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EDITORIAL COMMENT

Door-to-Balloon Time as a Process Metric for Treatment of ST-Segment Elevation Myocardial Infarction

Time to "Tap Out"?*

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Door-to-balloon time (DBT) has been a standard process metric in the treatment of ST-segment elevation myocardial infarction (STEMI) by primary percutaneous coronary intervention (PPCI) (1). As a result of national and state efforts, the improved efficiency and organization of PPCI centers have made DBT <90 min and even <60 min a commonplace occurrence (2). However, the further reduction of DBT has not been translated into a significant improvement in mortality and morbidity (3). The actual time of acute onset of ischemia in the individual patient and the time to meaningful mechanical reperfusion by PPCI without microvascular damage are a cloudy piece of the puzzle. In addition, microvascular injury despite timely PPCI and stent implantation continues to be a factor in mortality and morbidity.

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The paper by Prasad et al. (4), in this issue of *JACC: Cardiovascular Interventions* provides information on these vexing questions regarding STEMI metrics. This study consists of a subanalysis of 2,056 patients in the multicenter HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. The objective was to assess the association of treatment delay factors with impairment of microvascular reperfusion despite restoration of epicardial blood flow with PPCI for acute STEMI.

The authors studied the impact of symptom onset-to-balloon time (SBT) and DBT on subsequent myocardial reperfusion during PPCI in STEMI. Perfusion was quantitated by assessing the myocardial blush grade (MBG) and the resolution of ST-segment elevation (STR). The primary analysis consisted of the relationships between SBTs of ≤2, >2 to 4, and >4 h and DBTs of ≤1, >1 to 1.5, >1.5 to 2, and >2 h with outcomes of MBG and STR. Clinical risk was assessed using a modified version of the Thrombolysis In Myocardial Infarction risk score for STEMI.

The authors found that absent microvascular perfusion (MBG 0/1) and poor STR (STR <30%) were significantly more common in patients with a longer SBT, in both low and high clinical risk profile patients. Multivariable analysis indicated that SBT ($p < 0.0001$), anterior infarction ($p < 0.0001$), reference vessel diameter ($p = 0.005$), lesion minimal lumen diameter ($p < 0.0001$), hyperlipidemia ($p = 0.03$), and current smoking ($p = 0.001$) were independent predictors of an MBG 0/1. Multivariable analysis indicated that SBT ($p = 0.007$), anterior infarction ($p < 0.0001$), and history of renal insufficiency ($p = 0.0002$) were independent predictors of absent STR. The DBT ($p < 0.0001$) was also an independent predictor of MBG 0/1. In long-term outcomes, patients with an MBG 0/1 and an STR <30% had a higher 3-year mortality rate. The authors concluded that delay in mechanical reperfusion therapy during STEMI, particularly in patients with a prolonged SBT, is associated with greater injury to the microcirculation.

This substudy of the HORIZONS-AMI trial adds important information to the effective treatment of

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STEMI. The authors are all highly respected in the field of interventional cardiology and have tremendous experience in multicenter PPCI STEMI studies. The statistical analysis is exquisite. The basic findings of delay in reperfusion equating to poorer outcomes is not a surprise. The exception in this study is the attention to SBT, which is a stronger predictor of microvascular injury when PPCI is delayed regardless of DBT.

The clinical take-home messages from this study are 4-fold. First, we need to pay even more attention to an SBT >2 h and most certainly an SBT >4 h as they are independent risk factors for impaired myocardial perfusion and subsequent mortality and morbidity, despite timely systems processes and DBT. Even though the metric of onset of acute chest pain may be variable by patient perception or history, we should seek out this information and calculate this metric for our interventional strategy. The subset of patients with a prolonged SBT who present at outside non-PCI centers in the gray zone of timely transport (approaching 120 min) (1) to a PCI center may be better treated with intravenous thrombolytic therapy before transport followed by assertive rescue PCI if still symptomatic.

At the time of PPCI, the subset of patients with a prolonged SBT with potential large and mature thrombus burden may require more aggressive adjunctive pharmacological therapy. Even though the patient may have already been loaded with an oral $P2Y^{12}$ agent and aspirin, 1 consideration would be to give a bolus of intracoronary abciximab (5) or tirofiban (6) or a bolus of intravenous infusion of eptifibatide (7) in the cath lab before crossing the coronary occlusion. A direct pharmacological attack on mature platelet activation and thrombus in the patient with a protracted SBT may theoretically lead to less micro distal embolization. Recent studies have indicated that routine aspiration thrombectomy across the board in PPCI STEMI patients has disappointing outcomes (8). However, in this select patient group with a prolonged SBT and/or with low MBG and STR scores, selective aspiration may still be warranted. There have been reports of favorable outcomes in periprocedural treatment with exenatide (9) and cyclosporine infusion (10), but these findings need further verification. Another practical option would be to treat patients with a prolonged SBT, especially those with observed low MPG and/or low STR, with extended post-procedural infusions of intravenous bivalrudin or heparin or intravenous 2b/3a agents. A strategy of radial access (11) in patients with a prolonged SBT may reduce the risk of significant post-procedural bleeding if these intensive anticoagulation and antiplatelet strategies are adopted. Obviously, these strategies need to be confirmed by large randomized trials.

A second affirmation from this study is that DBT is still an independent predictor of impaired MBG. Third, if the SBT is <2 h, reductions in DBT intervals may further improve myocardial perfusion. So, even if the metric of DBT may be "tapped out," focus on this systems process metric should still be in the equation in these very early presenters.

The fourth major message of this study is that impaired myocardial perfusion strongly correlates with mortality at 3 years. In the post-PPCI treatment of patients who have had a prolonged SBG and/or subsequent low MPG and low STR, consideration should be given to keeping these patients on long-term dual antiplatelet therapy along with aggressive statin, beta-blocker, and afterload reduction therapy and close follow-up.

Put in perspective, these authors' superb statistical analyses are a good demonstration of how to use subsets of well-run multicenter trials such as the HORIZONS-AMI to help resolve issues of PPCI STEMI treatment.

In summary, is it time for DBT as a process metric to "tap out"? The answer is no. The DBT metric and the organizational systems in place are extremely valuable, can be quantitated, and should continue. Nevertheless, we need to pay even more attention to adjunctive metrics such as the symptoms and signs of acute onset of acute coronary ischemia. Patients with prolonged SBT are a high-risk group and should be treated accordingly with assertive strategies. We as an interventional cardiology community should continue to educate the public and health care providers regarding the importance of quantifying SBT and follow through with prompt action.

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