Should Beta-Blockers Continue to Be Used in Post-Percutaneous Coronary Intervention Patients Without Myocardial Infarction?*

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The routine use of beta-blockers for the treatment of coronary artery disease (CAD) dates back to the mid 1970s, when these agents were used primarily for the treatment of angina. During that time, there were also small studies showing the clinical benefit of beta-blocker use in survivors of acute myocardial infarction (MI). In 1982, the results of the BHAT (Beta Blocker Heart Attack) trial, conducted by the National Heart, Lung, and Blood Institute, were published and demonstrated that patients treated with propranolol early after an acute MI had a 26% relative risk reduction in mortality when compared with those who did not receive the drug—the first large, prospective, randomized controlled trial to show such a mortality benefit (1). After this seminal study, there were numerous randomized trials that showed a similar reduction in mortality with beta-blocker use after acute MI (2,3). Many of those studies, however, were conducted before the era of early reperfusion and the broad-based adoption of modern therapies for MI, whereas more contemporary studies have shown only a short-term reduction in MI and angina, but not overall mortality (4). Nonetheless, the American College of Cardiology Foundation/American Heart Association guidelines continue to promulgate the use of beta-blockers as a Class I recommendation for up to 3 years after an acute MI (5).

Although the salutary effects of beta-blockers in patients after MI have been perhaps less impressive in the modern era of clinical practice, their benefits in the subset of patients who have reduced left ventricular (LV) systolic function after an MI or chronic heart failure have been well validated in contemporary clinical trials (6,7).

They are also first line agents in both the U.S. and European guidelines for controlling angina and relieving myocardial ischemia in patients with stable ischemic heart disease (SIHD) due to their ability to decrease myocardial oxygen consumption. In fact, patients with SIHD who are treated with beta-blockers as part of an optimal medical therapy (OMT) regimen have similar cardiovascular outcomes as patients who also undergo myocardial revascularization (8).

For years, clinicians have extrapolated the evidence of beta-blocker benefit from the aforementioned older post-MI trials and applied it to all patients with CAD. This prevalent practice—fueled largely by clinical practice guideline recommendations of Class IA or 1B efficacy—occurs despite a lack of prospective, randomized trials evidence to show improved clinical outcomes in the large subsets of CAD patients who do not have reduced LV systolic function, a prior MI, or ongoing angina. In 2012, the REACH (Reduction of Atherothrombosis for Continued Health) Registry investigators showed that, after a median of 44-month follow-up, beta-blocker use was not associated with a reduction of composite cardiovascular outcomes in a large cohort of patients with SIHD. Furthermore, they also did not observe a difference in a separate large cohort of patients with a prior MI (9). In 2014, Andersson

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et al. (10) further challenged the notion of clinical benefit in patients with stable CAD when they examined the Kaiser Permanente health database and found only a modest benefit of beta-blocker use in a large cohort of patients with newly diagnosed CAD. However, this clinical benefit was confined solely to patients with a prior MI (10). It has been hypothesized that this lack of a cardioprotective benefit of beta-blockers in stable CAD patients is due to their inability to effectively reduce central aortic pressure, or is possibly a consequence of a worsening metabolic profile among patients taking this drug (11,12). Furthermore, subjects for whom beta-blockers are prescribed often experience untoward side effects and may discontinue their use abruptly, thus putting them at an increased risk for adverse cardiac events (13).

In this issue of JACC: Cardiovascular Interventions, Motivala et al. (14) attempt to shed more light on this important clinical question regarding the use of beta-blockers in patients with SIHD. Using the National Cardiovascular Data Registry (NCDR) CathPCI Registry and CMS database, the authors evaluated a cohort of SIHD patients ≥65 years of age who had undergone a recent percutaneous coronary intervention (PCI) and did not have some other compelling indication for beta-blocker use (e.g., LV systolic dysfunction, prior MI, or history of heart failure). They examined the clinical outcomes of these patients at both 30 days and 3 years of follow-up based on whether or not they were prescribed a beta-blocker after a PCI. They also examined predictors and trends of beta-blocker prescriptions in these patients. The data set included a total of 755,215 patients from 1,443 sites of whom 71.4% were discharged on beta-blockers. At 3 years of follow-up, the authors found no difference in the adjusted mortality rate among patients who were prescribed a beta-blocker at hospital discharge (14.0% vs. 13.3%; adjusted hazard ratio [HR]: 1.00; 95% confidence interval [CI]: 0.96 to 1.03; p = 0.84), MI (4.2% vs. 3.9%; adjusted HR: 1.00; 95% CI: 0.93 to 1.07; p = 0.92), stroke (2.3% vs. 2.0%; adjusted HR: 1.08; 95% CI: 0.98 to 1.18; p = 0.14), or revascularization (18.2% vs. 17.8%; adjusted HR: 1.97; 95% CI: 0.94 to 1.01; p = 0.10). They did, however, observe that discharge on beta-blockers was associated with a higher rate of heart failure readmissions at 3 years (8.0% vs. 6.1%; adjusted HR: 1.18; 95% CI: 1.12 to 1.25; p < 0.001). From these findings, the authors concluded that beta-blocker use at discharge in SIHD patients without prior MI, systolic heart failure, or prior bypass surgery undergoing PCI was not associated with any reduction in hard clinical events, as noted, at 30 days and 3 years of follow-up. Certain aspects of this important paper warrant comment. What is unknown, and not reported by the authors, is whether or not all of the patients with stable CAD, and presumably angina, were naive to beta-blocker therapy before undergoing a PCI. If so, it is possible that some of those patients may have been first treated with a beta-blocker as part of an OMT regimen and perhaps might not have required a PCI? This approach has been supported by clinical data such as the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) Trial and would now be recommended by the Appropriate Use Criteria for coronary revascularization (15). The authors highlight the fact that the study population represents only a very small percentage of the NCDR population, although there is little information provided on the details of beta-blocker use over time for the overall study cohort. Because this is a retrospective analysis, there is certainly the potential for confounding and selection bias with respect to which patients received a beta-blocker prescription after PCI. By focusing their analysis on a Medicare population, the investigators may have controlled some of the selection bias related to the ability of patients to obtain the medication, although we lack data on overall beta-blocker adherence. However, as the authors point out, the group of patients for whom beta-blocker therapy was prescribed had a higher prevalence of traditional cardiovascular risk factors, and hence it is quite possible that these subjects were prescribed a beta-blocker after PCI because of more complex anatomic CAD or an incomplete revascularization. In those cases, the treating physician also may have been concerned about the potential for ongoing ischemia. Considering these possibilities, one may interpret these data from the perspective that the use of beta-blocker therapy was effective therapeutically, because the patients in that group did not have a higher incidence of ischemic events. The investigators’ observation that there was an increased frequency in beta-blocker prescriptions over time is perhaps not surprising. They examined the NCDR CathPCI registry patient data between 2005 and 2013. This encompasses the time frame during which trials like COURAGE, BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes), and FAME 1 and 2 (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) were published (16-18). Based on those trials, there was an increased emphasis on medical therapy for SIHD and the performance of PCI for flow-limiting lesions as
assessed by fractional flow reserve. It is therefore likely that, as time passed, the treating physicians of this patient cohort would have felt more confident deferring PCI because the coronary stenoses were not hemodynamically significant by fractional flow reserve measurement. Theoretically, this might have resulted in more aggressive treatment and more beta-blocker prescriptions as part of the OMT regimen for residual CAD.

Finally, why there was an increased rate of hospitalization due to heart failure in the group discharged on beta-blockers is unclear, although this finding was likewise observed by Bangalore and colleagues who also found an increased incidence of heart failure in patients treated with beta-blockers in the reperfusion era (3). These findings from 2 studies suggest that there may be competing mechanisms of benefit and potential harm associated with beta-blocker usage in SIHD patients without prior MI or LV dysfunction—which perhaps may be another reason for a more cautious, selective use of these agents.

In conclusion, this study along with others (9,10,19), raises questions about the continued role of beta-blocker usage in patients with CAD undergoing PCI. It seems increasingly difficult to justify the continued class IA/IB Clinical Practice Guideline recommendations for beta-blocker use by professional cardiovascular societies where the evidence of clinical benefit in patients without prior MI or heart failure/LV dysfunction is largely lacking. It is highly unlikely that a definitive, prospective, randomized trial of beta-blocker treatment in such asymptomatic stable CAD patients will ever be conducted. Thus, absent new data to guide current therapy, clinicians will need to decide whether they will continue to extrapolate older scientific evidence of beta-blocker efficacy in selected post-MI populations from an earlier era before the advent of PCI and OMT to the current era of contemporary clinical practice, where perhaps such treatment decisions need to be guided more by physician judgment, and hence individualized to the level of patient benefit versus risk, because such definitive evidence is either imperfect or lacking.

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REFERENCES


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