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Beta-blockers for secondary prevention in stable coronary artery disease: can observational studies provide valid answers?

James S. Floyd, MD, MS

Cardiovascular Health Research Unit, University of Washington, Seattle, WA; Department of Medicine, University of Washington, Seattle, WA

Beta-blockers have been a cornerstone secondary prevention therapy for patients with acute myocardial infarction (AMI) since large randomized controlled trials (RCTs) conducted in the 1970s and 1980s demonstrated large treatment effects on mortality. In a meta-analysis of these trials, the long-term use of beta-blockers resulted in a 23% reduction in the risk of death, driven mostly by a 32% reduction in the risk of sudden death [1]. Since then, the widespread use of reperfusion therapy and effective pharmacologic treatment with antiplatelet drugs and statins has resulted in improved prognosis [2], so the benefits of beta-blockers may have declined over time. Nonetheless, the use of beta-blockers after an AMI hospitalization has been identified as a measure of healthcare quality, resulting in 90% prescribing rates in both the United States and Europe. Beta-blockers are similarly effective for the prevention of death in patients with heart failure due to left ventricular systolic dysfunction (LVSD).

The evidence supporting the use of beta-blockers for the treatment of stable coronary artery disease (CAD) is less clear. While effective in providing relief from anginal symptoms, beta-blockers do not prevent deaths or AMI in patients with stable angina when compared with placebo or active-control drugs in RCTs [3]. Guidelines on the management of stable CAD from the American Heart Association and the European Society of Cardiology distinguish between these two rationales for the use of beta-blockers [4, 5]: they make strong evidence-based recommendations about the use of beta-blockers for the treatment of anginal symptoms, but extrapolate from evidence in the post-MI setting to suggest that beta-blockers may prevent adverse cardiovascular events in patients with stable CAD. Whether beta-blockers are useful for secondary prevention in this population is an open question. This gap in evidence has motivated recent observational studies.

Using data from the REACH registry, which enrolled patients at physician practices in 44 countries from 2003 to 2004, Bangalore et al. evaluated two different stable CAD populations: patients who survived an AMI at least 1 year prior to enrollment and patients with established CAD but no previous AMI [6]. Information on the presence of

Corresponding Author: James Floyd, MD, MS, University of Washington, 1730 Minor Ave, Suite 1360, Seattle, WA 98101, Phone: 206-287-2777, Fax: 206-287-2662, jfloyd@uw.edu.

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comorbidities and medication use at baseline was collected using standardized case report forms. Propensity score matching was used to address confounding by factors associated with beta-blocker use at baseline for 6,758 patients in the prior-MI cohort and 7,198 patients in the CAD cohort. The primary outcome was a composite of nonfatal AMI events, nonfatal stroke events, and cardiovascular deaths, which were not adjudicated. After a median duration of follow up of 3.7 years, beta-blocker use was not associated with a reduced risk of the primary outcome compared with nonuse in either the prior-MI cohort (hazard ratio [HR] 0.90; 95% confidence interval [CI], 0.79-1.03) or the CAD cohort (HR 0.92; 95% CI, 0.79-1.08). Associations were nearly identical for the secondary outcome of cardiovascular mortality, but with slightly wider confidence intervals.

Reported in this issue of *Heart*, Bauters et al. conducted a similar study using data from the CORONOR registry, which enrolled 4,184 patients with stable CAD at cardiology practices in France from 2010 to 2011 [7]. Stable CAD was defined as a previous revascularization procedure, a 50% or greater lesion on coronary angiography, or a previous AMI at least 1 year prior to enrollment. Similar to the REACH study population, patients in CORONOR were mostly older (mean age 69) and male (>70%), and had little LVSD (3%). The amount of missing information on key prognostic markers was negligible. Beta-blocker users and nonusers were matched on propensity scores for beta-blocker use at baseline, and the primary outcome of cardiovascular mortality was adjudicated by blinded investigators. Most patients (79%) were beta-blocker users, so only 1,678 could be included in the propensity score-matched analysis. With a median follow up of 2.0 years, beta-blocker use was associated with a markedly reduced risk of cardiovascular death compared with nonuse (HR 0.43; 95% CI, 0.22-0.82).

Both of these studies collected high-quality information on tobacco use and other cardiovascular risk factors at the time of registry enrollment. They also used appropriate analytic methods to address confounding, which resulted in distributions of measured prognostic factors that were well balanced between beta-blocker users and nonusers. There were large differences in point estimates for the primary hypothesis tested in these studies, but the confidence intervals overlap and findings from both studies are consistent with a 20% lower relative risk of cardiovascular death associated with the use of beta-blockers compared with nonuse. Despite the several strengths of these studies, do these associations reflect causal relative risk estimates?

A common weakness of observational studies that attempt to evaluate the effectiveness of drug therapies is the potential for bias from confounding by indication, which can occur when the use of a drug is related to the duration, severity, or prognosis of the disease in question. In the REACH and CORONOR studies, beta-blockers may have been used more often by patients with ongoing angina or other unmeasured factors associated with an increased risk of death. On the other hand, during an era when beta-blockers are a standard of post-AMI care, patients who survived an AMI but did not receive beta-blockers are likely to have had a contraindication to beta-blocker therapy such as a bradycardia, hypotension, or decompensated heart failure, all of which pose a greater risk of death during follow up. Such confounding by contraindication may have inflated the mortality risks among beta-blocker nonusers. For example, the Cooperative Cardiovascular Project estimated treatment effects

for beta-blocker in post-AMI patients that exceeded the benefits seen in RCTs (HR 0.60), but excluding patients with a contraindication to beta-blocker therapy resulted in a more plausible estimate among those who underwent PCI (HR 0.86) [8, 9].

Other types of bias can result when the ascertainment of a treatment occurs at a point in time well after the initiation of therapy. In contrast with new user study designs, studies of prevalent users exclude patients who die shortly after the initiation of therapy and they misclassify as nonusers patients who discontinue therapy due to side effects or non-adherence, which may be associated with the outcome of interest [10]. As described by others, prevalent user studies can overestimate treatment benefits substantially and address questions of uncertain clinical importance [11]. The potential for confounding and selection bias, and the lack of information on adherence to beta-blocker therapy during follow-up, make a causal inference problematic.

Stable CAD encompasses long-term survivors of an acute coronary syndrome, patients with symptomatic stable angina, and asymptomatic patients who have previously undergone revascularization [4, 5]. An evaluation of the effects of beta-blockers in these heterogeneous populations requires study designs that carefully disentangle them and address the specific methodologic challenges of each one. One potential approach is to identify inception cohorts that include patients at the time of their CAD diagnosis. For patients with symptomatic stable angina, initiators of beta-blockers could be compared with initiators of other anti-anginal therapies, adherence and predictors of adherence assessed during follow up, and new analytic methods used to limit time-varying confounding and selection bias [12]. Because beta-blockers are recommended for nearly all post-AMI patients, an potential inception cohort study of AMI survivors might include only patients who tolerate beta-blocker therapy for at least a year and compare those who continue therapy with those who later discontinue therapy.

Patients and physicians must consider not only the potential benefits but also the potential harms of therapies to make informed decisions about their use. Beta-blockers can cause troublesome symptoms of fatigue, exercise intolerance, and insomnia, as well as life-threatening bradyarrhythmias and hypotension [4]. For example, in the COMMIT trial, the early treatment of AMI with intravenous beta-blockers reduced the risk of re-infarction and ventricular fibrillation by 0.5%, but these benefits were offset by a 1.1% increase in the risk of cardiogenic shock [13]. As a result, the routine use of intravenous beta-blockers for the treatment of AMI is no longer recommended [14].

For patients with stable CAD, evidence of effectiveness is needed to justify the use of beta-blockers as a secondary prevention therapy. The observational studies by Bangalore et al. and Bauters et al. are an important step toward providing this evidence, but additional studies that can overcome the methodologic limitations of previous ones are needed. For now, recommendations from guidelines to consider beta-blocker therapy for secondary prevention in this population are appropriately cautious, and clinicians should weight the potential benefits and harms of beta-blocker therapy for each patient individually.

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