (19.0)	1.07 (0.90–1.28)	0.43	
Age <75 yr, body weight ≥60 kg, and no history of stroke or TIA					
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary efficacy end point)	433/5421 (8.3)	569/5383 (11.0)	0.74 (0.66–0.84)	<0.001	0.008
Non-CABG-related TIMI major bleeding	91/5390 (2.0)	73/5337 (1.5)	1.24 (0.91–1.69)	0.17	0.64
Death from any cause, nonfatal MI, nonfatal stroke, or non-CABG-related nonfatal TIMI major bleeding	522/5421 (10.2)	641/5383 (12.5)	0.80 (0.71–0.89)	<0.001	0.006

* The rates of Thrombolysis in Myocardial Infarction (TIMI) major bleeding not related to coronary-artery bypass grafting (CABG) were calculated as Kaplan–Meier estimates for patients who received at least one dose of the study drug 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. The rates of the other end points were calculated as Kaplan–Meier estimates in the intention-to-treat cohort. TIA denotes transient ischemic attack, and MI myocardial infarction.

† P values for interaction were those for the interaction between the status of the risk factor and the hazard ratio for the end point.

ness to clopidogrel in patients with coronary artery disease who have undergone PCI.^{6–11} The data from our trial, which was adequately powered to evaluate clinical events, show that, as compared with standard-dose clopidogrel therapy, a regimen that improves the inhibition of platelet aggregation is associated with fewer ischemic events. This improvement in the rate of ischemic events as a

result of greater platelet inhibition was not assured, given the absence of increased efficacy with higher doses of aspirin³¹ and the higher rates of ischemic events seen with the addition of oral glycoprotein IIb/IIIa-receptor antagonists (potent inhibitors of platelet aggregation) to aspirin.³²

As a result of the intention to have all patients undergo PCI, our trial was largely a comparison of

prasugrel therapy and clopidogrel therapy among patients treated with a thienopyridine at the time of the identification of coronary anatomy appropriate for PCI, rather than a comparison of routine pretreatment with either agent before diagnostic cardiac catheterization. A strategy of clopidogrel loading when coronary anatomy is known is now used by many cardiologists because of concern about surgical bleeding if a patient receives clopidogrel and then (because of a finding on coronary angiography) goes on to undergo CABG.²⁵ Pharmacodynamic data have shown that the degree of inhibition of platelet aggregation achieved with prasugrel within 30 minutes after treatment is similar to the peak effect of clopidogrel 6 hours after administration, suggesting that prolonged pretreatment may not be necessary for prasugrel to achieve its therapeutic effect.¹³ The more rapid onset of an antiplatelet effect with prasugrel than with clopidogrel may have played an important role in the efficacy benefit, an assertion supported by the reduction in the rate of early myocardial infarction (before day 3) (Fig. 1B), despite the lack of pretreatment. However, when considering only end points occurring after day 3 (Fig. 1C), the time at which the use of each drug should have resulted in the steady-state inhibition of platelet aggregation, the significant reduction in the rate of ischemic end points persisted, suggesting a continued benefit of greater inhibition of platelet aggregation during maintenance therapy.

Partly because of data reporting an improved inhibition of platelet aggregation,^{33,34} many clinicians have adopted the use of a higher-than-standard loading dose of clopidogrel in patients with PCI, a practice endorsed by guideline committees.^{35,36} The clinical-efficacy data supporting the use of such higher-dose clopidogrel have been from small studies and have been inconsistent.^{37,38} The use of prasugrel (60 mg) has been shown to result in a greater inhibition of platelet aggregation than the use of clopidogrel (600 mg) in patients with chronic coronary artery disease.¹⁵ The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation (PRINCIPLE)-TIMI 44 trial¹⁶ showed a markedly superior inhibition of platelet aggregation, with regard to multiple measures of platelet function, in patients who had undergone elective PCI and who had received the regimen of prasugrel used in our study as compared with a higher-than-standard dose regimen of clopidogrel (a 600-mg load-

ing dose and a 150-mg maintenance dose) — though the PRINCIPLE-TIMI 44 trial was not powered to study clinical end points.

In our study of a selected population with moderate-to-high-risk acute coronary syndromes, on average, for every 1000 patients treated with prasugrel as compared with clopidogrel at the doses studied, 23 myocardial infarctions were prevented, with an excess of six non-CABG-related TIMI major hemorrhages. The estimated number of patients needed to be treated with prasugrel at the dosage studied, as compared with standard-dose clopidogrel, to prevent one primary efficacy end point during a 15-month period was 46. The number of patients who would have to be treated to result in an excess non-CABG-related TIMI major hemorrhage was 167.

Our data support the hypothesis that the greater inhibition of adenosine diphosphate-induced platelet aggregation by means of the tested regimen of prasugrel, a potent oral P2Y₁₂ inhibitor, is more effective at preventing ischemic events than is the inhibition conferred by a standard regimen of clopidogrel. However, this beneficial effect is accompanied by an increase in the rate of major bleeding. When considering the choice of antiplatelet regimens for the treatment of patients with acute coronary syndromes who are undergoing PCI, clinicians need to weigh the benefits and risks of intensive inhibition of platelet aggregation.

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APPENDIX

The members of the Operations and Steering Committees of the TRITON-TIMI 38 were as follows (with principal investigators at participating centers listed separately, in the Supplementary Appendix): **TIMI Study Group, Brigham and Women's Hospital, Boston:** E. Braunwald (study chair), E.M. Antman (principal investigator), S.D. Wiviott (investigator), C.M. Gibson (investigator), C.H. McCabe (director), S.A. Murphy (lead biostatistician), J. Buros (biostatistician), S. McHale (project manager); **Sponsors:** *Eli Lilly* — J. Riesmeyer, J.A. Ware, G. Weerakkody, W. Macias, E. Moscarelli, J. Croaning; *Daiichi Sankyo* — J. Warmke, F. Plat, T. Bocanegra, J. Hanyok, C. Hsu; **Data Coordinating Center (Quintiles):** K. Long, D. White, S. Boyle; **Steering Committee:** all members of the TIMI Study Group and sponsor staff listed above; *France* — G. Montalescot (coprincipal investigator), P.G. Steg; *Norway* — L. Aaberge; *Denmark* — H.R. Anderson; *Italy* — D. Ardissino, S. De Servi; *Australia* — P. Aylward; *Chile* — R. Corbalan; *South Africa* — A. Dalby; *Slovak Republic* — V. Fridrich; *United States* — M. Furman, D. Kereiakes, N. Kleiman, J. Popma; *Canada* — S. Goodman; *Israel* — S. Gottlieb; *Argentina* — E. Gurfinkel; *Austria* — K. Huber; *Hungary* — M. Keltai; *Spain* — J. Lopez-Sendon; *Switzerland* — T. Luscher; *Germany* — F.-J. Neumann, A. Schomig; *Brazil* — J. Nicolau; *Poland* — W. Ruzyllo; *Sweden* — F. Schersten; *Portugal* — R. Seabra-Gomes; *Iceland* — A. Sigurdsson; *Finland* — M. Syvanne; *Belgium* — F. Van de Werf; *the Netherlands* — F. Verheugt; *New Zealand* — H. White; *Czech Republic* — P. Widimsky; *United Kingdom* — R. Wilcox; **Data Monitoring Committee:** D.O. Williams (chair); D. DeMets (statistician); C. Bode, S. King, U. Sigwart; **Clinical Events Committee:** B. Scirica (administrative chair), E. Awtry, C. Berger, S. Bernard, A. Desai, E. Gelfand, C. Ho, F. Jaffer, S. Kathiresan, D. Leeman, M. Link, W. Maisel, F. Ruberg, U. Tedrow, J. Vita, P. Zimetbaum.

REFERENCES

1. The 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. [Errata, *N Engl J Med* 2001;345:1506, 1716.]
2. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;366:1607-21.
3. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;352:1179-89.
4. Mehta SR, Yusuf S. Short- and long-term oral antiplatelet therapy in acute coronary syndromes and percutaneous coronary intervention. *J Am Coll Cardiol* 2003;41:Suppl S:79S-88S.
5. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411-20. [Erratum, *JAMA* 2003;289:987.]
6. Gurbel PA, Bliden KP. Durability of platelet inhibition by clopidogrel. *Am J Cardiol* 2003;91:1123-5.
7. 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;45:246-51.
8. Buonamici P, Marcucci R, Migliorini A, et al. Impact of platelet reactivity after clopidogrel administration on drug-eluting stent thrombosis. *J Am Coll Cardiol* 2007;49:2312-7.
9. Gurbel PA, Bliden KP, Samara W, et al. Clopidogrel effect on platelet reactivity in patients with stent thrombosis: results of the CREST Study. *J Am Coll Cardiol* 2005;46:1827-32.
10. Hochholzer W, Trenk D, Bestehorn HP, et al. Impact of the degree of periprocedural platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. *J Am Coll Cardiol* 2006;48:1742-50.
11. Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. *Circulation* 2004;109:3171-5.
12. Niitsu Y, Jakubowski JA, Sugidachi A, Asai F. Pharmacology of CS-747 (prasugrel, LY640315), a novel, potent antiplatelet agent with in vivo P2Y12 receptor antagonist activity. *Semin Thromb Hemost* 2005;31:184-94.
13. Brandt JT, Payne CD, Wiviott SD, et al. A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. *Am Heart J* 2007;153:66.e9-66.e16.
14. Jernberg T, Payne CD, Winters KJ, et al. Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease. *Eur Heart J* 2006;27:1166-73.
15. Varenhorst C, Braun O, James S, et al. Greater inhibition of platelet aggregation with prasugrel 60 mg loading dose compared with a clopidogrel 600 mg loading dose in aspirin-treated patients. *Eur Heart J* 2007;28:Suppl:189. abstract.
16. Wiviott SD, Trenk D, Frelinger AL III, et al. Prasugrel compared to high loading and maintenance dose clopidogrel in patients with planned percutaneous coronary intervention: the PRINCIPLE-TIMI 44 trial. *Circulation* (in press).
17. Wiviott SD, Antman EM, Winters KJ, et al. 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;111:3366-73.
18. Wiviott SD, Antman EM, Gibson CM, et al. Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet Inhibition with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). *Am Heart J* 2006;152:627-35.
19. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284:835-42.
20. Mauri L, Hsieh W, Massaro JM, Ho KKL, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007;356:1020-9.
21. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86. [Erratum, *BMJ* 2002;324:141.]
22. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. *Lancet* 1997;349:1429-35. [Erratum, *Lancet* 1997;350:744.]
23. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998;338:1488-97. [Erratum, *N Engl J Med* 1998;339:415.]
24. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatid in patients with acute coronary syndromes. *N Engl J Med* 1998;339:436-43.
25. Fox KA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the

- Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. *Circulation* 2004;110:1202-8.
26. Alexander KP, Chen AY, Roe MT, et al. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. *JAMA* 2005;294:3108-16.
27. Mahaffey KW, Harrington RA, Simoons ML, et al. Stroke in patients with acute coronary syndromes: incidence and outcomes in the platelet glycoprotein IIb/IIIa in unstable angina. *Circulation* 1999;99:2371-7.
28. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004;364:331-7.
29. Carey RJ. Warfarin-induced rectal bleeding as clue to colon cancer. *Lancet* 1984;1:505-6.
30. Jaffin BW, Bliss CM, LaMont JT. Significance of occult gastrointestinal bleeding during anticoagulation therapy. *Am J Med* 1987;83:269-72.
31. Campbell CL, Smyth S, Montalescot G, Steinhubl SR. Aspirin dose for the prevention of cardiovascular disease: a systematic review. *JAMA* 2007;297:2018-24.
32. Cannon CP. Learning from the recently completed oral glycoprotein IIb/IIIa receptor antagonist trials. *Clin Cardiol* 2000; 23:Suppl 6:VI-14-VI-17.
33. Montalescot G, Sideris G, Meuleman C, et al. A randomized comparison of high clopidogrel loading doses in patients with non-ST-segment elevation acute coronary syndromes: the ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) trial. *J Am Coll Cardiol* 2006;48:931-8.
34. von Beckerath N, Taubert D, Pogatsa-Murray G, Schömig E, Kastrati A, Schömig A. Absorption, metabolism, and antiplatelet effects of 300-, 600-, and 900-mg loading doses of clopidogrel: results of the ISAR-CHOICE (Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) Trial. *Circulation* 2005; 112:2946-50.
35. Silber S, Albertsson P, Aviles FF, et al. Guidelines for percutaneous coronary interventions. *Eur Heart J* 2005;26:804-47.
36. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation* 2006; 113:e166-e286.
37. Patti G, Colonna G, Pasceri V, Pepe LL, Montinaro A, Di Sciascio G. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: results from the ARMYDA-2 (Antiplatelet therapy for Reduction of Myocardial Damage during Angioplasty) study. *Circulation* 2005;111:2099-106.
38. Wolfram RM, Torguson RL, Hassani SE, et al. Clopidogrel loading dose (300 versus 600 mg) strategies for patients with stable angina pectoris subjected to percutaneous coronary intervention. *Am J Cardiol* 2006;97:984-9.

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