Beta-Blockers in Asymptomatic Coronary Artery Disease
No Benefit or No Evidence?*

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The benefit of beta-blockers in the management of patients with heart failure and left ventricular dysfunction has been incontrovertibly established in multiple contemporary randomized clinical trials (1–5). The recommendation for use of beta-blockers after acute myocardial infarction (MI) is mainly based on studies (6–8) that predate routine implementation of a contemporary strategy of early reperfusion and modern medical therapy, although some observational data suggest that beta-blocker therapy may be associated with reduced long-term mortality after early percutaneous coronary intervention for acute MI (9,10).

In stable coronary artery disease (CAD), there is solid evidence to show that beta-blockers effectively relieve anginal symptoms and improve myocardial ischemia (11), and are therefore recommended as first-line agents for symptom relief in both U.S. (12) and European (13) guidelines. However, the evidence base for the use of beta-blockers to improve prognosis in asymptomatic patients, who represent ~80% of the stable CAD population (14), is less robust and not supported by data from an appropriately powered randomized trial. A recent report from the REACH registry has examined the benefit of beta-blockers in patients with stable CAD (15). In that analysis of 21,860 patients, beta-blocker usage was not associated with a reduced rate of cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for an atherothrombotic event, or revascularization, even in patients with previous MI. These data challenge the extrapolation of the benefits of beta-blockade observed in patients with heart failure or left ventricular dysfunction to all patients with stable CAD.

In this issue of the Journal, Andersson et al. (16) conducted an important, rigorous analysis of the Kaiser Permanente health records database. They observed a modest benefit of beta-blockade in patients with stable CAD. There was a clear interaction between a prior history of MI and treatment effect, with benefits confined to those patients with a history of prior MI. Although these data are informative, there are a number of issues inherent to the study design, warranting consideration when interpreting the results.

Key clinical parameters, such as the presence and severity of anginal symptoms, ischemic burden, left ventricular function, and importantly, the type and dose of beta-blocker therapy, were unavailable. For beta-blocker therapy to confer clinical benefit, significant pharmacological beta-blockade is likely required, although it is well known that full beta-blockade is rarely achieved in routine clinical practice (15). The study population comprised approximately 80% of acute coronary syndrome (ACS) patients, while the remainder consisted of patients referred for elective revascularization procedures, which would exclude patients with incident, stable CAD who may be managed medically without revascularization. Therefore, the results may be in

* Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.
part attributable to insufficient power to detect a benefit of beta-blockade in stable CAD patients without previous MI, and of uncertain relevance to the broader population of stable CAD patients not captured in the current analysis.

Despite careful attempts by the authors to adjust for potential confounders, interpretation of the current findings needs to be tempered by the weaknesses inherent to observational studies, including unmeasured confounders, nonuniformity of patient inclusion criteria and event adjudication, imbalanced patient groups, and the retrospective ascertainment of the study cohort, which necessitates “on-treatment” rather than “intention-to-treat” analyses. The assumption that patients are adherent to prescribed medication on the basis of filling of prescriptions is also a potential weakness (17). That said, both the REACH (15) and Kaiser Permanente data are consistent with lack of demonstrable prognostic benefit from beta-blocker therapy in a number of settings of stable cardiovascular disease (18,19).

Beta-blockers may benefit patients with stable CAD through both anti-ischemic and antiarrhythmic effects. A major mechanism of action of beta-blockers is reduction of heart rate, which is thought to be a determinant of clinical outcome and cardiovascular disease progression (20). The SIGNIFY trial is testing the effects of beta-blocker therapy in a number of settings of stable cardiovascular disease (21). This type of study is relevant as undesirable effects of beta-blockers such as impaired reduction of central aortic pressure (22), symptomatic bradycardia, high-grade atrioventricular block, hypotension, and depression may contribute to observed differences in clinical outcomes between patients on and off beta-blocker therapy. Importantly, both the REACH registry and the Kaiser Permanente analysis did not suggest harm from beta-blockade.

Andersson et al. (16) argue that their findings support a prospective, randomized, controlled trial to test the prognostic benefit of beta-blockade in asymptomatic patients with stable CAD. In an ideal world, that may be true. However, given the excellent clinical outcomes in this patient group with contemporary treatment (23), it will be a major challenge to attract the resources needed to conduct what would necessarily be an extremely large trial.

**WHAT ARE THE CLINICAL IMPLICATIONS?**

The analysis by Andersson et al. (16) strengthens the view that systematic use of beta-blockers is not mandated on prognostic grounds for all patients with stable CAD, especially in the absence of previous MI. These drugs should be used for symptomatic angina relief, as recommended in the ACC/AHA (12) and ESC (13) guidelines. This recommendation will come as welcome relief for stable CAD patients, the vast majority of whom are asymptomatic and are prescribed a plethora of pharmacologic agents, including anti-platelet therapy, statins, and blockade of the renin-angiotensin system to improve prognosis. For those patients with a known history of MI, routine administration of beta-blockers seems reasonable, although the benefits of prolonged treatment in the asymptomatic patient without left ventricular dysfunction remains debatable. While guidelines currently recommend 3 years of beta-blocker treatment after presentation with ACS (12), should side effects occur there is no definitive evidence to insist on continued treatment. The report by Andersson et al. (16) supports tailoring treatment decisions for patients with stable CAD: defining the most parsimonious bespoke therapeutic regimen, which renders an individual patient free of symptoms and improves prognosis with minimal side effects, is particularly important, to ensure treatment compliance as well as optimize quality-of-life and clinical outcomes, especially in an era of constrained healthcare resources.

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**KEY WORDS** beta-blockers, coronary artery disease