Effect of the Novel Thienopyridine Prasugrel Compared With Clopidogrel on Spontaneous and Procedural Myocardial Infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction

An Application of the Classification System From the Universal Definition of Myocardial Infarction

David A. Morrow, MD, MPH; Stephen D. Wiviott, MD; Harvey D. White, DSc; Jose C. Nicolau, MD; Ezio Bramucci, MD; Sabina A. Murphy, MPH; Marc P. Bonaca, MD; Christian T. Ruff, MD; Benjamin M. Scirica, MD, MPH; Carolyn H. McCabe, BS; Elliott M. Antman, MD; Eugene Braunwald, MD

Background—Prasugrel is a novel thienopyridine that reduces new or recurrent myocardial infarctions (MIs) compared with clopidogrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention. This effect must be balanced against an increased bleeding risk. We aimed to characterize the effect of prasugrel with respect to the type, size, and timing of MI using the universal classification of MI.

Methods and Results—We studied 13,608 patients with acute coronary syndrome undergoing percutaneous coronary intervention randomized to prasugrel or clopidogrel and treated for 6 to 15 months in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI 38). Each MI underwent supplemental classification as spontaneous, secondary, or sudden cardiac death (types 1, 2, and 3) or procedure related (Types 4 and 5) and examined events occurring early and after 30 days. Prasugrel significantly reduced the overall risk of MI (7.4% versus 9.7%; hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.67 to 0.85; \( P < 0.0001 \)). This benefit was present for procedure-related MIs (4.9% versus 6.4%; HR, 0.76; 95% CI, 0.66 to 0.88; \( P = 0.0002 \)) and nonprocedural (type 1, 2, or 3) MIs (2.8% versus 3.7%; HR, 0.72; 95% CI, 0.59 to 0.88; \( P = 0.0013 \)) and consistently across MI size, including MIs with a biomarker peak ≥5 times the reference limit (HR, 0.74; 95% CI, 0.64 to 0.86; \( P = 0.0001 \)). In landmark analyses starting at 30 days, patients treated with prasugrel had a lower risk of any MI (2.9% versus 3.7%; HR, 0.77; \( P = 0.014 \)), including nonprocedural MI (2.3% versus 3.1%; HR, 0.74; 95% CI, 0.60 to 0.92; \( P = 0.0069 \)).

Conclusion—Treatment with prasugrel compared with clopidogrel for up to 15 months in patients with acute coronary syndrome undergoing percutaneous coronary intervention significantly reduces the risk of MIs that are procedure related and spontaneous and those that are small and large, including new MIs occurring during maintenance therapy. (Circulation. 2009;119:2758-2764.)

Key Words: angioplasty • myocardial infarction • platelets • prasugrel • unstable angina

Prasugrel is a novel thienopyridine that inhibits adenosine diphosphate–induced platelet aggregation more rapidly with less intra-individual variability and to a greater magnitude than do standard and higher doses of clopidogrel.1–3 In patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI), prasugrel reduces the risk of the composite of cardiovascular death, new or recurrent myocardial infarction (MI), or stroke compared...
with the approved dose of clopidogrel. This benefit of prasugrel was accompanied by an increase in the risk of bleeding, including severe bleeding. Given that the reduction in major cardiovascular events observed with prasugrel comprised predominantly a reduction in MI, the types of MI prevented with prasugrel take on particular clinical relevance, eg, whether the MIs were small or large or were periprocedural or spontaneous.

Clinical Perspective on p 2764

To characterize more completely the effect of prasugrel on new or recurrent MI, we applied the newly developed classification system from the universal definition of MI from the Joint European Society of Cardiology, American College of Cardiology, American Heart Association, and World Heart Federation Task Force for the redefinition of MI in the large (n=13,608), phase III Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction (TRITON—TIMI 38). The universal definition of MI has incorporated a new classification for the type of MI that distinguishes spontaneous (type 1), secondary (type 2), and procedure-related MI (types 4 and 5) as described in Table 1. In addition, the universal definition has specified reporting criteria for the size of MI, using the peak value of biomarkers of necrosis relative to the upper reference limit (URL). Using this classification system from the universal definition of MI, we investigated the efficacy of prasugrel with respect to the type, size, and whether the MI occurred early after presentation up to 30 days or during maintenance therapy with prasugrel versus clopidogrel after 30 days. In addition, we used this study as an opportunity to assess the value of this new classification system for detailed characterization of the MI end points within a clinical trial.

Methods

Study Population

The study design and primary results of TRITON-TIMI 38 have been published previously. TRITON-TIMI 38 was a multinational, randomized, double-blind, parallel-group study of prasugrel compared with clopidogrel in patients with ACS with planned PCI. Patients with moderate- to high-risk unstable angina, non–ST-segment elevation MI (NSTEMI), or ST-elevation MI (STEMI) were randomly assigned to receive either prasugrel, administered with a loading dose of 60 mg followed by 10 mg daily, or clopidogrel, administered with a loading dose of 300 mg followed by 75 mg daily. The loading dose of blinded study medication was given anytime between randomization and 1 hour after the patient left the catheterization laboratory.

The inclusion criteria for patients with unstable angina or NSTEMI were ischemic symptoms lasting at least 10 minutes and occurring within 72 hours before randomization, a TIMI risk score ≥3, and either an ST-segment deviation of ≥1 mm or an elevated concentration of cardiac troponin or creatine kinase-MB (CK-MB). Patients with STEMI 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 STEMI. All patients were planning to undergo PCI, and it was required that the coronary anatomy be defined before randomization in patients with unstable angina, those with NSTEMI, and patients undergoing delayed PCI for STEMI. Exclusion criteria relevant to this analysis included an increased risk of bleeding, cardiogenic shock, or the use of any thienopyridine within 5 days of enrollment. All patients provided written informed consent, and the protocol was approved by the institutional review board of each participating center.

End Points

The end point of MI was defined at the outset of the trial using criteria adapted from the earlier definition developed by the American College of Cardiology Task Force on Clinical Data Standards. Formulation of the end-point definition preceded the development of the universal definition of MI; thus, the criteria for MI differ in some aspects. To meet the trial end-point criteria, the MI had to be distinct from the index event and was defined by symptoms suggestive of ischemia/infarction, ECG data, cardiac biomarker, or pathological evidence of infarction depending on the clinical situation as follows: (1) For those without persistent biomarker elevation from the index event: CK-MB or troponin elevation above the URL, along with either ischemic chest symptoms lasting >20 minutes or ST-segment deviation ≥0.1 mV; (2) for those with persistent biomarker elevation known to be falling from the index event: biomarker increase of at least 50% of the preceding nadir (and above URL), along with either ischemic chest symptoms lasting >20 minutes or ST-segment deviation ≥0.1 mV; (3) for STEMI patients: elevation or re-elevation of ST segments, along with ischemic chest symptoms lasting >20 minutes or hemodynamic decompensation; (4) within 48 hours after PCI: CK-MB >3 times the URL on 2 samples after PCI or >5 times the URL on a single sample, provided that it is the final sample and >12 hours after PCI; and (5) within 48 hours after coronary artery bypass graft surgery (CABG): CK-MB >10 times the URL. For periprocedural MI, the biomarker had to be falling on serial measurements after the index event, with a subsequent rise in CK-MB of at least 50% of the preceding nadir. All end points, including MI, were adjudicated by an independent Clinical End Points Committee blinded to treatment assignment before locking the database.

CK-MB was measured in a central laboratory for serial samples obtained for up to 48 hours after randomization. Local CK-MB and troponin data were collected during the qualifying hospitalization and for suspected ischemic events throughout the study period. Potential myocardial ischemic events were identified through reporting by the investigator and programmatic checks of biomarker data.

For the purpose of this analysis, each Clinical End Points Committee–determined MI underwent a separate supplemental classification after database lock using the categories (Table 1) recommended by the universal definition of MI by reviewers who were blinded to treatment allocation. In addition, events were categorized on the basis of the peak biomarker concentration, either CK-MB or cardiac-specific troponin, using the reporting scheme as multiples of the URL (1 to <2, 2 to <3, 3 to <5, 5 to <10, and ≥10 times) as recommended by the Task Force for the Redefinition of MI. A nonprocedural MI was classified as type 1 (spontaneous) unless there was clear evidence of a secondary (type 2) cause of MI from the available source documentation. Source narratives, progress notes,
discharge summaries, and laboratory and ECG data were reviewed for clear evidence of a secondary cause of MI (eg, arrhythmia, profound anemia, or severe hypertension). Type 4b MI (associated with stent thrombosis) was defined using the Academic Research Consortium definition for definite angiographic stent thrombosis or pathologically confirmed stent thrombosis.9 The primary analysis of MI size was made using CK-MB when available and cardiac troponin in cases for which this was the only available biomarker at the time of the recurrent MI (n=123). Secondary analyses were performed using CK-MB or troponin data alone. The requisite biomarker data or reference limit was not available in 55 patients (4.5%) in whom the diagnosis was based on new Q waves, diagnostic ST-segment elevation, and angiographic data or for whom only narrative information on the biomarker results was available. The proportion of patients without the requisite biomarker data was particularly low among those with periprocedural MI for PCI (0.7%) or CABG (0%).

Details of each local assay manufacturer and platform were not collected in this trial. Therefore, the URL was defined by the MI limit reported by the local laboratory. Each MI also was classified on the basis of the presence or absence of diagnostic ST-segment elevation as determined by the reviewer.

Statistical Methods

Efficacy comparisons were performed on the basis of the time to the first event according to the intention-to-treat principle. Event rates for clinical outcomes were determined with the Kaplan–Meier method and compared by use of the log-rank test. Analyses of each MI type and size category were conducted using the time to the first event according to the intention-to-treat principle. Event rates for clear evidence of a secondary cause of MI (eg, arrhythmia, profound anemia, or severe hypertension). Type 4b MI (associated with stent thrombosis) was defined using the Academic Research Consortium definition for definite angiographic stent thrombosis or pathologically confirmed stent thrombosis.9 The primary analysis of MI size was made using CK-MB when available and cardiac troponin in cases for which this was the only available biomarker at the time of the recurrent MI (n=123). Secondary analyses were performed using CK-MB or troponin data alone. The requisite biomarker data or reference limit was not available in 55 patients (4.5%) in whom the diagnosis was based on new Q waves, diagnostic ST-segment elevation, and angiographic data or for whom only narrative information on the biomarker results was available. The proportion of patients without the requisite biomarker data was particularly low among those with periprocedural MI for PCI (0.7%) or CABG (0%).

Details of each local assay manufacturer and platform were not collected in this trial. Therefore, the URL was defined by the MI limit reported by the local laboratory. Each MI also was classified on the basis of the presence or absence of diagnostic ST-segment elevation as determined by the reviewer.

Statistical Methods

Efficacy comparisons were performed on the basis of the time to the first event according to the intention-to-treat principle. Event rates for clinical outcomes were determined with the Kaplan–Meier method and compared by use of the log-rank test. Analyses of each MI type and size category were conducted using the time to the first event according to the intention-to-treat principle. Event rates for clear evidence of a secondary cause of MI (eg, arrhythmia, profound anemia, or severe hypertension). Type 4b MI (associated with stent thrombosis) was defined using the Academic Research Consortium definition for definite angiographic stent thrombosis or pathologically confirmed stent thrombosis.9 The primary analysis of MI size was made using CK-MB when available and cardiac troponin in cases for which this was the only available biomarker at the time of the recurrent MI (n=123). Secondary analyses were performed using CK-MB or troponin data alone. The requisite biomarker data or reference limit was not available in 55 patients (4.5%) in whom the diagnosis was based on new Q waves, diagnostic ST-segment elevation, and angiographic data or for whom only narrative information on the biomarker results was available. The proportion of patients without the requisite biomarker data was particularly low among those with periprocedural MI for PCI (0.7%) or CABG (0%).

Details of each local assay manufacturer and platform were not collected in this trial. Therefore, the URL was defined by the MI limit reported by the local laboratory. Each MI also was classified on the basis of the presence or absence of diagnostic ST-segment elevation as determined by the reviewer.

Statistical Methods

Efficacy comparisons were performed on the basis of the time to the first event according to the intention-to-treat principle. Event rates for clinical outcomes were determined with the Kaplan–Meier method and compared by use of the log-rank test. Analyses of each MI type and size category were conducted using the time to the first event according to the intention-to-treat principle. Event rates for clear evidence of a secondary cause of MI (eg, arrhythmia, profound anemia, or severe hypertension). Type 4b MI (associated with stent thrombosis) was defined using the Academic Research Consortium definition for definite angiographic stent thrombosis or pathologically confirmed stent thrombosis.9 The primary analysis of MI size was made using CK-MB when available and cardiac troponin in cases for which this was the only available biomarker at the time of the recurrent MI (n=123). Secondary analyses were performed using CK-MB or troponin data alone. The requisite biomarker data or reference limit was not available in 55 patients (4.5%) in whom the diagnosis was based on new Q waves, diagnostic ST-segment elevation, and angiographic data or for whom only narrative information on the biomarker results was available. The proportion of patients without the requisite biomarker data was particularly low among those with periprocedural MI for PCI (0.7%) or CABG (0%).

Details of each local assay manufacturer and platform were not collected in this trial. Therefore, the URL was defined by the MI limit reported by the local laboratory. Each MI also was classified on the basis of the presence or absence of diagnostic ST-segment elevation as determined by the reviewer.

Results

Among the 13 608 patients enrolled, there were 1218 new or recurrent MIs among 1118 patients during a mean follow-up of 14.5 months. The clinical characteristics of the study population have been reported previously.2,6 Among study participants, 19% qualified for the trial with unstable angina, 55% with NSTEMI, and 26% with STEMI. The mean time from symptom onset to randomization for each of these qualifying syndromes was 29 hours for both unstable angina and NSTEMI and 6 hours for STEMI.

Classification of MI End Points

All 1218 MI end points were classified according to the type of MI, and 1163 (95.5%) had the requisite biomarker data and reference limit to determine the size of MI according to the universal definition of MI.5 The majority of new or recurrent MIs in this population with ACS undergoing PCI were spontaneous (type 1; n=397, 32.6%) or peri-PCI (type 4a; n=603, 49.5%). Secondary (type 2) MIs were infrequent (n=43, 3.5%). The full distribution of MIs according to MI type is shown in Figure 1A. Of the MIs with available biomarker data, 748 (66.1%) were associated with a peak biomarker value of at least 5 times the URL (Figure 1B). This finding was consistent using either CK-MB results alone (n=929) or troponin results alone (n=506) with 66.7% and 72.9% of values ≥5 times the URL, respectively.

Effect of Prasugrel on Procedure-Related and Nonprocedural MI

Compared with clopidogrel, prasugrel significantly reduced the incidence of both nonprocedural MI (type 1, 2, or 3; 2.8% versus 3.7%; hazard ratio [HR], 0.72; 95% confidence interval [CI], 0.59 to 0.88; P=0.0013) and procedure-related MI (type 4 or 5; 4.9% versus 6.4%; HR, 0.76; 95% CI, 0.66 to 0.88; P=0.0002). The benefit with respect to nonprocedural MI was driven predominantly by a significant reduction in spontaneous (type 1) MI with prasugrel compared with clopidogrel (2.5% versus 3.4%; HR, 0.71; 95% CI, 0.58 to 0.88; P=0.0015; Figure 2). Given the small number of CABG-related events (Table 2), the reduction in the incidence of procedure-related MI (Figure 3) with prasugrel was related entirely to a lower incidence of PCI-related (type 4) MI (4.8% versus 6.4%; HR, 0.76; 95% CI, 0.66 to 0.88; P=0.0002).
The effect of prasugrel compared with clopidogrel with respect to all MI types is detailed in Table 2. Overall, the effect of prasugrel on MI was consistent, including with respect to new or recurrent STEMI (1.0% versus 2.1%; HR, 0.47; 95% CI, 0.35 to 0.63; P \leq 0.001) or NSTEMI (6.5% versus 7.9%; HR, 0.82; 95% CI, 0.72 to 0.93; P = 0.0024), whether procedure related or nonprocedural (Table 2). In addition, the effect of prasugrel on MI was consistent when the analysis was limited to patients with MI (n = 413) reported by the investigator (2.7% versus 3.9%; HR, 0.67; 95% CI, 0.55 to 0.82; P < 0.0001).

**Effect of Prasugrel on MI by Peak Biomarker Concentration**

The effect of prasugrel on new or recurrent MI was directionally consistent across the entire spectrum of MI sizes (Figure 4), including MIs associated with a \( \geq 5 \)-fold elevation in the peak biomarker of necrosis (4.7% versus 6.4%; HR, 0.74; 95% CI, 0.64 to 0.86; P = 0.0001). Both the absolute and relative reductions in recurrent MI were numerically greatest with respect to MIs associated with \( \geq 10 \)-fold elevation of the peak biomarker (Figure 4). This observation was consistent when limited to MIs associated with a \( \geq 10 \)-fold elevation of CK-MB (n = 339; HR, 0.73; 95% CI, 0.59 to 0.90; P = 0.0036) and those with a \( \geq 10 \)-fold elevation of cardiac troponin (n = 289; HR, 0.57; 95% CI, 0.45 to 0.73; P < 0.0001).

**Effect of Prasugrel by Timing of New or Recurrent MI**

By design of the trial, the majority of periprocedural events occurred with revascularization procedures for the qualifying event performed at the time of randomization. In contrast, the majority of spontaneous (type 1) MIs occurred after 30 days. Assessment of the effect of prasugrel on recurrent MI, both early and late, revealed a consistent benefit compared with clopidogrel (Figures 5 and 6). Specifically, prasugrel admin-

### Table 2. Effect of Prasugrel Compared With Clopidogrel on New or Recurrent MI Stratified by MI Type

<table>
<thead>
<tr>
<th>MI Type</th>
<th>Prasugrel ( (n=6813), ) n (%)</th>
<th>Clopidogrel ( (n=6795), ) n (%)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150 (2.5)</td>
<td>209 (3.4)</td>
<td>0.71 (0.58–0.88)</td>
<td>0.0015</td>
</tr>
<tr>
<td>2</td>
<td>19 (0.3)</td>
<td>23 (0.4)</td>
<td>0.82 (0.45–1.51)</td>
<td>0.53</td>
</tr>
<tr>
<td>3</td>
<td>1 (0.0)</td>
<td>4 (0.1)</td>
<td>0.25 (0.03–2.23)</td>
<td>0.18</td>
</tr>
<tr>
<td>4</td>
<td>324 (4.8)</td>
<td>424 (6.4)</td>
<td>0.76 (0.66–0.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4a</td>
<td>279 (4.1)</td>
<td>321 (4.7)</td>
<td>0.86 (0.74–1.01)</td>
<td>0.07</td>
</tr>
<tr>
<td>4b</td>
<td>48 (0.8)</td>
<td>107 (1.7)</td>
<td>0.45 (0.32–0.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5</td>
<td>4 (0.1)</td>
<td>3 (0.0)</td>
<td>1.33 (0.30–5.94)</td>
<td>0.71</td>
</tr>
<tr>
<td>1–3</td>
<td>169 (2.8)</td>
<td>232 (3.7)</td>
<td>0.72 (0.59–0.88)</td>
<td>0.0013</td>
</tr>
<tr>
<td>4–5</td>
<td>328 (4.9)</td>
<td>427 (6.4)</td>
<td>0.76 (0.66–0.88)</td>
<td>0.0002</td>
</tr>
<tr>
<td>STEMI*</td>
<td>63 (1.0)</td>
<td>134 (2.1)</td>
<td>0.47 (0.35–0.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1–3</td>
<td>21 (0.4)</td>
<td>39 (0.6)</td>
<td>0.54 (0.32–0.91)</td>
<td>0.019</td>
</tr>
<tr>
<td>4–5</td>
<td>42 (0.7)</td>
<td>97 (1.5)</td>
<td>0.43 (0.30–0.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NSTEMI*</td>
<td>424 (6.5)</td>
<td>513 (7.9)</td>
<td>0.82 (0.72–0.93)</td>
<td>0.0024</td>
</tr>
<tr>
<td>1–3</td>
<td>148 (2.4)</td>
<td>193 (3.1)</td>
<td>0.76 (0.62–0.95)</td>
<td>0.013</td>
</tr>
<tr>
<td>4–5</td>
<td>288 (4.3)</td>
<td>333 (5.0)</td>
<td>0.86 (0.73–1.01)</td>
<td>0.059</td>
</tr>
</tbody>
</table>

\*New or recurrent after randomization. Data are presented as the No. of MIs and the Kaplan–Meier estimated cumulative incidence (%) at 15 months. Note that subjects may have experienced a new or recurrent MI in \( >1 \) category.

istered long term beyond 30 days was associated with a significant reduction in nonprocedural MI during this maintenance phase of therapy (2.3% versus 3.1%; HR, 0.74; 95% CI, 0.60 to 0.92; \( P=0.0069 \)).

**Discussion**

In this analysis of >1200 new or recurrent MIs during 15 months of follow-up in patients with ACS treated with PCI, more potent and less variable inhibition of platelet aggregation with prasugrel compared with standard dosing of clopidogrel translated into a significant reduction in MI that was consistent across the spectrum of MIs of varying type, size, and timing. These data are likely to be valuable to clinicians in weighing the relative benefit and potential risks of prasugrel in the management of this population. Moreover, in what we believe to be the first reported application of the classification system recommended by the universal definition of MI in a large multinational phase III trial, this approach was found to be useful in providing a more complete characterization of the effect of the investigational treatment on new or recurrent MI.

**Clinical Implications**

Our findings demonstrate that the reduction in MI with prasugrel compared with clopidogrel observed in TRITON-TIMI 38 was not limited to periprocedural events during the invasive management of the qualifying ACS. Rather, prasugrel also was superior to approved dosing of clopidogrel for the reduction in spontaneous MI with a pattern of the event curves that showed continued separation over time. This late benefit during the maintenance period of treatment with prasugrel (after 30 days) was verified with the landmark analysis that revealed a 26% reduction in nonprocedural MI during long-term follow-up. These observations on the effect of prasugrel on spontaneous MI portend a potential advantage of prasugrel compared with clopidogrel for the medical management of patients with ACS being treated without an early invasive strategy, a hypothesis that is being tested prospectively in the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial (http://www.clinicaltrials.gov, NC T00699998).

In addition, the late benefit of prasugrel after 30 days provides additional evidence for a benefit of extended treatment with potent antiplatelet therapy in patients with angiographically confirmed coronary atherothrombosis. This finding corroborates observations from an exploratory analysis revealing a possible benefit of clopidogrel compared with placebo in the subsets of patients with prior MI and stroke enrolled in a large trial of patients with stable disease or at high risk for atherosclerosis.\(^9\) However, for each of these indications, the reduction of ischemic events should be weighed against the risk of major bleeding.

We also found that the majority of new or recurrent MIs in TRITON-TIMI 38 were associated with a >5-fold elevation of biomarkers and that the reduction in MI with prasugrel was consistent in pattern across MIs of all sizes (Figure 4) and numerically greatest with respect to the largest MIs. Only 59 patients would need to be treated to avoid 1 MI with a biomarker peak ≥3 times the URL. Although some studies have supported the prognostic significance of even small periprocedural MIs (CK-MB ratio 1 to 3 times the URL) with respect to long-term prognosis,\(^10\) greater consistency of an independent relationship with survival is established for periprocedural MIs with a peak CK-MB that is ≥3 times the URL.\(^11\) For example, in a study of patients undergoing PCI, a new periprocedural MI with peak CK-MB ≥3 times the URL was associated with a doubling of the risk of death over 3 years of follow-up,\(^12\) an association that is even stronger in patients with ACS undergoing PCI.\(^10\) In addition, the observation that the greatest benefit obtained with prasugrel was in the reduction of larger MIs is consistent with these events being platelet mediated rather than being limited to microinfarctions resulting from the downstream embolization of atherosclerotic material. This finding and the reduction in spontaneous MI point toward the benefit of more potent and consistent platelet inhibition for preventing platelet-mediated recurrent ischemic events. Finally, we have reported previously that the rate of MI with subsequent cardiovascular death was reduced with prasugrel compared with clopidogrel (0.4% versus 0.7%; HR, 0.58; 95% CI, 0.36 to 0.93; \( P=0.02 \)).\(^2\) Overall, our findings provide clear evidence that prasugrel reduces the risk of clinically relevant MIs in this ACS population.
Implications for Clinical Trials
We found that it was feasible to apply the complete classification system recommended by the universal definition of MI in a large multicenter trial using the case report form data and source documents routinely provided to our Clinical End Points Committee for adjudication of potential coronary ischemic end-point events. We believe that these results illustrate the value of this classification system for a detailed characterization of the MI end points recorded in a clinical trial and the enhanced insight that these data may provide for interpretation of the trial results. These data also begin to establish an expanded epidemiology of MI using the new universal definition classification system within the context of a clinical trial of patients with ACS. This system will also be valuable for collecting similar observational data in community-based cohorts and other clinical trials. It is possible that specific therapies may have different effectiveness with respect to the various types of MI owing to differences in underlying pathobiology. In addition, because this trial was initiated before the development of the universal MI criteria, it is important to recognize how the trial end-point definition of MI relates to the universal definition of MI. For example, the trial definition was constructed to preserve greater specificity for discrimination of a peri-PCI MI, requiring at least 2 samples with increased CK-MB >3 times the URL or 1 sample >5 times the URL compared with a single sample >3 times the URL considered to define PCI-related MI in the universal definition of MI. Similarly for periprocedural MI after CABG, an increase in CK-MB >10 times the URL was required compared with >5 times the URL in conjunction with additional noninvasive or invasive evidence of new loss of myocardium in the universal definition of MI. Finally, again aiming toward specificity, the trial definition required a >50% increase in a biomarker value following a declining pattern to support a diagnosis of reinfarction compared with a 20% change recommended in the universal criteria.

Study Limitations
The TRITON-TIMI 38 protocol was completed and the trial initiated recruitment before the finalization and publication of the universal definition of MI. Therefore, this analysis was performed retrospectively but used prospectively collected data available from the case report form and source documents. An investigator classification of MI type was not available for this analysis. It is possible that investigators had additional clinical information that could have enhanced the differentiation of type 2 from type 1 MI and that we may have underestimated the overall number of type 2 MIs in this analysis. In addition, articulation of more detailed criteria for the diagnosis of type 2 MI may be a worthwhile consideration for future iterations of the universal definition of MI. Nevertheless, because our analysis was performed by researchers blinded to treatment allocation, we would not expect bias in our results that would favor either treatment arm. In addition, the small proportion of type 2 MIs in this population is plausible, given that entry into the trial was based on ACS. Finally, because the details of each local assay manufacturer and platform were not collected in this trial, the URL was defined by the MI limit reported by the local laboratory. Given that some laboratories continue to use an MI limit above the level of the 99th percentile, our findings may underestimate the relative size of the MIs as a multiple of the URL.

Conclusions
Intensive oral antplatelet therapy with prasugrel compared with clopidogrel for up to 15 months in patients with ACS undergoing PCI significantly reduces the risk of both procedure-related and spontaneous MIs and small and large MIs, including new MIs during maintenance therapy. These results demonstrate consistency in the effect of prasugrel with respect to new or recurrent MIs of varying type, size, and timing.

Sources of Funding
This study was supported by a grant from Daiichi Sankyo Co, Ltd, and Eli Lilly and Co.

Disclosures
The TIMI Study Group has received significant research grant support from Accumetics, Amgen, AstraZeneca, Beckman Coulter, Bristol-Myers Squibb, CV Therapeutics, Daiichi Sankyo Co Ltd, Eli Lilly and Co, GlaxoSmithKline, Integrated Therapeutics, Merck and Co, Merck-Schering Plough Joint Venture, Nanosphere, Novartis Pharmaceuticals, Nuvelo, Ortho-Clinical Diagnostics, Pfizer, Roche Diagnostics, Sanofi-Aventis, Sanofi-Synthelabo, Schering-Plough, Siemens Medical Solutions, and Singulex. Dr Morrow has received honoraria for educational presentations from Beckman-Coulter, CV Therapeutics, and Eli Lilly. He has received consulting fees from Beckman-Coulter, Sanofi-Aventis, Schering Plough, and Siemens and remuneration from AstraZeneca for adjudication as a member of a Clinical Events Committee. Dr Wiviott reports receiving consulting fees or paid advisory board fees from Sanofi-Aventis and lecture fees from Daiichi Sankyo Co Ltd and Eli Lilly and Co. Dr White has received advisory fees from Sanofi-Aventis and GlaxoSmithKline. Dr Nicolau has received research grant support and honoraria from AstraZeneca, Bayer, Daiichi Sankyo Co Ltd, Eli Lilly and Co, Johnson and Johnson, Sanofi-Aventis, and Schering Plough and has participated in advisory activities for AstraZeneca, Sanofi-Aventis, and Schering-Plough. Dr Scirica reports having received consulting fees from AstraZeneca, Cogentus, and Eli Lilly and Co. Dr Antman has received consulting fees or paid advisory board fees from Sanofi-Aventis and lecture fees from Eli Lilly and Co and Sanofi-Aventis. Dr Braunwald reports receiving consulting fees or paid advisory board fees from Daiichi Sankyo Co Ltd and Sanofi-Aventis and lecture fees from Eli Lilly and Co and Sanofi-Aventis. The other authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

Prasugrel is a novel thienopyridine that reduces new or recurrent myocardial infarctions (MIs) compared with clopidogrel in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). This effect must be balanced against an increased bleeding risk. We characterized the effect of prasugrel with respect to the type, size, and timing of MI using the universal classification of MI among 13,608 patients with acute coronary syndrome undergoing percutaneous coronary intervention treated for 6 to 15 months with prasugrel or clopidogrel in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI 38). Prasugrel significantly reduced the overall risk of MIs (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.67 to 0.85; P < 0.0001). This benefit was present for procedure-related MIs (HR, 0.76; 95% CI, 0.66 to 0.88; P = 0.0002) and nonprocedural MIs (HR, 0.72; 95% CI, 0.59 to 0.88; P = 0.0013) and consistently across MI size, including MIs with a biomarker peak ≥5 times the reference limit (HR, 0.74; 95% CI, 0.64 to 0.86; P = 0.0001). In analyses starting at 30 days, patients treated with prasugrel had a lower risk of subsequent nonprocedural MI (P = 0.0069).

Therefore, we found that in patients with acute coronary syndrome treated with percutaneous coronary intervention, more potent and less variable inhibition of platelet aggregation with prasugrel compared with standard dosing of clopidogrel translated into a significant reduction in MI that was consistent across the spectrum of MIs of varying type, size, and timing. These data are likely to be valuable to clinicians in weighing the relative benefit and potential risks of prasugrel. In addition, we found that the classification system of the universal definition of MI was useful in providing a more complete characterization of the effect of the investigational treatment on new or recurrent MI.
Effect of the Novel Thienopyridine Prasugrel Compared With Clopidogrel on Spontaneous and Procedural Myocardial Infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38: An Application of the Classification System From the Universal Definition of Myocardial Infarction


_Circulation_. 2009;119:2758-2764; originally published online May 18, 2009; doi: 10.1161/CIRCULATIONAHA.108.833665

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/119/21/2758

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/