**EDITORIAL COMMENT**

**Beta-Blocker Therapy and Primary Angioplasty**

**What Is the Controversy?**

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Beta-blocker therapy has long been recommended for the treatment of ST-elevation myocardial infarction (STEMI) and is listed as a class 1 indication in the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the treatment of acute myocardial infarction (MI) (1). Studies prior to the use of thrombolysis have demonstrated both short- and long-term benefits, and a meta-analysis of these trials showed a 25% reduction in mortality at one year (2). Likewise, a similar analysis of the meta-analysis of these trials showed a 25% reduction in mortality (3). Early intravenous beta-blocker therapy has also been shown to improve both short-term and long-term outcome in the Thrombolysis in Myocardial Infarction II-B trial (4). In the Carvedilol Post Overall 23% reduction in mortality (3). Early intravenous studies in patients treated with thrombolysis showed an early mortality at one year (2). In this study, 2,537 patients enrolled in four PAMI studies were pooled. Patients receiving pretreatment with beta-blockers before primary angioplasty were compared with those not receiving pretreatment. After adjustment for baseline differences between patient groups, a significantly lower incidence of in-hospital death with use of beta-blocker therapy was found (1.3% vs. 3.7%; p = 0.0035). A strong trend toward a lower mortality at one year was also reported (p = 0.055).

However, not all patients were receiving beta-blockers during follow-up (66% to 89%). When only those receiving beta-blockers during follow-up were included in the analysis, there was a significantly improved one-year mortality with its use (odds ratio [OR] = 0.43; p = 0.001). In this issue of the *Journal*, Kernis et al. (8) examined 2,442 patients with successful primary angioplasty that participated in four of the PAMI studies. This patient group was slightly different from the group in the previous report (two trials were the same, two were different from the previous publication); however, the findings were remarkably similar. In this study the authors evaluated only post-procedural beta-blocker use after PCI on six-month outcomes. Again, a significant reduction in mortality was observed (2.2 vs. 6.6; p < 0.001), and the multivariate analysis demonstrated an OR remarkably similar to the first study (OR = 0.43; p = 0.0016). Importantly, the authors showed a survival benefit in high-risk sub-groups such as those with ejection fractions <50% (OR = 0.34; p > 0.0001) and those with multivessel disease (OR = 0.26; p < 0.001).

Also, in this issue of the *Journal*, Halkin et al. (9) evaluated the effect of beta-blockers on 30-day mortality in the 2,082 patients undergoing primary PCI for STEMI as part of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications trial, a randomized trial of balloon angioplasty versus stenting with or without glycoprotein IIb/IIIa agent abciximab. The study demonstrated a lower 30-day mortality in the beta-blocker group (1.5% vs. 2.8%; p = 0.03). The improved survival was not realized at one year; although an absolute difference between groups (1.7%) was similar, suggesting the benefit was largely an early benefit. The lack of long-term benefit, however, might not have been realized owing to the high percentage of patients in both groups receiving beta-blockers during follow-up (86% for initial beta-blocker use vs. 70% for initial non-beta-blocker users). The benefit, however, was confined to those who were not receiving long-term beta-blocker therapy before hospital admission.

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This finding is surprising because a benefit has been observed previously in such patients (12). Together, these studies provide powerful support for the use of beta-blocker therapy in patients with STEMI undergoing primary angioplasty, and they support the ACC/AHA guideline recommendations (1). Pre-procedural administration resulted in a 50% to 65% reduction in hospital mortality. Likewise, long-term beta-blocker therapy had a favorable impact on long-term outcome by an equal degree.

The mechanism of benefit from beta-blocker therapy in STEMI is still unclear. It has been suggested that early beta-blocker treatment decreases myocardial oxygen consumption, favorably influences coronary blood flow, and reduces infarct size. The improvements in ejection fraction in a study by Halkin et al. (9) support a reduction in the infarct size as contributing. Another mechanism of benefit might be a reduction in procedural MI. In a recent retrospective study by Sharma et al. (13), 1,676 patients undergoing non-STEMI coronary interventions were reviewed. Previous beta-blocker therapy reduced the incidence of post-procedural creatine kinase-MB release and improved short-term mortality over a 15-month period (13). It remains controversial whether intravenous or intracoronary beta-blockers immediately before PCI reduce peri-procedural risk of MI after angioplasty (14,15). However, long-term therapy, particularly in high-risk patients undergoing PCI, has shown benefit (16). Another potential mechanism for benefit is a reduction in fatal ventricular arrhythmias. In a study from the PAMI group, Mehta et al. (10), in this issue of the Journal, demonstrated a reduced incidence of procedural ventricular tachycardia/ventricular fibrillation (VT/VF) in patients receiving beta-blocker therapy and undergoing primary angioplasty. Although VT/VF was rare (4.3%), it was a marker of poor outcome. Interestingly, this study failed to demonstrate a benefit with beta-blockers on post-procedural or late VT/VF. It has been postulated that the anti-ischemic effects of beta-blockers may contribute to the improved long-term outcome. However, in both the PAMI and Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications trials reported in this issue of the Journal, beta-blockade was not associated with the reduction in ischemic-driven target vessel revascularization or re-infarction.

Is the case closed on beta-blockers and STEMI undergoing primary angioplasty? Not quite yet. Although these studies are persuasive, we still have not had a single randomized trial of beta-blocker therapy in primary angioplasty. The potential selection bias that naturally occurs in non-randomized studies diminishes the powers of the observations reported in this issue of the Journal. It is also not clear whether all patients receiving primary angioplasty benefit from pre-procedural or long-term oral beta-blocker therapy. Kernis et al. (8) showed that in patients with either a normal ejection fraction or single-vessel disease and no in-hospital major adverse coronary events, long-term benefits of beta-blocker therapy could not be demonstrated. What should we do today based on the available data? It is clear that all patients without contraindication should receive beta-blockers before primary angioplasty and that those receiving long-term oral beta-blockers before admission should continue to receive beta-blockers. Patients who develop an in-hospital complication, have reduced LV function, or have multi-vessel disease derive the greatest benefit from long-term oral therapy. The question remains, however, whether a patient with normal ejection fraction and single-vessel disease who undergoes a successful angioplasty receives any benefit from either short- or long-term beta-blocker therapy. This question remains an unanswered one and will need to await further data from clinical trials to be resolved. In the absence of additional studies, the data would strongly support the current guidelines for the use of beta-blockers in all eligible patients, regardless of the revascularization strategy. In primary PCI, it is clear that pre-procedural beta-blocker therapy also is of significant benefit. Our major challenge in the future to ensure that all eligible patients with STEMI are treated with beta-blockers both before angioplasty and during long-term follow-up. The health implications of widespread use of beta-blockers after MI are enormous, given the magnitude of benefit reported in clinical trials. National efforts to improve compliance with guidelines, such as the AHA’s “Get with the Guidelines” program, have already shown improvements in the use of beta-blockers and other secondary prevention treatments. Let’s hope that the benefit now observed in patients with primary angioplasty will help further increase their use.

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REFERENCES


