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EDITORIAL COMMENT

Beta-Blocker Therapy After Myocardial Infarction

More Questions Than Answers*

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Beta-blocker therapy improves survival in patients following acute myocardial infarction (MI). Their routine use in this setting became so well established that a hospital performance measure, the percentage of patients with acute MI prescribed beta-blockers within 7 days of hospital discharge, was retired in 2007 by the National Committee for Quality Assurance after documented success rates beyond 90% (1). Yet questions have lingered regarding the optimal type, dose, and duration of beta-blocker therapy, especially for patients whose post-MI course is not complicated by heart failure, left ventricular (LV) systolic dysfunction, recurrent ischemia, or arrhythmia. It is also unclear whether outcomes reported from the early randomized trials of post-MI beta-blocker therapy (2,3) would still pertain today given the widespread use of percutaneous coronary intervention, antithrombotic agents, high-intensity statins, and renin-angiotensin-aldosterone system antagonists.

Clinical practice guidelines (4-6) provide a Class I recommendation for the use of beta-blockers in patients without contraindications during and after presentation with acute coronary syndromes, with a preference for the long-term use of extended release metoprolol, carvedilol, or bisoprolol in those patients with heart failure or LV systolic dysfunction (5,6). The evidence base supporting the recommendation that beta-blockers be continued for 3 years in acute coronary syndromes patients with normal LV function is not robust. It has long been recognized that the majority of post-MI survivors are prescribed doses of beta-blockers well below those used in randomized trials, despite acknowledgment that beta-blocker dose-dependent heart rate lowering may play a role in extending survival.

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In this issue of the *Journal*, Goldberger et al. (7) examine the association between doses of prescribed beta-blockers and survival after MI using data from a prospective multicenter registry, the OBTAIN (Outcomes of Beta-Blocker Therapy After Myocardial INfarction) study. The OBTAIN study was initiated in 2007 as a companion registry to the PACE-MI (PACEmaker and Beta-blocker Therapy Post-Myocardial Infarction) trial, an National Heart, Lung, and Blood Institute-sponsored randomized controlled trial designed to assess whether pacemaker facilitated beta-blocker therapy improves survival after MI in patients with a bradycardia contraindication to beta-blockers (8). Data from the PACE-MI trial revealed near universal beta-blocker utilization, but at doses that were mostly ≤25% of target doses used in clinical trials (9).

In the OBTAIN study, 6,682 consecutive patients discharged alive after MI were assessed over a median follow up of 2.1 years. The 91.5% of patients discharged on a beta-blocker were grouped into 1 of 4 categories defined by the percent of target dose prescribed (0% to 12.5%, >12.5% to 25%, >25% to 50%, >50%). The most frequently prescribed dose was >12.5% to 25% of target dose; fewer than 15% of patients were discharged on >50% of target dose. The vast majority (92%) of treated patients received either metoprolol or carvedilol, with target doses defined as 200 mg/day and 50 mg/day, respectively. At last follow-up, just over one-half of the patients remained on the initial dose of beta-blocker provided, and <5% of patients reported discontinuing therapy. Very few patients were

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advanced to >50% of target doses. Not surprisingly, the survival rate was higher for patients discharged on a beta-blocker compared with patients who did not receive them. Contrary to the study's primary hypothesis, higher doses of beta-blockers were not associated with improved survival. Beta-blocker side effects and safety were not evaluated. Additional statistical analyses intended to overcome some of the limitations imposed by the observational nature of the study did not alter this fundamental conclusion.

How should we interpret these findings? Have clinicians known empirically that achieving doses of beta-blockers used in previous trials of MI survivors is unnecessary? Is it simply a matter of "some is better than none"? This study draws attention to a seldom-discussed reality of MI care in an era of bundled performance measures and short hospital lengths of stay, namely that prescribed doses of oral beta-blockers are modest by historical (and clinical trial) standards, not predictably or uniformly adjusted before discharge, and infrequently readdressed at follow-up. The notion that beta-blockers should be prescribed with greater attention to biologic, hemodynamic, and/or electrical mediators of their effects is attractive but unproven. Whether clinical equipoise and the resources to support prospective dose-ranging studies exist remains to be seen.

As with many observational studies, the study's results must be interpreted with caution. In the OBTAIN study, beta-blocker use and dosing at time of discharge were not pre-specified. Prescribing decisions were left to the treating physician, who presumably exercised judgment regarding the safety and efficacy of a beta-blocker rather than simply failed to provide it absent a clear contraindication. As a group, patients discharged without a beta-blocker were older and more likely to have a history of heart failure or chronic obstructive pulmonary disease, lower admission blood pressure, greater incidence of non-ST-segment elevation MI relative to ST-segment elevation MI, and a higher mortality rate compared with those patients discharged on any beta-blocker. Some of the patients who were considered not to be candidates for beta-blockers may constitute a group for which their use is particularly beneficial, especially those with heart failure or unstable rhythms. Such patients usually require more cautious drug initiation and dose titration, aspects of care that are not accommodated by rapid discharge planning. Despite careful efforts at multivariable adjustment and propensity score matching, additional differences unaccounted for among the 4 pre-specified patient subgroups may have influenced outcomes. To what extent did differences in clinical characteristics (Table 1 of Goldberger et al. [7]) dictate the dose of beta-blocker prescribed? Were patients who received >50% target dose sicker, with more complicated hospital courses and at higher risk, or did they have greater physiologic reserve and/or different beta-blocker pharmacokinetics? Just as we cannot know why clinicians discharged patients on certain beta-blocker doses, we cannot know when and why they decided to continue or change the dose at follow-up, whether patients complied with medication instructions, or whether dosing changes affected outcomes.

We can also speculate regarding the degree to which the effectiveness of beta-blockers in MI survivors may be attenuated by the inclusion of patients who sustain myocardial injury for reasons other than atherosclerotic plaque destabilization. Did the original beta-blocker trialists envision a future with high sensitivity troponin assays and MI types 1 to 5 (10)? Of note, a subgroup analysis in the OBTAIN study demonstrated a significant interaction with beta-blocker dose effect for patients who underwent revascularization during the index hospitalization, with lower hazard ratios for death observed among the 3 groups receiving ≤50% target dose, compared with the >50% cohort. That revascularization could reset the threshold for beta-blocker effectiveness would seem consistent with its ability to reduce recurrent ischemia and infarction in certain patient subsets. Based on several limitations emphasized in their report, Goldberger et al. (7) conclude appropriately that we cannot ascertain a dose-response relationship between beta-blocker dose after MI and mortality from this observational study.

Will these findings affect clinical practice? Advanced heart failure specialists have long advocated disciplined attempts to treat patients with doses of beta-blockers and renin-angiotensin-aldosterone system inhibitors shown to be useful in clinical trials, and there is evidence that high dose neurohormonal blocking medications may promote reverse remodeling (11). Yet, for the typical patient encountered in clinical practice, hemodynamic, rhythm, renal function and/or electrolyte considerations often preclude such an approach. In addition, the role of beta-blockers has come under increased scrutiny across a range of indications, including hypertension (12,13) perioperative management for noncardiac surgery (14) and stable ischemic heart disease without recent MI, active angina, or heart failure (15). As such, have we overestimated their benefits, underestimated the effects of relatively lower doses (as compared to target trial doses), or, perhaps, intuitively practiced appropriately a type of patient-centered care guided by the physiologic responses to and side effects from these drugs?

To address these lingering questions, should a prospective randomized controlled trial of beta-blocker dosing be undertaken? How many patients would such a trial entail, followed for how long and at what cost? Broadly, the work by Goldberger et al. (7) highlights the inherent limitations of a 1-trial, 1-drug, 1-dose approach to treating entire populations, especially when individual responsiveness cannot be predicted. The study of beta-blockers in a post MI population may not lend itself to the Large Simple Trial (16) construct for which momentum is building. As is true for several other drug therapies including lipid-lowering, antiplatelet, and anticoagulant agents, patient- and environment-specific factors may interact in complex ways to affect the desired therapeutic outcome. In the case of beta-blockers, heart rate and blood pressure represent important physiologic biomarkers, yet there are many other biomarkers of interest to aid in our understanding of when and under what circumstances these drugs may be effective. Can harnessing big data help? In 2015, at a time when pinprick comprehensive blood tests and systematic real-time data collection using wearable devices are no longer science fiction, we will hopefully soon find ourselves moving beyond a 1 drug, 1 dose fits all to a "precision" medicine approach.

Goldberger et al. (7) have exposed another gap in our application of evidence-based therapies and raised provocative questions regarding the nature of clinical research necessary to bring clarity to this aspect of post-MI care in the modern era. Despite the excitement inherent in designing future trials, and notwithstanding the very high rates of early beta-blocker use after MI (albeit at below "target" doses), clinicians are left today with the sobering statistics that 50% or fewer of patients prescribed *any* dose of beta-blockers following acute MI at hospital discharge are still using them 1 or 2 years later (17,18). We look forward to a personalized approach to cardiovascular care that moves toward patient-specific drug target effects while reducing major morbidity and mortality, but recognize that this will require a better partnership between us and our patients.

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