American College of Cardiology/American Heart Association/European Society of Cardiology/World Heart Federation Universal Definition of Myocardial Infarction Classification System and the Risk of Cardiovascular Death

Observations From the TRITON-TIMI 38 Trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38)

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Background—The availability of more sensitive biomarkers of myonecrosis and a new classification system from the universal definition of myocardial infarction (MI) have led to evolution of the classification of MI. The prognostic implications of MI defined in the current era have not been well described.

Methods and Results—We investigated the association between new or recurrent MI by subtype according to the European Society of Cardiology/American College of Cardiology/American Heart Association/World Health Federation Task Force for the Redefinition of MI Classification System and the risk of cardiovascular death among 13,608 patients with acute coronary syndrome in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38). The adjusted risk of cardiovascular death was evaluated by landmark analysis starting at the time of the MI through 180 days after the event. Patients who experienced an MI during follow-up had a higher risk of cardiovascular death at 6 months than patients without an MI (6.5% versus 1.3%, P < 0.001). This higher risk was present across all subtypes of MI, including type 4a (peri–percutaneous coronary intervention, 3.2%; P < 0.001) and type 4b (stent thrombosis, 15.4%; P < 0.001). After adjustment for important clinical covariates, the occurrence of any MI was associated with a 5-fold higher risk of death at 6 months (95% confidence interval 3.8–7.1), with similarly increased risk across subtypes.

Conclusions—MI is associated with a significantly increased risk of cardiovascular death, with a consistent relationship across all types as defined by the universal classification system. These findings underscore the clinical relevance of these events and the importance of therapies aimed at preventing MI.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00097591.

(Circulation. 2012;125:577-583.)

Key Words: myocardial infarction ■ mortality ■ outcomes

The epidemiology of myocardial infarction (MI) has changed in the era of newer, more sensitive biomarker assays and the new universal definition of MI clinical classification system. The ability to detect myocardial injury at increasingly lower concentrations of cardiac troponin has raised uncertainty for some clinicians as to the prognostic implications of these forms of infarction. Moreover, some have questioned the significance of MIs that occurred in specific clinical contexts, such as after percutaneous intervention (PCI) or when secondary to increased myocardial oxygen demand. This uncertainty poses a challenge to clinicians balancing the risks of therapies aimed at preventing these events. In addition, researchers have grappled with refining criteria for recurrent MI, particularly periprocedural events, in the design of clinical trials in acute coronary syndromes (ACS).
We previously described the epidemiology of new (or recurrent) MI after ACS using the universal definition of MI classification system to characterize MI subtypes (eg, type 1–spontaneous, type 2–demand) and the effect of the novel thienopyridine prasugrel across each class of MI. However, the prognostic implications of each MI type have not been explored adequately. Therefore, we assessed the risk of cardiovascular death after a new (or recurrent) MI in this setting, including according to the clinical subtypes defined by the universal definition of MI classification system.

Methods

Study Population
The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) was a randomized, double-blind, multinational study evaluating the efficacy and safety of the novel thienopyridine prasugrel compared with clopidogrel in patients across the spectrum of ACS. The design and primary results have been reported previously. Patients presenting with ACS who were undergoing PCI were randomized to treatment with either clopidogrel or prasugrel. The study cohort comprised 10 074 patients with non–ST-segment elevation ACS (NSTE-ACS) who met the inclusion criteria of ischemic symptoms of 10 minutes or more within 72 hours of randomization, TIMI risk score of 3 or higher, and either ST-segment deviation or elevated cardiac biomarkers of necrosis, as well as 3534 patients with ST-segment elevation myocardial infarction (STEMI), enrolled within 12 hours of symptom onset for those planned for PCI or within 14 days from initially treated medically. Exclusion criteria have been published previously: exclusions relevant to the present analysis included cardiogenic shock or any other medical condition that in the opinion of the investigator was associated with reduced survival over the expected treatment period (maximum of 15 months). All patients provided written informed consent, and the protocol was approved by the institutional review board or ethics committee according to local regulations.

Classification of MI
The criteria for new or recurrent MI were prespecified and developed on the basis of contemporary standardized definitions and have been described previously in detail. To meet the trial end-point criteria, the MI had to be distinct from the index event and was defined by recurrent symptoms suggestive of ischemia/infarction, ECG data, cardiac biomarker elevation (cardiac-specific troponin or creatine kinase-MB [CK-MB]), or pathological evidence of infarction. CK-MB was measured centrally (ADVIA Centaur, Siemens, Wallpole MA) after the qualifying PCI and used for the adjudication of periprocedural MI. Local biomarker data were used for adjudication of all other events. The Clinical End-points Committee (CEC) had access to all local biomarker information; however, cardiac troponin was used preferentially for the diagnosis of spontaneous MI, and CK-MB was used preferentially for the diagnosis of peri-PCI events. MI in the setting of biomarker elevation from a preceding event required a falling biomarker concentration before the new event with a subsequent increase of at least 50% in addition to symptoms or ECG changes. For periprocedural MI, MI within 48 hours of PCI required CK-MB >3 times the upper reference limit on 2 samples after PCI or >5 times on a single sample, and MI within 48 hours of coronary artery bypass grafting (CABG) required CK-MB >10 times the upper reference limit. All MIs were adjudicated by a blinded CEC. In addition, as a post hoc analysis, blinded reviewers subsequently classified all CEC-confirmed MIs using the categories defined by the universal definition of MI classification system, as well as by peak biomarker concentration.

Using the universal MI classification system, a type 1 MI was defined as a spontaneous event caused by a primary coronary event (eg, plaque erosion, plaque rupture, dissection). Type 2 MI was defined as myocardial injury caused by ischemia from either increased oxygen demand (eg, anemia, hypertension, hypotension) or decreased supply (eg, coronary artery spasm). Type 3 MI was defined as sudden unexpected cardiac death with symptoms or testing (eg, ECG, angiographic, or pathologic findings) suggestive of myocardial ischemia but without biomarkers of myocardial necrosis. Type 4a MI was defined as occurring in the setting of percutaneous intervention (PCI), and MI associated with stent thrombosis documented at angiography or at autopsy was classified as type 4b MI. Type 5 MI was defined as occurring in the setting of CABG surgery. The analysis of MI size was based on the relative elevation of biomarker concentration compared with the upper limit of normal and has been described in detail previously.

Cardiovascular Death
The primary end point for the present analysis was the occurrence of cardiovascular death, defined as any death with a demonstrable cardiovascular cause or any death that was not clearly attributable to a noncardiovascular cause. All deaths were adjudicated by use of prespecified definitions by the blinded CEC.

Statistical Analysis
Baseline characteristics were compared with the \( \chi^2 \) test for categorical variables and the Wilcoxon rank-sum test for continuous ones. The risk of cardiovascular death was analyzed by Cox regression with a landmark analysis starting from the first new MI experienced during study follow-up through 180 days after the MI. A duration of 180 days was chosen to ensure consistent duration of follow-up after the recurrent MI occurred, with the recognition that the majority of new MIs occurred more than 30 days after enrollment. Adjusted analyses were performed that included the known risk indicators of age, sex, diabetes, hypertension, dyslipidemia, renal function, prior heart failure, prior MI, randomization group, severity of coronary artery disease at the index angiogram (1, 2, or 3 vessel/left main disease), and presenting syndrome (unstable angina, non-STEMI, or STEMI). Event rates presented are Kaplan-Meier estimates of the cumulative incidence at 180 days from the time of the new MI. Sensitivity analyses were performed with both a landmark analysis from the last MI experienced (in patients with repeated MI end points) and with a time-dependent covariate to include all observation time accrued before and after a recurrent MI. Additional sensitivity analyses of outcome related to MIs that occurred at least 30 days and at least 4 months from the index event were performed to assess the impact of early versus late recurrent MI.

For analyses of each subtype of MI, the first MI of the specified subtype was counted. Type 3 MIs (sudden unexpected cardiac death) are not presented separately because this event was defined by cardiovascular death at the time of the event. The referent for risk associated with type 5 MI (CABG related) was the cohort of patients who had CABG but no MI during follow-up; the Cox modeling was the same but excluded disease severity. Because of a longer average duration of follow-up after MI, the Cox modeling for type 4a MI, when analyzed alone, was conducted with follow-up to 450 days. All analyses were performed with STATA version 9.2 (StataCorp LP, College Station, TX).

Results
A total of 13 608 patients were enrolled in the trial, with 1118 patients experiencing a total of 1218 new MIs during a mean follow-up of 14.5 months. The baseline characteristics of patients with or without MI are shown in Table 1. Patients who had an MI during the follow-up period were older, who more likely to have impaired renal function and 3-vessel coronary disease or left main coronary disease at index presentation, and were more likely to have a history of...
diabetes mellitus, hypertension, prior MI, or congestive heart failure. The median duration of follow-up after the first new MI was 265 days for type 1 MI, 351 days for type 2 MI, and 447 days for type 4a MI.

New MI and Risk of Cardiovascular Death

Patients who experienced a new MI of any type during the study period had a significantly higher rate of cardiovascular death in the 180 days after the event than patients who had no MI end point (6.5% versus 1.3%, \(P<0.001\); Figure 1). After adjustment for age, sex, diabetes mellitus, hypertension, dyslipidemia, renal function, prior heart failure, prior MI, randomized treatment, severity of coronary artery disease, and presenting ACS subtype, patients who had a new MI were at >5-fold higher risk of cardiovascular death than those with no MI (adjusted hazard ratio [HR] 5.2; 95% confidence interval [CI] 3.3–7.1, \(P<0.001\); online-only Data Supplement Table I). Among the 77 patients who had more than 1 recurrent MI, the risk of cardiovascular death was similar after the occurrence of the last MI (adjusted HR 5.7; 95% CI, 4.2–7.6, \(P<0.001\)). In addition, in a sensitivity analysis with incorporation of the timing of a new MI relative to the qualifying event by use of a time-varying covariate and use of the entire observation period through 450 days, the estimated risk of cardiovascular death associated with a recurrent MI was even stronger (adjusted HR 6.2; 95% CI, 4.7–8.2, \(P<0.001\)).

When stratified by time from index event to MI, both those MIs that occurred early (within 30 days of the index event) and later (30 days or more from the index event) were associated with similar significant increases in the risk of cardiovascular death over the following 180 days, except for type 4a MIs, for which there were an insufficient number of events occurring after 30 days because of trial design to assess a relationship with cardiovascular death (Table 2; online-only Data Supplement Table II). In the present study, we observed a qualitatively similar risk associated with type 1 MI that occurred early and late after the initial ACS presentation and a particularly high risk of early type 4b MI (Table 2). Similarly, MIs that occurred after an even later time point (120 days) remained strongly associated with cardiovascular death (\(P<0.0001\)). Moreover, in an analysis that added time to MI to the multivariable model, the results were consistent, showing a highly significant relationship between recurrent MI and cardiovascular death at 180 days (\(P<0.001\)).

Impact of MI Size

When stratified by peak biomarker elevation, there was a consistent pattern of increased risk across the range of MI
Table 2. Cardiovascular Death at 180 Days After a New MI, Stratified by Time From Index Event

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>MI ≤30 Days From Index Event</th>
<th>MI &gt;30 Days From Index Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>No MI</td>
<td>Any MI</td>
<td>No MI*</td>
</tr>
<tr>
<td>1.26%</td>
<td>6.41% (n = 756)</td>
<td>0.49%</td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>5.1 (3.6–7.3)†</td>
<td>11.7 (7.0–19.5)†</td>
</tr>
<tr>
<td>Type 1 MI</td>
<td>10.6% (n = 67)</td>
<td>7.9% (n = 292)</td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>4.0 (1.6–9.8)</td>
<td>10.2 (6.1–17.2)</td>
</tr>
<tr>
<td>Type 2 MI</td>
<td>12.5% (n = 8)</td>
<td>6.2% (n = 34)</td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>6.9 (0.95–50.1)</td>
<td>5.4 (1.3–22.9)</td>
</tr>
<tr>
<td>Type 4a MI</td>
<td>3.3% (n = 592)</td>
<td>NS‡</td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>2.4 (1.6–3.7)</td>
<td>NS‡</td>
</tr>
<tr>
<td>Type 4b MI</td>
<td>22.0% (n = 96)</td>
<td>3.7% (n = 59)</td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>16.7 (10.1–27.6)</td>
<td>5.8 (1.4–24.0)</td>
</tr>
<tr>
<td>Type 5 MI</td>
<td>33.3% (n = 3)</td>
<td>NS‡</td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>36.6 (5.0–270.0)</td>
<td>NS‡</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; KM%, Kaplan-Meier percentage; HR, hazard ratio; CI, confidence interval; and NS, not significant.
*Landmark analysis at 30 days.
†P<0.001.
‡Insufficient number of events.

Table 3. Risk of Cardiovascular Death at 180 Days After MI by MI Size

<table>
<thead>
<tr>
<th>Peak Biomarker</th>
<th>n</th>
<th>HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No MI</td>
<td>12,490</td>
<td>1.0</td>
<td>1.0</td>
<td>NA</td>
</tr>
<tr>
<td>First MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3×ULN</td>
<td>154</td>
<td>2.3 (0.9–5.6)</td>
<td>0.074</td>
<td></td>
</tr>
<tr>
<td>3 to &lt;5×ULN</td>
<td>195</td>
<td>3.0 (1.4–6.5)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>&gt;5×ULN</td>
<td>725</td>
<td>5.5 (3.9–7.9)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Last MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3×ULN</td>
<td>160</td>
<td>3.6 (1.7–7.4)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>3 to &lt;5×ULN</td>
<td>201</td>
<td>2.6 (1.2–5.5)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>&gt;5×ULN</td>
<td>706</td>
<td>5.8 (4.1–8.3)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; HR, hazard ratio; CI, confidence interval; NA, not applicable; and ULN, upper limit of normal.

MI Classification and Outcome

When stratified by MI categories as defined by the universal definition of MI classification system, patients experiencing any of the subtypes of MI had an increased risk of cardiovascular death over the following 180 days compared with patients without an MI end point during follow-up (Figure 1; online-only Data Supplement Tables). Patients experiencing type 1 MI (spontaneous) had rates of cardiovascular death that were >6 times higher than those who had no MI. Notably, type 4a MI (peri-PCI) was associated with increased risk of cardiovascular death at 180 days (3.2%, P<0.001), albeit lesser in magnitude than with spontaneous or other procedural MIs. When adjusted for clinical covariates, all subtypes of MI were associated with an increased risk of cardiovascular death (Figure 2). There was a 4-fold increased risk in patients experiencing type 1 MI (spontaneous; adjusted HR 4.1; 95% CI, 2.7–6.3, P<0.001) and an approximately 3-fold increased risk (adjusted HR 2.8; 95% CI, 0.9–8.8, P=0.085) in patients experiencing type 2 MI (demand related). The risk of cardiovascular death was increased more than 2-fold (adjusted HR 2.4; 95% CI, 1.6–3.7, P<0.001) in patients experiencing type 4a MI (peri-PCI) and more than 10-fold (adjusted HR 10.5; 95% CI, 1.18–93.6, P=0.035) in those experiencing type 5 MI (CABG related).

Additional Characterization of Type 4a MI

Of the 600 patients who experienced a type 4a MI during study follow-up, 490 (82%) had elevated markers of myocardial injury before PCI and therefore had an index diagnosis of MI (335 [56%] non-STEMI; 155 [26%] STEMI). The remaining 110 patients had an index diagnosis of unstable angina, an ACS without baseline elevation in markers of myocardial injury. Because TRITON-TIMI 38 was an ACS...
trial, with most patients receiving invasive care in association with the index event, the type 4a MIs occurred overwhelmingly early. When stratified by index diagnosis, patients both with an index diagnosis of unstable angina and an index MI who had a detectable new type 4a MI had significantly increased rates of cardiovascular death over the following 180 days compared with those with no MI (Figure 3). When further stratifying those with an index presentation of MI by non-STEMI and STEMI, a new MI was associated with a directionally increased risk of cardiovascular death in both groups compared with those with no MI during follow-up (non-STEMI group HR 2.4; 95% CI, 1.3–4.4; \( P=0.004 \); STEMI group HR 2.1; 95% CI, 0.95–4.6; \( P=0.07 \)). When adjusted for important clinical covariates, a periprocedural MI was associated with an increased risk of cardiovascular death regardless of index presentation.

**Discussion**

This study of more than 1100 patients with a new or recurrent MI in a well-characterized cohort of patients after ACS demonstrates an almost 5-fold increase in the risk of cardiovascular death after MI. This study is among the first to assess the prognostic implications of MI across each of the subtypes of MI described by the universal definition of MI classification system. We found that the increased risk associated with MI was significant and consistent across size and subtype. This relationship was also apparent whether the new MI occurred early (within 30 days) or later after the qualifying ACS. Importantly, there was a >2-fold higher risk of cardiovascular death among patients who experienced type 4a (peri-PCI) MI using our definition, with consistent findings in those who presented with or without an index MI and elevated biomarkers related to the presenting event.

**Clinical and Research Implications**

Our findings have several important clinical and research implications. These observations underscore the clinical importance of MI as defined by modern definitions and in the era of highly sensitive troponin assays and are qualitatively consistent with the magnitude of risk reported by use of older criteria and testing for MI.\(^{11,18}\) A risk associated with an MI end-point event as defined by our criteria was present regardless of the degree of biomarker elevation or the clinical context of the event as described by the universal definition classification system. Importantly, we observed a gradient of risk according to MI subtype. In the present analysis, we found that although type 2 (demand-related) and type 4a (peri-PCI) MIs both were associated with an increased risk of mortality, the hazard was less than that seen with type 1 (spontaneous), type 4b (sten thrombosis), and CABG-related (type 5) MIs. This finding is consistent with prior studies with CK-MB.\(^{6,19,20}\) In the era of a substantially increased frequency of detected MIs, clinicians are often tempted to dismiss the prognostic importance of demand-related MI in the setting of other illness or periprocedural MI. The present findings indicate that at least in a population with a history of ACS, such MIs carry prognostic relevance and support the use of MI as a component of composite end points in clinical trials examining the efficacy and safety of cardiovascular therapies.\(^{12}\)

In addition, the present findings demonstrate that it is possible to define and identify type 4a MIs (peri-PCI) that carry relevance for outcomes in the setting of a clinical trial of ACS and PCI. Although prior studies using CK-MB have shown an association between type 4a MI (peri-PCI) and long-term mortality,\(^{19,21,22}\) more recent studies examining the association of periprocedural MI have been inconsistent in showing a relationship with long-term outcomes.\(^{7,23,24}\) This assessment is complicated by changes in biomarkers and assays, variable definitions, and the difficulty in ascertaining, particularly for patients presenting with elevated biomarkers. The present findings indicate that the systematic evaluation for these events using modern standardized definitions is possible and support the importance of therapies and strategies to reduce the frequency of these events.

We have shown that it is possible to incorporate the universal definition of MI classification system into cardiovascular clinical trials and that the results are prognostically meaningful. Integration of the universal classification system into all such trials that include MI as an end point will be important in the provision of data to gauge the relative benefits of therapies, as well as to construct more specific measures of net clinical benefit. The use of standardized and more specific definitions will allow professional societies and clinicians to better understand and compare therapies aimed at reducing ischemic events.

**Study Limitations**

A clear association between MI and death was observed; however, this finding should not be interpreted as establishing causality. Although modeling was used to adjust for differences in baseline characteristics, it is possible that unmeasured confounders could explain some of the relationship...
between MI and cardiovascular death. The standard Cox regression used in the present analysis may bias the results toward the null and therefore present a conservative estimate of the risk of cardiovascular death associated with MI. Methods accounting for differences in follow-up time such as that presented using the time-dependent covariate analysis indicate that the risk may be even greater. The ascertainment of periprocedural MI in patients who present with an index MI and are treated with early PCI is limited, because new myocardial injury may not be detectable in the setting of prior biomarker elevation. As such, there may be underascertainment of type 4a MI in patients who have elevated biomarkers at the time of PCI. In addition, to support specificity of the criteria for peri-PCI MI, the TRITON-TIMI 38 trial definition required a CK-MB value >3 times the upper reference limit on 2 samples after PCI or >5 times the upper reference limit on a single sample, and in addition, the biomarker had to be falling on serial measurement after the index event, with a subsequent rise in CK-MB of at least 50% of the preceding nadir. These criteria also may have resulted in small peri-PCI MIs not being detected. Because of the definition of type 4a MI used in the present analysis, the relationship of periprocedural events associated with smaller degrees of biomarker elevation or based on low-level elevation of cardiac troponin and outcome could not be assessed in the present data set. A more liberal definition of type 4a MI would have identified more small events and may not have observed the same risk relationship. Finally, analyses using other modes of defining periprocedural events, such as angiography, could not be performed in the present data set and may show a different relationship with outcome. Studies that include detailed angiographic analysis of angiographically evident periprocedural complications may be of value to explore whether the combined use of biomarker, clinical, and angiographic data is useful to refine further the risk associated with subtypes of type 4a MI. Overall, however, the present findings indicated that those MIs that were detected with this end-point definition had prognostic importance. Type 5 MI (CABG associated) was infrequent in the present study cohort (7 events), and thus, observations related to this group should be interpreted cautiously. Finally, information on other clinical factors, such as left ventricular function before and after an event and presence of heart failure, would be helpful to in better understanding the relationship between MI and cardiovascular death but was not available in the present research cohort.

Conclusions
MI is associated with a significantly increased risk of cardiovascular death across all MI types as defined by the universal MI classification system. These findings demonstrate the applicability of the ESC/ACCF/AHA/WHF universal MI classification system and underscore the clinical relevance of MI and the need for better therapies aimed at attenuating the risk of recurrent MI after ACS.

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 Abbott Laboratories, Accutens, Amgen, AstraZeneca, Beckmann Coulter, Bristol-Myers Squibb, CV Therapeutics, Daiichi Sankyo Co Ltd, Eli Lilly and Co, GlaxoSmithKline, Integrated Therapeutics, Merck and Co, Nanosphere, Novartis Pharmaceuticals, Nuvelo, Ortho-Clinical Diagnostics, Pfizer, Roche Diagnostics, sanofi-aventis, Sanofi-Synthelabo, Siemens Medical Solutions, and Singulex. 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 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. 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 Morrow has received honoraria for educational presentations from CV Therapeutics and Eli Lilly. He has received consulting fees from Beckmann-Coulter, Boehringer Ingelheim, Cardiokinetix, Gilead, Instrumentation Laboratory, Ikaria, Merck, Ortho Clinical Diagnostics, Roche Diagnostics, and Siemens and remuneration from AstraZeneca for adjudication as a member of a clinical events committee. The remaining authors report no conflicts.

References
CLINICAL PERSPECTIVE

The ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction (MI) includes a classification system that incorporates the diverse clinical settings in which myocardial injury can be detected, particularly in the era of sensitive biomarkers of myonecrosis. This evolution in the classification of MI has important implications for clinicians and researchers. We investigated the association between new or recurrent MI by subtype according to the ESC/ACCF/AHA/WHF Task Force for the Redefinition of MI Classification System and the risk of cardiovascular death among 13 608 patients with acute coronary syndrome in TRITON-TIMI 38. We found that patients who experienced an MI during follow-up had a higher risk of cardiovascular death than patients without an MI. Importantly, this higher risk was present across all subtypes of MI, including type 1 (spontaneous), type 4a (peri–percutaneous coronary intervention), and type 4b (stent thrombosis). Our findings demonstrate the applicability of the ESC/ACCF/AHA/WHF Universal MI Classification System and underscore the clinical relevance of MI and the need for better therapies aimed at attenuating the risk of recurrent MI after acute coronary syndromes.
Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction 38)
Supplemental Table 1. The risk of CV death associated with new or recurrent MI by initial presentation

<table>
<thead>
<tr>
<th>Index</th>
<th>ACS</th>
<th>No MI</th>
<th>Any MI</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 4a</th>
<th>Type 4b</th>
<th>Type 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI</td>
<td>N=3,534</td>
<td>KM 2.1%</td>
<td>KM 8.5%</td>
<td>KM 11.5%</td>
<td>KM 4.6%</td>
<td>KM 16.2%</td>
<td>Adj HR 5.1 (3.1 – 8.5)</td>
<td>Adj HR 4.5 (2.13 – 9.5)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>N=7,541</td>
<td>KM 1.0%</td>
<td>KM 6.0%</td>
<td>KM 6.4%</td>
<td>KM 7.4%</td>
<td>KM %</td>
<td>Adj HR 5.5 (3.5 – 8.6)</td>
<td>Adj HR 3.7 (1.9 – 7.0)</td>
</tr>
<tr>
<td>UA</td>
<td>N=2,528</td>
<td>KM 0.8%</td>
<td>KM 5.5%</td>
<td>KM 11.1%</td>
<td>KM 2.80%</td>
<td>KM 7.8%</td>
<td>Adj HR 5.9 (2.6 – 13.7)</td>
<td>Adj HR 6.9 (2.6 – 18.0)</td>
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Supplemental Table 2. The risk of CV death associated with new or recurrent MI, stratified by timing of event

<table>
<thead>
<tr>
<th></th>
<th>No MI</th>
<th>MI &lt;= 30 Days from index</th>
<th>No MI (30-day landmark)</th>
<th>MI &gt; 30 Days from index</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>KM 1.26% Referent</td>
<td>KM 6.4%</td>
<td>KM 0.5% Referent</td>
<td>KM 6.9%</td>
</tr>
<tr>
<td>Any MI</td>
<td>N=12,490</td>
<td>N=756</td>
<td>N=756</td>
<td>N=362</td>
</tr>
<tr>
<td>Type 1</td>
<td>KM 10.6%</td>
<td>Adj HR 4.0 (1.6 – 9.8)</td>
<td>KM 7.9%</td>
<td>Adj HR 10.2 (6.1 – 17.2)</td>
</tr>
<tr>
<td>Type 2</td>
<td>KM 12.5%</td>
<td>Adj HR 6.9 (0.95 – 50.1)</td>
<td>KM 6.2%</td>
<td>Adj HR 5.4 (1.3 – 22.9)</td>
</tr>
<tr>
<td>Type 4a</td>
<td>KM 3.3%</td>
<td>Adj HR 2.4 (1.6 – 3.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 4b</td>
<td>KM 22.0%</td>
<td>Adj HR 16.7 (10.1 – 27.6)</td>
<td>KM 3.7%</td>
<td>Adj HR 5.8 (1.4 – 24.0)</td>
</tr>
<tr>
<td>Type 5</td>
<td>KM 33.3%</td>
<td>Adj HR 36.6 (5.0 – 270.0)</td>
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</tr>
</tbody>
</table>
Supplemental Table 3. The risk of CV death associated with new or recurrent MI stratified by size of MI

<table>
<thead>
<tr>
<th></th>
<th>No MI</th>
<th>MI Anytime</th>
<th>&lt; 3x ULN</th>
<th>3 - &lt; 5 x ULN</th>
<th>&gt; 5 x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any MI</strong></td>
<td>KM 1.3%</td>
<td>KM 6.5%</td>
<td>KM 4.7%</td>
<td>KM 3.6%</td>
<td>KM 6.7%</td>
</tr>
<tr>
<td></td>
<td>Adj HR = 5.2 (3.8 – 7.1)</td>
<td>Adj HR = 2.3 (0.9 – 5.6)</td>
<td>Adj HR = 3.0 (1.4 – 6.5)</td>
<td>Adj HR = 5.5 (3.9 – 7.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Type 1</strong></td>
<td>KM 8.3%</td>
<td>KM 5.5%</td>
<td>KM 9.5%</td>
<td>KM 10.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adj HR 4.1 (2.7 – 6.3)</td>
<td>Adj HR 2.4 (1.04 – 5.5)</td>
<td>Adj HR 4.2 (1.7 – 10.4)</td>
<td>Adj HR 5.7 (3.3 – 10.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Type 2</strong></td>
<td>KM 7.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adj HR = 2.8 (0.9 – 8.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type 4a</strong></td>
<td>KM 3.2%</td>
<td></td>
<td></td>
<td></td>
<td>KM 3.8%</td>
</tr>
<tr>
<td></td>
<td>Adj HR = 2.4 (1.6 – 3.7)</td>
<td></td>
<td></td>
<td>Adj HR 2.96 (1.94 – 4.53)</td>
<td></td>
</tr>
<tr>
<td><strong>Type 4b</strong></td>
<td>KM 15.4%</td>
<td>KM 5.6%</td>
<td>KM 12.0%</td>
<td>KM 15.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adj HR = 10.8 (6.7 – 17.3)</td>
<td>--</td>
<td>Adj HR 9.9 (3.1 – 31.5)</td>
<td>Adj HR 10.4 (5.8 – 18.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Type 5</strong></td>
<td>KM 14.3%</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adj HR = 10.5 (1.18 – 93.64)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>