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EDITORIAL COMMENT

# Uncovering the Shroud on Antiplatelet Therapy for Patients With ST-Segment Elevation Myocardial Infarction Undergoing Percutaneous Coronary Intervention*

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The contemporary management of patients with acute ST-segment elevation myocardial infarction (STEMI) in the United States has focused upon increasing the timely access to primary percutaneous coronary intervention (PCI) through nationwide quality improvement efforts and the establishment of regional STEMI systems of care across the country (1,2). Nonetheless, because only one-third of the approximately 5,000 acute care hospitals in the United States have PCI

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capabilities, primary PCI is not rapidly available to all patients with STEMI. As an alternative to primary PCI, initial reperfusion with fibrinolytic agents is endorsed as a Class IA recommendation by the revised STEMI guidelines when it is estimated that the transfer time to a PCI-capable hospital cannot be expedited to achieve the goal of first medical contact to device activation of <120 min (3–5). Although the nationwide use of primary PCI versus fibrinolytic agents as the initial reperfusion strategy in contemporary practice is unknown, data from a comprehensive statewide STEMI program conducted from 2008 to 2009 demonstrated that approximately 80% of patients eligible for reperfusion therapy received primary PCI, 15% received fibrinolytic therapy initially, and 5% did not receive reperfusion therapy (6).

Recommendations for the use of adjunctive oral antiplatelet therapies (in addition to aspirin) were clarified in the recently updated STEMI guidelines (5). These guidelines endorse a Class IB recommendation for clopidogrel, prasugrel, or ticagrelor for use during primary PCI, a Class IA recommendation for clopidogrel to be given together with fibrinolytic therapy, a Class IC recommendation for clopidogrel when PCI is performed after fibrinolytic therapy, and a Class IIA-B recommendation for prasugrel when PCI is performed after fibrinolytic therapy (with specifications on the timing and type of fibrinolytic used relative to the timing of the PCI procedure) (5). Although the more potent, third-generation $P2Y_{12}$ antagonists, prasugrel and ticagrelor, have both been shown to be superior to clopidogrel, these agents appear to have preferential benefit when used during primary PCI for STEMI (7,8). However, the relative benefits of a third-generation $P2Y_{12}$ antagonist compared with clopidogrel during secondary PCI for STEMI (performed in the non-emergent setting after fibrinolytic agents are administered or more than 12 h after symptom onset for patients who present late into the course of their infarct) are uncertain as reflected in the cautious guidelines recommendation for prasugrel for this indication (5).

In this issue of *JACC: Cardiovascular Interventions*, Udell et al. (9) present the data from the TRITON–TIMI 38 trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) for the relative benefits of prasugrel versus clopidogrel during PCI for the subgroup of STEMI patients stratified by primary versus secondary PCI (68% vs. 32% of the STEMI patients, respectively). Patients in this trial did not receive a $P2Y_{12}$ antagonist as part of routine care before randomization, and the median time from symptom onset to randomization was approximately 4 h versus 48 h for the 2 groups, respectively. Although there was no significant interaction by PCI type for the treatment effect of prasugrel versus clopidogrel in reducing the incidence of the primary endpoint of cardiovascular death, MI, or stroke through 15 months, patients undergoing secondary PCI appeared to derive enhanced relative benefit with an apparent augmentation of the event rate in the clopidogrel treatment arm in this group. When events through 30 days were analyzed, a significant treatment interaction was observed for all MI events ($p = 0.01$) that was driven by a differential reduction of periprocedural MI events with prasugrel in the secondary versus primary PCI groups, whereas there was a consistent treatment benefit with prasugrel for nonprocedural MI events in both groups. Formal interaction testing confirmed these findings, whereas landmark analyses starting 3 days after the index PCI procedure demonstrated consistent relative reductions in the primary endpoint with prasugrel for both the primary and secondary PCI groups.

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Collectively, these results provide important clarifications for the relative benefits of prasugrel observed in the STEMI population, but also uncover a number of interesting findings from the trial. First, although 29% of the secondary PCI patients received fibrinolytic therapy at a median time of 2.2 days before randomization, this group ostensibly should not have included patients with failed fibrinolytic therapy and who underwent rescue PCI because patients treated with fibrinolytic agents in the prior 24 to 48 h (depending upon fibrin specificity of the agent used) were excluded from the TRITON trial. However, data regarding initial reperfusion success following fibrinolytic agents and the occurrence and timing of recurrent ischemic events before randomization and PCI for this group were not collected. Second, the reasons for nonuse of reperfusion therapy for the 71% of secondary PCI patients not treated with fibrinolytic therapy, such as delayed presentation after symptom onset or contraindications to fibrinolytic agents were also not collected, so the secondary PCI patients are likely a heterogeneous group who may not relate to the typical STEMI patients treated in U.S. practice. Third, the divergent bleeding results (significant treatment interaction with a higher risk of non-coronary artery bypass graft Thrombolysis In Myocardial Infarction major bleeding with prasugrel in the primary PCI group versus a lower risk with prasugrel in the secondary PCI group) are perplexing and do not appear to be explained by differences in key bleeding risk factors (older age, low body weight, prior stroke/transient ischemic attack) between the groups, yet these findings are not emphasized in the paper. Finally, this analysis carefully delineates a major impediment for the conduct and interpretation of a trial for a novel antithrombotic agent administered for STEMI patients undergoing PCI: that is, confounding by the ascertainment of periprocedural MI events in the primary versus secondary PCI setting. Except for obvious angiographic complications detected through core laboratory review or verification of ST-segment re-elevation after initial ST-segment resolution, the adjudication of periprocedural MI events for STEMI patients undergoing primary PCI by evaluation of cardiac marker trend patterns is very difficult, given the expected marker elevations related to the index STEMI events. For patients undergoing secondary PCI, initial marker elevations likely down trended by the time PCI was performed, so the detection of periprocedural MI events was inadvertently facilitated by the inherent delays to the PCI procedure in this group.

Although the results in the secondary PCI group from the TRITON trial are hard to extrapolate to contemporary U.S. practice, these findings should inform practice guideline recommendations and the conduct of future trials for STEMI patients undergoing PCI. The current Class IIA-B recommendation for the use of prasugrel for STEMI patients undergoing nonrescue PCI after fibrinolytic therapy (after the specified time delays to allow for resolution of the lytic effect to minimize bleeding risk) should be reconsidered for upgrade in light of these results. Additionally, given the specifications of the most recent revisions to the Universal MI Definition for the ascertainment of periprocedural MI events, the MI adjudication plan for a new STEMI PCI trial should include angiographic core laboratory review, detailed data collection regarding symptoms and electrocardiographic changes during the procedure, and careful documentation of the specifications of the local cardiac marker assays utilized (if cardiac marker core laboratory specimens are not collected) (10,11). Finally, data are needed from U.S. practice on how STEMI patients who do not undergo primary PCI are managed in order to better inform treatment decisions and risk prognostication for this important and sizable group of patients.

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