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ORIGINAL INVESTIGATIONS

# Nonculprit Lesion Myocardial Infarction Following Percutaneous Coronary Intervention in Patients With Acute Coronary Syndrome

Benjamin M. Scirica, MD, MPH,[a,*] Brian A. Bergmark, MD,[a,*] David A. Morrow, MD, MPH,[a] Elliott M. Antman, MD,[a] Marc P. Bonaca, MD, MPH,[a,b] Sabina A. Murphy, MPH,[a] Marc S. Sabatine, MD, MPH,[a] Eugene Braunwald, MD,[a] Stephen D. Wiviott, MD[a]

## ABSTRACT

**BACKGROUND** Recent emphasis on reduced duration and/or intensity of antiplatelet therapy following percutaneous coronary intervention (PCI) irrespective of indication for PCI may fail to account for the substantial risk of subsequent nontarget lesion events in acute coronary syndrome (ACS) patients.

**OBJECTIVES** The authors sought to examine the effect of more potent antiplatelet therapy on the basis of the timing and etiology of recurrent myocardial infarction (MI) or cardiovascular death following PCI for ACS.

**METHODS** In the TRITON-TIMI 38 study (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction 38), which randomized patients to prasugrel or clopidogrel, 12,844 patients with ACS received at least 1 stent. MI and cardiovascular death were categorized as: 1) procedural (related to revascularization); 2) definite or probable stent thrombosis (ST); or 3) spontaneous (non-ST or non–procedure-related). Median follow-up was 14.5 months.

**RESULTS** Among the first events occurring within 30 days, 584 (69.0%) were procedural, 126 (14.9%) ST-related, and 136 (16.1%) spontaneous. After 30 days, 22 (4.7%) were procedural, 63 (13.5%) were ST-related, and 383 (81.8%) spontaneous. Prasugrel significantly reduced the incidence of MI or cardiovascular death for ST-related (1.0% vs. 2.1%; $p < 0.001$) and spontaneous events (3.9% vs. 4.8%; $p = 0.012$), with a directionally consistent numerical reduction for procedural events (4.4% vs. 5.1%; $p = 0.078$). Prasugrel increased spontaneous, but not procedural, major bleeding.

**CONCLUSIONS** Long-term potent antithrombotic therapy reduces de novo (spontaneous) atherothrombotic events in addition to preventing complications associated with stenting of the culprit lesion following ACS. In patients undergoing PCI for ACS, spontaneous events predominate after 30 days, with the later-phase cardiovascular benefit of potent dual antiplatelet therapy driven largely by reducing de novo atherothrombotic ischemic events. (Comparison of Prasugrel [CS-747] and Clopidogrel in Acute Coronary Syndrome Subjects Who Are to Undergo Percutaneous Coronary Intervention; NCT00097591) (J Am Coll Cardiol 2020;75:1095–106) © 2020 by the American College of Cardiology Foundation.

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From the [a]TIMI Study Group, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; and the [b]CPC Clinical Research, University of Colorado School of Medicine, Denver, Colorado. *Dr. Scirica and Dr. Bergmark contributed equally to this work. The TRITON-TIMI 38 trial was sponsored by Daiichi-Sankyo and Eli Lilly. All authors are members of the TIMI Study Group, which has received institutional research grant support through Brigham and Women's Hospital from Abbott, Amgen, Aralez, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., BRAHMS, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Intarcia, Janssen, MedImmune, Merck, Novartis, Pfizer, Poxel, Quark Pharmaceuticals, Roche, Takeda, The Medicines Company, and Zora Biosciences. Dr. Scirica has received consultant fees/honoraria from AbbVie,

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**ABBREVIATIONS AND ACRONYMS**

**ACS** = acute coronary syndrome

**CABG** = coronary artery bypass graft

**CI** = confidence interval

**CV** = cardiovascular

**DAPT** = dual antiplatelet therapy

**DES** = drug-eluting stents

**MI** = myocardial infarction

**NSTEMI** = non-ST-segment elevation myocardial infarction

**PCI** = percutaneous coronary intervention

**ST** = stent thrombosis

**STEMI** = ST-segment elevation myocardial infarction

**TIMI** = Thrombolysis In Myocardial Infarction

Current practice guidelines recommend dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor for at least 1 year following an acute coronary syndrome (ACS), regardless of whether or not percutaneous coronary intervention (PCI) is performed (1–7). In the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial, which first examined extended treatment with DAPT in ACS (8), a major mechanism underlying the benefit of clopidogrel in medically managed patients was felt to be a reduction in the risk of rethrombosis of the culprit artery in addition to ongoing risk from nonculprit lesions (9,10).

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As the frequency of PCI for ACS has increased over time, the emphasis on DAPT following ACS came to focus on preventing periprocedural and stent-related complications. Accordingly, with the emergence of newer-generation drug-eluting stents (DES) with lower thrombotic risk, there is now debate over diminished need for long-term antithrombotic therapy (11–18). This focus on stent- and target lesion–related events does not account for a possibly heightened risk of spontaneous myocardial infarction (MI) in the "vulnerable" post-ACS patient.

A question central to the debate concerning DAPT duration and intensity following PCI for ACS is whether the primary therapeutic target of DAPT in ACS is to pacify the culprit lesion, reduce periprocedural injury, prevent stent thrombosis (ST), minimize the risk of de novo atherothrombotic lesions in the entire coronary arterial bed, or all of the above. We previously reported the overall effect of prasugrel as compared with clopidogrel by type of MI in TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) and showed a consistent effect of prasugrel by type of MI in the overall trial population (19). Given the heightened interest in DAPT duration following PCI, we now report on the type and timing of recurrent ischemic events after PCI for ACS and the corresponding effectiveness of more potent $P2Y_{12}$ inhibition for early and late events.

## METHODS

As previously described, a total of 13,608 patients with an ACS (both unstable angina/non-ST-segment elevation myocardial infarction [NSTEMI] and ST-segment elevation myocardial infarction [STEMI]) were randomized in TRITON-TIMI 38 (20). Because the objective was to compare the use of prasugrel with clopidogrel in patients with ACS who were undergoing PCI, the coronary anatomy of all patients had to be known to be suitable for PCI before randomization. Randomization occurred before PCI,

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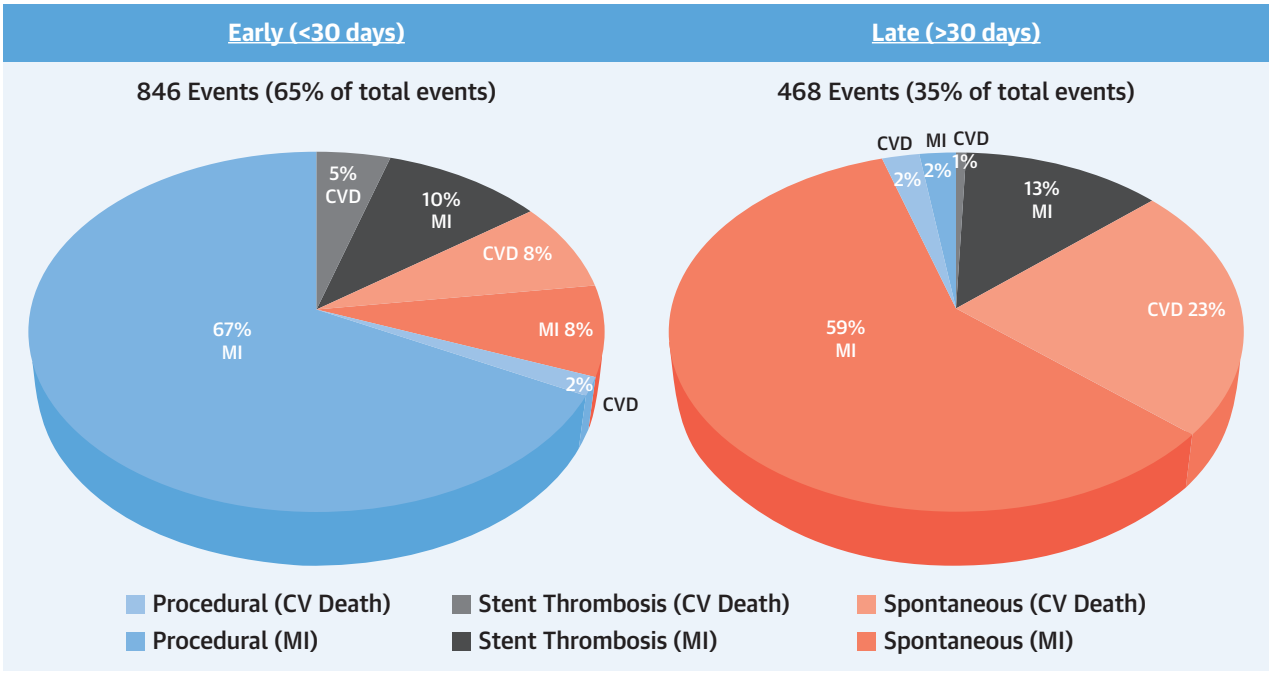
**FIGURE 1** Timing and Etiology of MI and CV Death in Patients Receiving at Least 1 Stent




A total of 65% (n = 846) of first myocardial infarction (MI) or cardiovascular (CV) death events occurred in the early phase (≤30 days), and 35% (n = 468) occurred in the late phase (>30 days); 82% of late events were spontaneous.

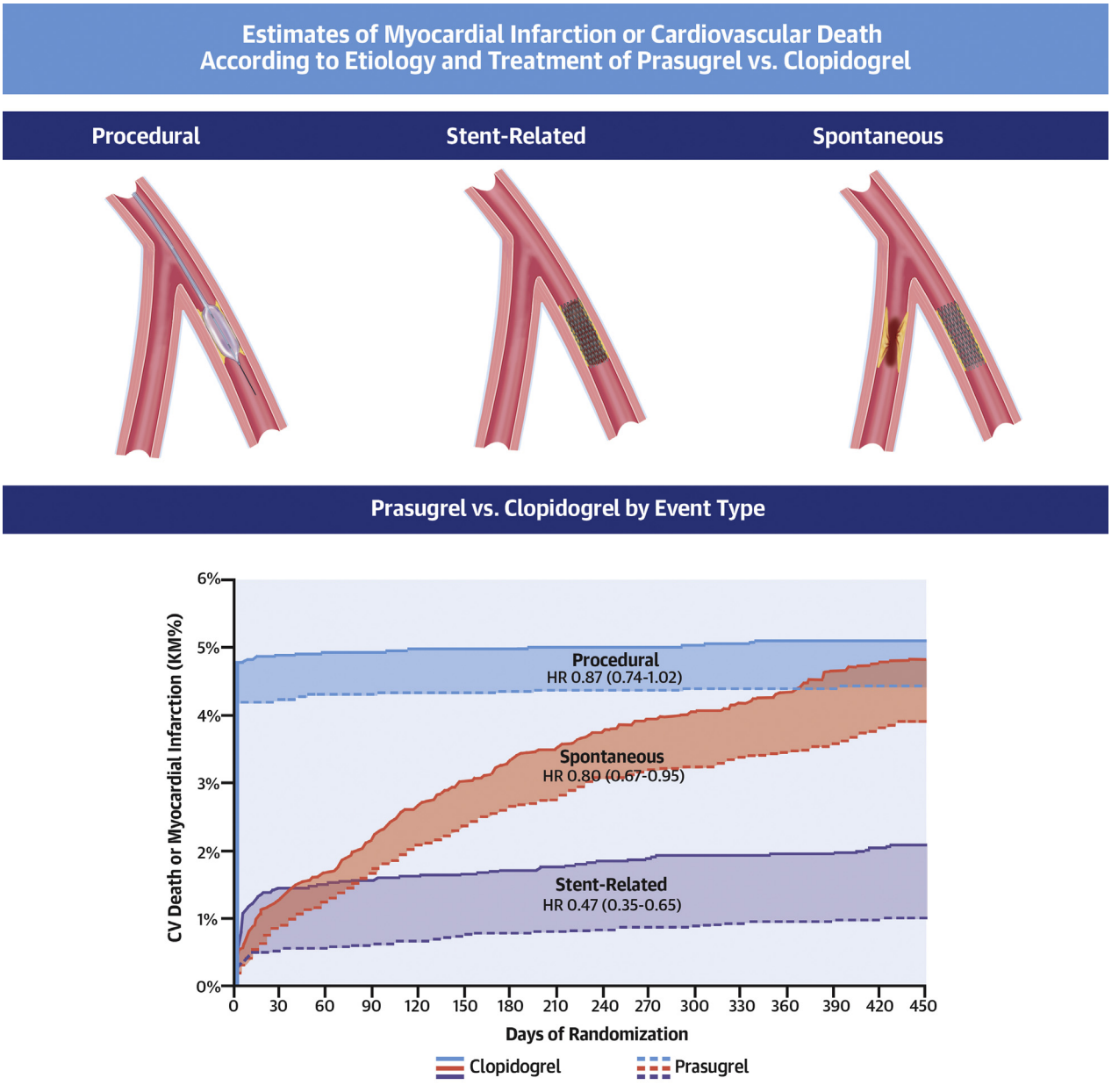
and blinded study drug was administered as soon as possible after randomization. During the maintenance phase, low-dose aspirin (75 to 162 mg) was recommended in addition to study drug. After hospital discharge, follow-up visits were conducted for a minimum of 6 months and a maximum of 15 months, with a median follow-up of 14.5 months. A total of 12,844 patients received at least 1 stent and form the cohort for the subsequent analyses because they were at risk for all types of events considered.

**ENDPOINTS.** Details of the definitions of the endpoints of cardiovascular (CV) death and myocardial infarction (MI) have been described previously (Type 1: spontaneous MI; Type 2: MI due to supply/demand mismatch not related to coronary atherothrombosis; Type 3 cardiac death due to MI; Type 4a: peri-PCI MI; Type 4b: MI related to ST; Type 4c: MI related to in-stent restenosis; Type 5: MI related to coronary artery bypass graft surgery [CABG]) (20-24). In this analysis, we further divided events into 3 distinct categories. Procedure-related events were CV deaths or MI directly related to PCI (MI type 4a) (22-24). Stent-related deaths or MI were events that were classified as an Academic Research Consortium definite or probable ST (MI type 4b) (25). Spontaneous CV deaths or MI were events that were not related to a procedure or stent and/or were classified as type 1 or 3 MI. Thrombolysis In Myocardial Infarction (TIMI) major non-CABG-associated bleeding was defined as in the main trial. CV death was defined in the clinical endpoint committee charter to be a death due to a documented CV cause, including, but not limited to, MI, sudden death, or a complication of a CV procedure, or a death not clearly attributable to a non-CV cause (20,21).

Members of an independent clinical endpoint committee that was blinded to the treatment assignment adjudicated all endpoints used in the analyses in this report. Classification of type of MI was established after the initiation of the trial and therefore assessed in a separate blinded review (23).

**STATISTICAL ANALYSES.** All efficacy analyses were performed according to the intention-to-treat principle. The time to first event in the 2 treatment groups was analyzed using Kaplan-Meier curves and compared using the log-rank test. Sequential landmark analyses were performed starting from randomization, day 30, day 90, and day 180. Hazard

**CENTRAL ILLUSTRATION** **Kaplan-Meier Estimates of Myocardial Infarction or Cardiovascular Death According to the Etiology and Treatment With Prasugrel Versus Clopidogrel**

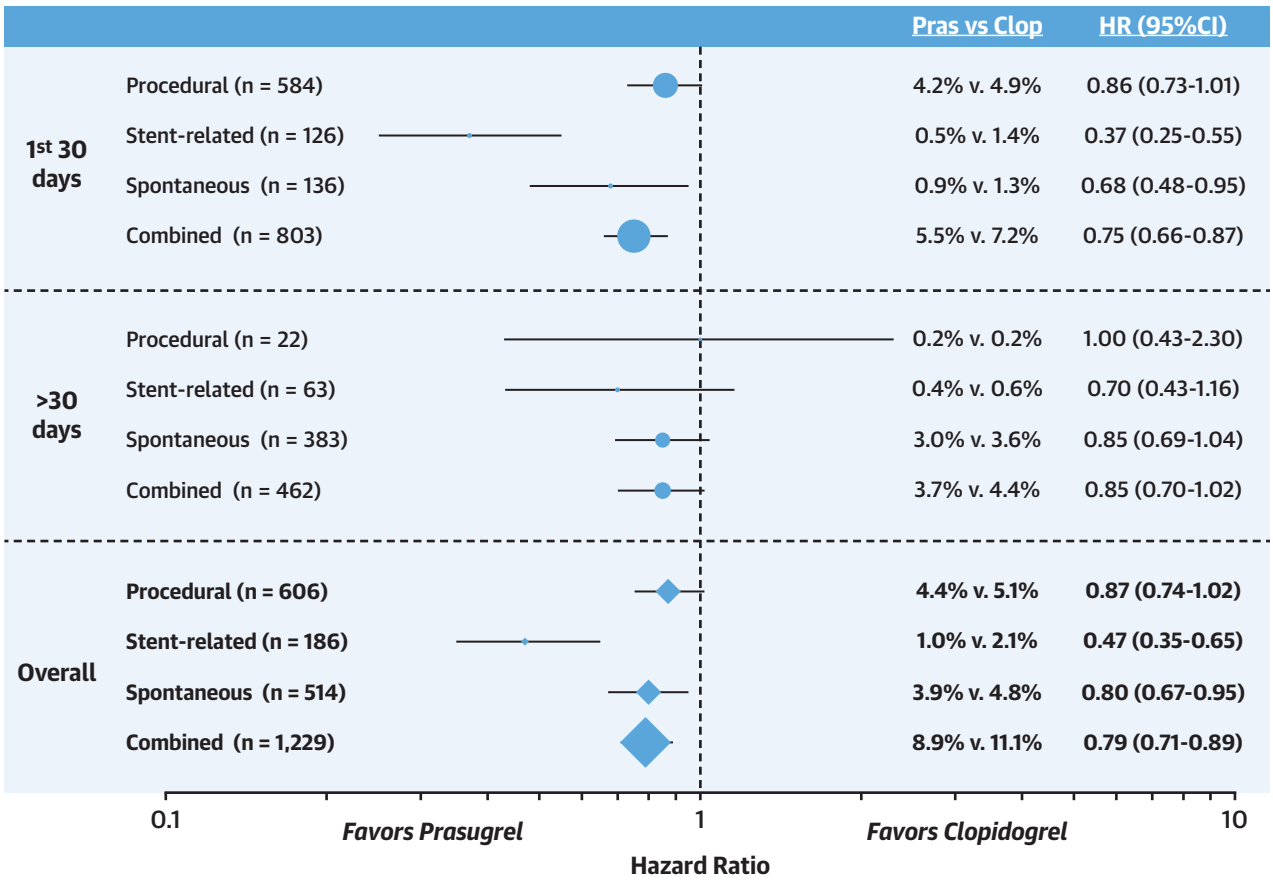



**Scirica, B.M. et al. J Am Coll Cardiol. 2020;75(10):1095–106.**

Prasugrel reduced the rate of myocardial or cardiovascular death overall (8.9% vs. 11.1%; hazard ratio: 0.79; 95% confidence interval: 0.71 to 0.89) with directional consistency for the individual components of procedural, stent-related, and spontaneous events.

ratios (HRs) and associated 95% confidence intervals (CIs) were calculated with a Cox proportional hazards survival model to evaluate the relative treatment effect. The proportional hazards assumption was not violated based on Schoenfeld residuals ($p = 0.76$ for procedural; $p = 0.21$ for stent-related; and $p = 0.45$ for spontaneous). The investigators had complete access to the data used for these analyses. Members of the

**FIGURE 2** Relative Risk of MI or CV Death According to Timing, Etiology, and Treatment With Prasugrel Versus Clopidogrel




The reduction in the risk of MI or CV death was directionally consistent in both the early phase (within 30 days after acute coronary syndrome) and in the later phase (from day 30 onwards), with the exception of late procedure-related events, which occurred infrequently. CI = confidence interval; Clop = clopidogrel; HR = hazard ratio; Pras = prasugrel; other abbreviations as in Figure 1.

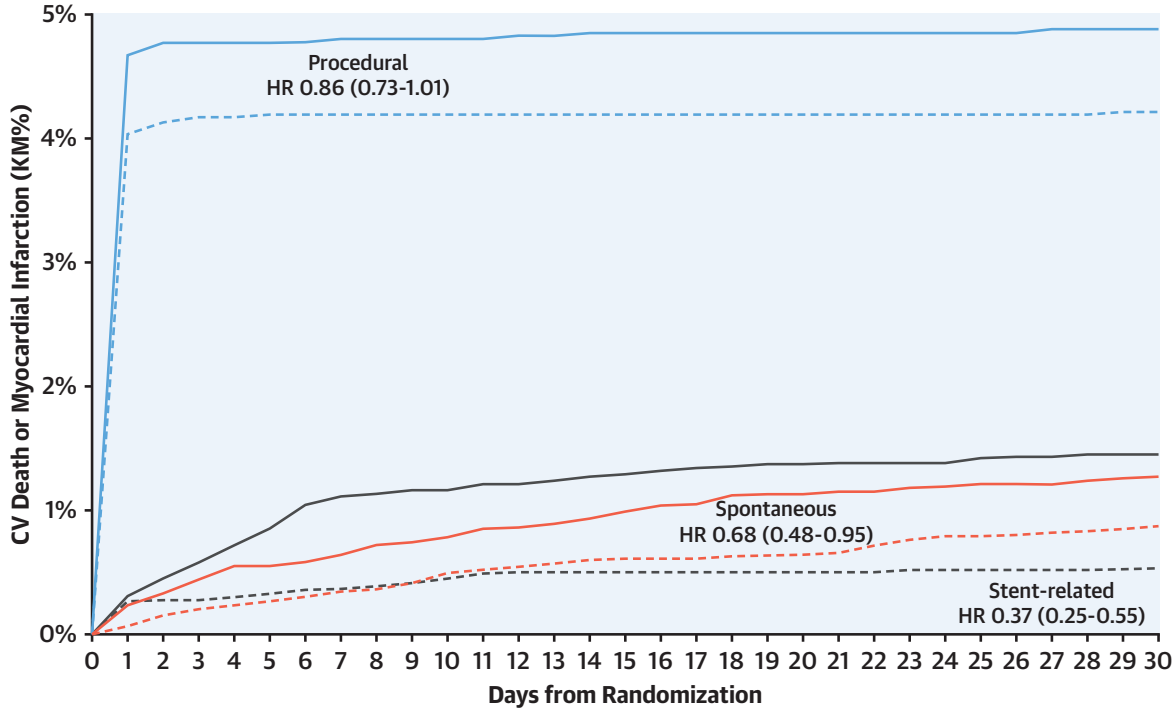
TIMI Study Group independently conducted the analyses, wrote this paper using a copy of the raw database for the main trial, and take full responsibility for this report. All analyses were performed with the use of STATA/SE version 9.2 software (StataCorp, College Station, Texas).

## RESULTS

There were 1,149 total MI and 254 CV deaths in the 12,844 patients who received at least 1 stent as part of the treatment for the qualifying ACS. Among the 1,306 first events, 606 (46%) were procedural, 186 (14%) stent-related, and 514 (39%) spontaneous. Twenty-five percent of MI events were STEMI, and 75%, NSTEMI. Among the 846 events (65% of all events) that occurred within the first 30 days after randomization, 584 (69%) were procedural, 126 (15%) stent-related, and 136 (16%) spontaneous. From day 30 to the end of the trial, the great majority of events were spontaneous (n = 383, 82%), followed by stent-related (n = 63, 13%), with few procedure-related events (n = 22, 5%; $p < 0.001$ compared with before 30 days) (Figure 1).

Kaplan-Meier estimates of MI or CV death from randomization to the end of trial are presented in the Central Illustration according to the type of recurrent ischemic event and by treatment allocation to prasugrel or clopidogrel. Prasugrel reduced the rate of MI or CV death overall (8.9% vs. 11.1%; HR: 0.79; 95% CI: 0.71 to 0.89) with directional consistency for the individual components of procedural, stent-related, and spontaneous events (Central Illustration). The rate of procedural MI or CV death was 4.4% in patients receiving prasugrel and 5.1% in patients receiving clopidogrel

**FIGURE 3** Landmark Analysis Comparing the Rates of MI or CV Death in the Early Phase




Number at Risk

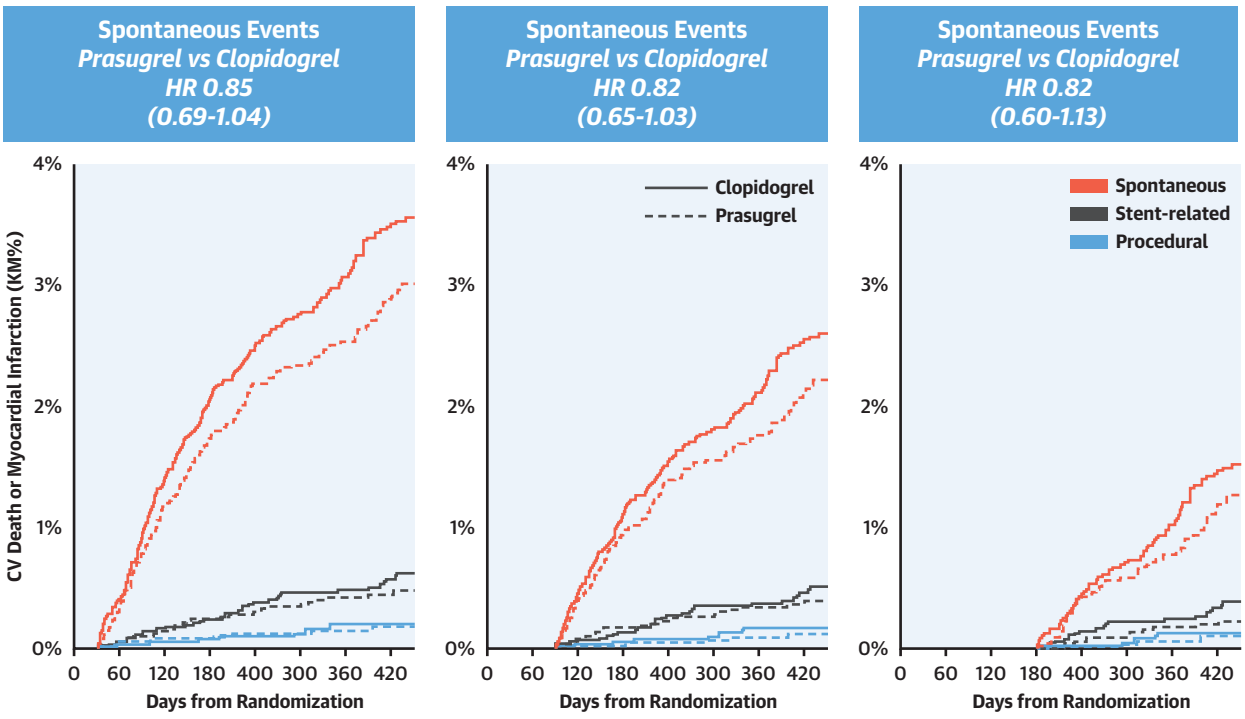
| | | | | |
|---|---|---|---|---|
| Proc. Clop | 6,422 | 6,007 | 5,977 | 5,956 |
| Proc. Pras | 6,422 | 6,059 | 6,040 | 6,016 |
| Stent. Clop | 6,422 | 6,245 | 6,212 | 6,186 |
| Stent. Pras | 6,422 | 6,302 | 6,279 | 6,256 |
| Spont. Clop | 6,422 | 6,285 | 6,243 | 6,215 |
| Spont. Pras | 6,422 | 6,305 | 6,280 | 6,247 |

This landmark analysis compares the rates of MI or CV death according to the etiology and treatment with prasugrel versus clopidogrel at 0 to 30 days. Prasugrel reduced the rate of early MI or CV death (5.5% vs. 7.2%; HR: 0.75; 95% CI: 0.66 to 0.87) with directional consistency for the individual components of procedural, stent-related, and spontaneous events. KM = Kaplan-Meier; other abbreviations as in Figures 1 and 2.

(HR: 0.87; 95% CI: 0.74 to 1.02; p = 0.078). For stent-related events, the rates were 1.0% and 2.1% (HR: 0.47; 95% CI: 0.35 to 0.65; p < 0.001), and for spontaneous events, 3.9% vs. 4.8% (HR: 0.80; 95% CI: 0.67 to 0.95; p = 0.012). These reductions in the risk of MI or CV death were directionally consistent in both the early phase (within 30 days after ACS) and in the later phase (from day 30 onwards), with the exception of late procedure-related events, which occurred infrequently (Figures 2 and 3). The effect of prasugrel compared with clopidogrel by event type was consistent for STEMI and NSTEMI for all 3 event types (procedural STEMI 4.3% vs. 5.3%; HR: 0.80; 95% CI: 0.59 to 1.10; procedural NSTEMI 4.4% vs. 5.0%; HR: 0.89; 95% CI: 0.74 to 1.07; stent-related STEMI 1.4% vs. 2.7%; HR: 0.51; 95% CI: 0.31 to 0.85; stent-related NSTEMI 0.9% vs. 1.9%; HR: 0.46; 95% CI: 0.31 to 0.67; spontaneous STEMI 3.2% vs. 4.6%; HR: 0.70; 95% CI: 0.49 to 1.00; spontaneous NSTEMI 4.2% vs. 5.0%; HR: 0.84; 95% CI: 0.69 to 1.02).

Separate landmark analyses starting at days 30, 90, and 180, and continuing to the end of study are presented in Figure 4. Although the absolute risk of spontaneous events is lower with each subsequent landmark analysis, reflective of both the time from the index event and shorter duration of follow-up, these events are much more frequent than either procedural or stent-related events. The relative

**FIGURE 4** Landmark Analysis Comparing the Rates of CV Death or MI in the Later Phase




Number at Risk

| | | | | |
|---|---|---|---|---|
| **Proc.** Clop | **6,200** | **6,143** | **6,043** | **4,105** |
| **Proc.** Pras | **6,221** | **6,152** | **6,031** | **4,038** |
| **Stent.** Clop | **6,198** | **6,135** | **6,033** | **4,089** |
| **Stent.** Pras | **6,222** | **6,149** | **6,022** | **4,031** |
| **Spont.** Clop | **6,183** | **6,070** | **5,942** | **4,005** |
| **Spont.** Pras | **6,206** | **6,102** | **5,959** | **3,976** |

This landmark analysis compares the rates of CV death or MI according to the etiology and treatment with prasugrel versus clopidogrel at 30 days **(left)**, 90 days **(center)**, and 180 days **(right)**. Hazard ratios and 95% CIs are for spontaneous events. The relative reduction in the risk of spontaneous events is similar for each landmark analysis. Abbreviations as in Figures 1 to 3.

reduction in the risk of spontaneous events is similar for each landmark analysis.

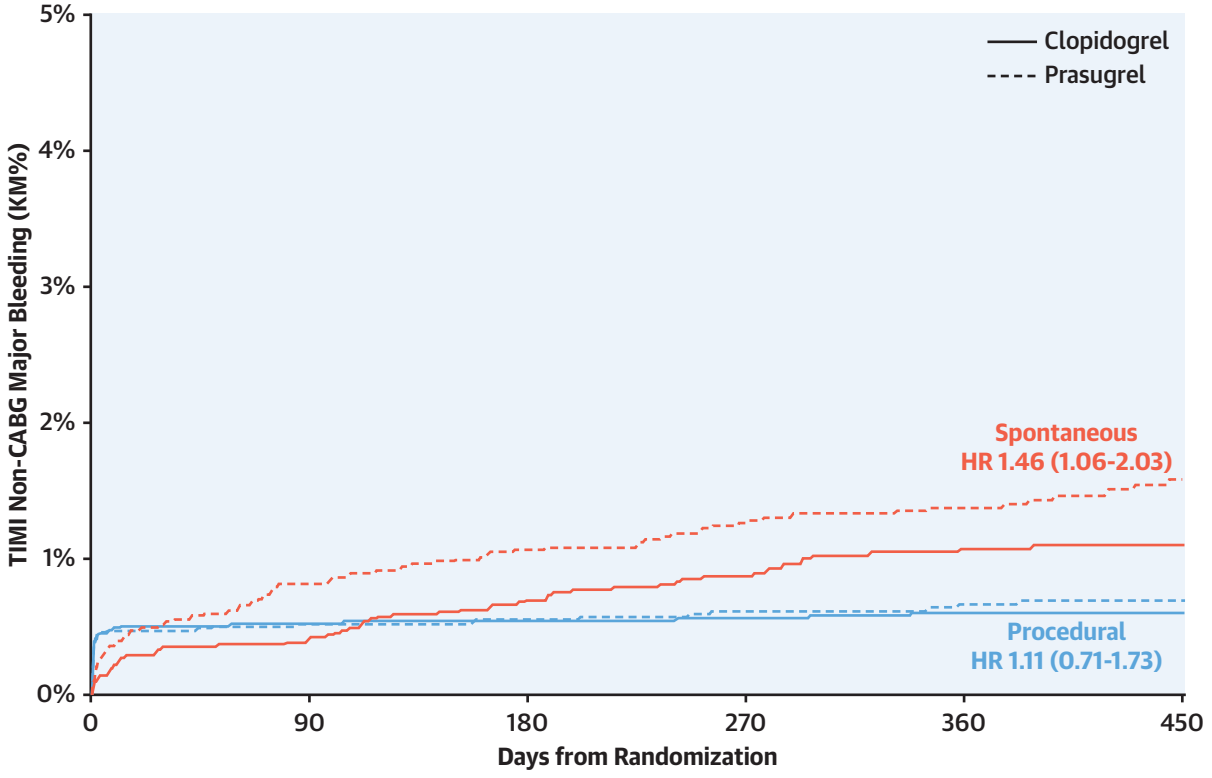
**SAFETY.** The most common non-CABG TIMI major bleeding episodes were spontaneous events (n = 150, 60.2%), followed by procedure-related (n = 78, 31.3%) and trauma (n = 21, 8.4%). Most spontaneous events (63.3%) occurred more than 30 days after randomization, whereas most procedure-related events occurred within 30 days (79.5%) (Figure 5). Prasugrel increased the risk of spontaneous bleeding (1.6% vs. 1.1%; HR: 1.46; 95% CI: 1.06 to 2.03; p = 0.022), whereas there was no significant difference observed in the rate of procedure-related non-CABG major bleeding (0.7% vs. 0.6%; HR: 1.11; 95% CI: 0.71 to 1.73; p = 0.65) (Figure 5). The risk of spontaneous non-CABG TIMI major bleeding was increased with prasugrel within the first 30 days after randomization (0.52% vs. 0.35%; HR: 1.50; 95% CI: 0.87 to 2.57; p = 0.14) as well as after 30 days (1.06% vs. 0.75%; HR: 1.44; 95% CI: 0.96 to 2.17; p = 0.078).

## DISCUSSION

In this study of nearly 13,000 patients with ACS who received PCI, over 80% of ischemic events occurring after 30 days were unrelated to the stented lesion, but were rather spontaneous, or de novo, events. More potent dual platelet inhibition for at least 1 year after ACS showed similar efficacy for late ST and de novo atherothrombosis.

With the greater utilization of revascularization and stent placement in ACS, much of the emphasis

**FIGURE 5** TIMI Non-CABG Major Bleeding for Prasugrel Versus Clopidogrel by Type of Bleeding Event and Time From Index ACS




Number at Risk

| | | | | |
|---|---|---|---|---|
| Proc. Clop | 6,397 | 5,610 | 4,042 | 2,725 |
| Proc. Pras | 6,402 | 5,572 | 3,989 | 2,670 |
| Spont. Clop | 6,397 | 5,613 | 4,041 | 2,727 |
| Spont. Pras | 6,402 | 5,568 | 3,989 | 2,671 |

Prasugrel increased the risk of spontaneous bleeding (1.6% vs. 1.1%; HR: 1.46; 95% CI: 1.06 to 2.03; p = 0.022), whereas there was no significant difference observed in the rate of procedure-related non-CABG major bleeding (0.7% vs. 0.6%; HR: 1.11; 95% CI: 0.71 to 1.73; p = 0.65). ACS = acute coronary syndrome; CABG = coronary artery bypass graft; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Figures 2 and 3.

regarding DAPT for ACS has focused on preventing peri-procedural and stent-related complications. Although current guidelines recommend at least 6 months to 1 year of DAPT after DES implantation for most patients, several studies suggest that with the use of newer-generation stents, a shorter duration of therapy or early transition to less intense $P2Y_{12}$ inhibition may be as beneficial and cause less bleeding (11-18,26-32).

However, these studies, with the exception of the TROPICAL-ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes) trial (32), were not performed specifically in ACS patients, and in some cases, excluded patients with actual MI, who are at the greatest risk of recurrent spontaneous and procedural thrombotic events. It has been demonstrated that early discontinuation of DAPT within 30 days after PCI for ACS is associated with increased risk of CV thrombotic events, including ST (33-36). Moreover, studies of reduced DAPT duration and/or intensity with newer DES have been relatively underpowered to examine late events. Therefore, the optimal duration of therapy after ACS treated with PCI should be based on appropriately powered studies performed specifically in patients with ACS.

Analyses from 3 principal trials of adenosine diphosphate (ADP) inhibitors in ACS found reductions in ischemic events with either clopidogrel compared with placebo (10), or prasugrel (19,20,37) or ticagrelor

(38) compared with clopidogrel. More recently, the ISAR-REACT 5 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5) trial showed a 26% reduction in ischemic events with prasugrel as compared with ticagrelor in patients with ACS and a planned invasive strategy (39), further demonstrating the benefit of more potent $P2Y_{12}$ inhibition following ACS. In a previous analysis from the TRITON-TIMI 38 trial, the effect of prasugrel was shown to be consistent across types of MI in the full trial population (19). However, neither of these investigations evaluated both the timing and etiology of recurrent ischemic events to elucidate more precisely how more potent antiplatelet therapy improves ischemic complications after ACS. We are not aware of another analysis examining the effect of potent $P2Y_{12}$ inhibition on early and late stent-related and spontaneous ischemic events in patients with ACS treated with PCI.

The evidence supporting the recommendation for 1 year of DAPT after ACS rests primarily on the fact that each of the key trials with clopidogrel, prasugrel, and ticagrelor lasted for 12 to 15 months. The decision to continue DAPT beyond 1 year remains controversial, accounting for the varied clinical practice of extended DAPT after 1 year (40). The CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) trial, which evaluated the addition of clopidogrel to aspirin in a broad population of stable patients with and without established atherothrombotic disease, found no benefit in the overall trial population, though there was a benefit in patients with a previously documented MI (41). The TRA 2°P (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events)-TIMI 50 trial compared vorapaxar, a platelet thrombin receptor inhibitor, versus placebo in almost 18,000 patients randomized 2 weeks to 12 months from the index MI and found that the addition of another antiplatelet agent to aspirin with or without a thienopyridine significantly reduced the risk of CV death, MI, or stroke over a median of 2.5 years of treatment (42).

Reductions in ischemic events with extended $P2Y_{12}$ inhibition beyond 1 year were shown in the DAPT (Dual Antiplatelet Therapy) trial, which evaluated the benefit of DAPT with aspirin plus clopidogrel or prasugrel versus aspirin alone 12 to 30 months after stent placement (43,44), and the PEGASUS (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin)-TIMI 54 trial (45,46), which tested ticagrelor versus placebo in aspirin-treated patients with prior MI. Our data from the TRITON-TIMI 38 trial provide insight into the reasons for the benefit of extended treatment with DAPT beyond 1 year. Even at the end of the trial, the risk of de novo atherothrombotic lesions persisted and was reduced with the extended use of a more potent antiplatelet agent. Currently, extended DAPT beyond 12 months after ACS is given a Class IIb recommendation in both the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines (5,7,47,48).

Oral anticoagulant trial results may further support the premise of intensive antithrombotic therapy in the "vulnerable" patient. In the ATLAS ACS 2 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin With or Without Thienopyridine Therapy in Subjects With Acute Coronary Syndrome)-TIMI 51 trial, low-dose rivaroxaban reduced the composite ischemic endpoint of CV death, MI, or stroke at a mean follow-up of 13 months (49). The majority of post-randomization MIs were spontaneous, with rivaroxaban providing significant protection against these events (50). Further, the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial investigating low-dose rivaroxaban in stable patients with coronary artery disease or peripheral artery disease showed a reduction in ischemic events across vascular territories with low-dose rivaroxaban (51).

Finally, the COMPLETE (Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI) trial showed that PCI of flow-limiting nonculprit lesions in patients within 45 days of primary PCI for STEMI reduces the composite of CV death or MI by 26% (52). This finding further emphasizes the importance of residual nonculprit lesion risk in the vulnerable post-ACS patient, in this case, pacified with a pharmaco-mechanical intervention.

As expected, procedure-related bleeding in the TRITON-TIMI 38 trial predominately occurred in the first days after randomization, when catheterizations were most frequent. Prasugrel did not increase the risk of procedure-related bleeding but did increase the risk of spontaneous bleeding. After 30 days, the absolute risk difference for prasugrel versus clopidogrel remained only 0.29% for major bleeding. This excess in bleeding risk, although small, does emphasize the importance of avoiding a "one-size-fits-all" approach to antiplatelet therapy intensity and duration after PCI for ACS. Numerous attempts have been made or are underway to quantify an individual

patient's risk for ischemic and bleeding events on the basis of clinical and genetic characteristics, and to personalize antithrombotic therapy accordingly (53). Mechanistically, the findings here of ischemic event reduction paired with increased bleeding are consistent with the more potent inhibition of the $P2Y_{12}$ receptor by prasugrel compared with clopidogrel. To what extent genetic variation in response to clopidogrel may have also influenced these findings cannot be determined here, but has been a topic of renewed interest (54). As point-of-care platelet function testing and rapid genetic assays evolve, so too may the relative efficacy and safety of prasugrel versus clopidogrel in selected patients.

**STUDY LIMITATIONS.** This analysis benefits from a large sample size and prospectively acquired and adjudicated events. There are, however, several limitations. Because events accumulate at different rates in the treatment arms, landmark analyses beyond 30 days cannot formally be considered randomized. In this mechanistic analysis examining the rates of early and late events, though, such analyses are necessary to determine differential event rates. In addition, there was no requirement for angiography in the setting of recurrent events, or autopsy in the setting of death; event classification was based on the clinical assessment of a blinded events committee. These analyses present characteristics of recurrent ischemic events following index ACS without a randomized comparison of different DAPT durations. This description of recurrent events in each treatment arm may provide insight into the relationship between DAPT potency/duration and types of recurrent events, but the TRITON-TIMI 38 trial did not test the efficacy or safety of varied DAPT durations.

Finally, stent technology and medical therapy have evolved rapidly over the past decade. Most stents used in the TRITON-TIMI 38 trial were early-generation DES and improved stent technology, including strut size and drug delivery, have reduced the risk of stent-related thrombotic events. Therefore, with contemporary practice, the ratio of spontaneous- to stent-related events would likely be even higher than observed in this study, heightening the importance of spontaneous events. Conversely, with more potent lipid-lowering therapies now available, more nuanced approaches to nonculprit lesions, and other improvements in secondary prevention, it is possible that rates of spontaneous MI may be decreased in current practice. It is important to note, however, that despite compelling clinical data to support their use, many efficacious therapies remain markedly underused in modern practice (55). Lastly, the clinical relevance of these different event types may not be equivalent. As has been previously reported, the rates of death following MI vary by type of MI (56). Endpoint-endpoint analyses are subject to confounding by underlying patient comorbidities, but highlight the importance of an individualized approach to risk assessment.

## CONCLUSIONS

Much of the focus concerning DAPT centers on reducing periprocedural complications and ST. Without a doubt, DAPT, and more potent DAPT in particular, dramatically reduces the risk of ST and procedural MI. However, the decision regarding the duration and potency of DAPT should incorporate the overall CV risk of the vulnerable patient, in particular the risk of recurrent de novo coronary arterial thrombosis. The number of spontaneous events in such patients, which account for the greatest burden of ischemic events beyond 1 month following ACS, suggests a role for intensive antithrombotic therapy beyond the period necessary for management of stent- and procedure-related risk. Such protection must be balanced against ongoing risks of bleeding with intensive therapy. Our data suggest that extended DAPT improves CV outcomes in patients after ACS, predominately by reducing de novo atherothrombotic ischemic events.

**ADDRESS FOR CORRESPONDENCE:** Dr. Benjamin M. Scirica, TIMI Study Group/Cardiovascular Division, Brigham and Women's Hospital, 60 Fenwood Road, Suite 7022, Boston, Massachusetts 02115. E-mail: bscirica@partners.org. Twitter: @swiviott.

## PERSPECTIVES

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** Extended, high-potency DAPT improves cardiovascular outcomes after ACS in patients treated with PCI, predominantly by reducing de novo atherothrombotic events in these high-risk patients.

**TRANSLATIONAL OUTLOOK:** Further studies are needed to identify patients treated with PCI likely to derive the greatest benefit of extended-duration DAPT following ACS.

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