EDITORIAL COMMENT

Assessing Oral Beta-Blocker Therapy After Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction

The Role of Observational Data*

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Randomized clinical trials have conclusively shown that beta-blocker therapy reduces mortality by about 20% during the 2-year period following myocardial infarction (MI) (1–3). On the basis of these data, international guidelines recommend beta-blocker therapy as a class 1 recommendation for patients who have MI, including ST-segment elevation myocardial infarction (STEMI), initiated within the first 24 h and continued after hospitalization if there is no contraindication (4).

Most of the evidence for benefit of beta-blockers following acute MI predates the era of reperfusion, and in particular, primary percutaneous coronary intervention (PCI). Given that PCI results in less residual myocardial damage and lower mortality, it is possible that the benefits of beta-blocker therapy, which are thought to be due to a decrease in myocardial oxygen demand in regions downstream of stenoses by decreasing heart rate and inotropy, may be less following primary PCI. Thus it is an important question to understand whether beta-blocker therapy following primary PCI offers a benefit to these patients (5).

Few randomized trials are available that address the effects of beta-blockers following reperfusion therapy. The COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) examined the effect of early intravenous then oral metoprolol in 45,852 patients with STEMI and found no difference in mortality at 30 days. The trial did find that beta-blockers resulted in less reinfarction and ventricular fibrillation at the expense of more cardiogenic shock, which is consistent with the benefit of this therapy in hemodynamically stable patients (who are not susceptible to shock) (6). A more recent, small trial, the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction Trial, showed patients with primary PCI had reduced infarct size and improved left ventricular function with no excess of adverse events during the first 24 h with intravenous metoprolol (7).

Observational studies have also addressed the effects of beta-blockers following primary PCI. The CADILLAC (Controlled Abciximab and Device Investigation to Low Late Angioplasty Complications) trial looked at 2,082 patients to address the association of intravenous beta-blocker therapy before primary PCI and outcome. They found lower 30-day mortality (1.5% vs. 2.8%, p = 0.03) and improved left ventricular ejection fraction from baseline to 7 months (3.8% vs. 1.3%, p = 0.01) (8).

When considering the benefit of oral beta-blocker therapy after primary PCI for patients with STEMI, even fewer data are available. A retrospective review of observational data from 4 of the PAMI (Primary Angioplasty in Myocardial Infarction) studies, including 2,442 patients, found lower 6-month mortality associated with oral beta-blocker therapy at discharge (2.2% vs. 6.6%, p > 0.0001; odds ratio [OR]: 0.43, p = 0.0016) (9). This study also showed that the associated lower mortality was confined to high-risk subgroups defined as those with an ejection fraction (EF) <50% (OR: 0.34, p > 0.0001) and those with multivessel coronary disease (OR: 0.26, p < 0.001). In a prospective observational study, OACIS (Osaka Acute Coronary Insufficiency Study), which included 5,628 patients with median follow-up of 1,430 days, the reduction in mortality associated with oral beta-blocker therapy was also seen in high-risk patients (hazard ratio [HR]: 0.60, 95% confidence interval [CI]: 0.42 to 0.85, p = 0.005) or those who received diuretic agents (HR: 0.60, 95% CI: 0.40 to 0.91, p = 0.016) (10). For low-risk patients with a preserved EF who had STEMI treated with PCI, registry data from Japan including 12,824 patients with an EF >40% did not show a difference in 3-year mortality associated with oral beta-blocker therapy at hospital discharge (11). Thus, most but not all observational data have suggested a benefit, varying with risk, with oral beta-blockers.

The question about the benefits of beta-blocker therapy might be similarly asked of angiotensin-converting enzyme...
(ACE) inhibitors or angiotensin–receptor blockers after primary PCI. It seems prudent to extrapolate that for patients with heart failure and/or left ventricular dysfunction, and probably for all patients with significant anterior MI, ACE inhibitors are equally important with or without primary PCI. It is also notable that in the overall effect of ACE inhibitors on mortality over the first 4 to 6 weeks after acute MI, 40% of the survival benefit occurred in the first day (12). Thus early initiation of ACE inhibitors following a large MI (in the absence of hypotension) may be as or more important than early initiation of beta-blockers.

The results in this issue by Yang et al. (13) are from a high-quality, large registry of 8,510 patients with STEMI treated with primary PCI and focus on outcomes associated with oral beta-blocker therapy. Consistent with previous studies, beta-blocker therapy at discharge was associated with lower mortality during a median follow-up of 1-year (HR: 0.52, 95% CI: 0.38 to 0.70, p < 0.001). Interestingly, the subgroup analysis of this study showed a consistent association with lower mortality among low-risk patients defined as those with a preserved EF and single-vessel coronary disease.

These findings are supportive of the conclusion that oral beta-blocker therapy at discharge in patients treated with primary PCI results in better outcomes. The 50% lower mortality in this study is substantially more than the 20% estimate from randomized trials and therefore raises some question regarding the degree of benefit seen in this study. As with all observational data, inference of treatment effect in this study is hazardous. This and related studies have selection bias for the use of beta-blockers that is related to measured and unmeasured factors. Whereas propensity scoring can control confounding, it cannot account for unmeasured confounders. As an example, propensity scoring was used in observational studies to evaluate whether right heart catheterization is beneficial to guide therapy in critically ill patients. Propensity score adjustment found that right heart catheterization was associated with higher mortality. A subsequent randomized clinical trial, the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial (14) found no effect on overall total mortality. This provides an example of propensity scoring not being reliable to adjust for confounders in order to estimate treatment effect that leaves the randomized comparison as a “gold standard.”

Another limitation of this study (and other related observational studies) is that beta-blocker therapy was defined as having a beta-blocker prescribed at the time of discharge, with little information about whether and how beta-blockers were continued. Despite these limitations, however, this observational study provides some evidence that the well-established benefits of beta-blockers are likely consistent for patients treated with primary PCI, including patients at lower risk.

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