JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 13, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.07.047

Effect of Beta-Blocker Dose on Survival After Acute Myocardial Infarction

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ABSTRACT

BACKGROUND Beta-blocker therapy after acute myocardial infarction (MI) improves survival. Beta-blocker doses used in clinical practice are often substantially lower than those used in the randomized trials establishing their efficacy.

OBJECTIVES This study evaluated the association of beta-blocker dose with survival after acute MI, hypothesizing that higher dose beta-blocker therapy will be associated with increased survival.

METHODS A multicenter registry enrolled 7,057 consecutive patients with acute MI. Discharge beta-blocker dose was indexed to the target beta-blocker doses used in randomized clinical trials, grouped as >0% to 12.5%, >12.5% to 25%, >25% to 50%, and >50% of target dose. Follow-up vital status was assessed, with the primary endpoint of time-to-death right-censored at 2 years. Multivariable and propensity score analyses were used to account for group differences.

RESULTS Of 6,682 patients with follow-up (median 2.1 years), 91.5% were discharged on a beta-blocker (mean dose 38.1% of the target dose). Lower mortality was observed with all beta-blocker doses ($p < 0.0002$) versus no beta-blocker therapy. After multivariable adjustment, hazard ratios for 2-year mortality compared with the >50% dose were 0.862 (95% confidence interval [CI]: 0.677 to 1.098), 0.799 (95% CI: 0.635 to 1.005), and 0.963 (95% CI: 0.765 to 1.213) for the >0% to 12.5%, >12.5% to 25%, and >25% to 50% of target dose groups, respectively. Multivariable analysis with an extended set of covariates and propensity score analysis also demonstrated that higher doses were not associated with better outcome.

CONCLUSIONS These data do not demonstrate increased survival in patients treated with beta-blocker doses approximating those used in previous randomized clinical trials compared with lower doses. These findings provide the rationale to re-engage in research to establish appropriate beta-blocker dosing after MI to derive optimal benefit from this therapy. (The PACE-MI Registry Study—Outcomes of Beta-blocker Therapy After Myocardial Infarction [OBTAIN]: NCT00430612) (J Am Coll Cardiol 2015;66:1431–41) © 2015 by the American College of Cardiology Foundation.

Beta-blocker therapy after myocardial infarction (MI) improves survival. On the basis of randomized clinical trials (1,2) and large observational studies (3–5), guidelines for the management of patients after ST-segment elevation MI (6) and non-ST-segment elevation MI (7) recommend beta-blocker therapy in essentially all post-MI patients without contraindications. The randomized clinical trials did not assess the effects of different doses of beta-blockers, and there have been no large-scale studies that have addressed this topic. Although the guidelines do not refer to specific

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Manuscript received May 23, 2015; revised manuscript received July 20, 2015, accepted July 21, 2015.

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

CI = confidence interval

HR = hazard ratio

MI = myocardial infarction

beta-blockers or doses, basic evidence-based medicine principles support the use of beta-blockers that have been studied in trials at the doses used or targeted; trials that report dosing indicate that the majority of patients achieved target doses. However, doses of clinically used beta-blocker are substantially lower (8,9). The impact of this large-scale underdosing of beta-blockers on the beneficial effects of beta-blocker therapy is unknown. Analyses of post-MI beta-blocker trials have related mortality reduction to heart rate reduction (10,11); because heart rate reduction is dose dependent, this supports the notion that there could be a dose-dependent reduction in mortality. The OBTAIN (Outcomes of Beta-blocker Therapy After Myocardial Infarction) study is an observational multicenter registry in which beta-blocker dosing information was collected in all patients with acute MI at participating centers to assess the effect of dose on survival. The OBTAIN hypothesis was that higher dose beta-blocker therapy is associated with increased survival.

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METHODS

STUDY DESIGN AND OVERSIGHT. Initiated in 2007, OBTAIN was a companion registry to the PACE-MI (PACEmaker and ß-Blocker Therapy Post-Myocardial Infarction) trial (12). Detailed information on beta-blocker dosing was collected in the registry. There were 26 participating centers in the United States and 1 in Canada. When the trial was terminated in 2009, it was noted that beta-blocker utilization was nearly universal, but that most patients were treated with doses ≤25% of the target doses used in clinical trials. At that time, the decision was made to continue the registry and evaluate vital status for at least 2 years to test the hypothesis that there is a dose-response relationship in the beneficial effect of beta-blocker therapy on survival. After protocol modification to include vital status assessment and resubmission for institutional review board approval, 21 of the original sites continued their participation (including 92% of the registry patients). An additional 5 U.S. sites were recruited.

The study was funded by the National Heart, Lung, and Blood Institute, and an observational study monitoring board, appointed by the institute, monitored study conduct. The study was approved by each site's institutional review board with a waiver of consent for registry enrollment. Participating centers and study committees and personnel are listed in the Online Appendix.

PATIENTS. Consecutive patients admitted with acute MI at participating sites were entered into the registry. Acute MI was diagnosed by: 1) either creatine kinase elevation >2 times or troponin elevation >3 times the upper limit of normal; and 2) either chest pain (or equivalent symptoms suggestive of MI) or electrocardiographic changes consistent with MI.

Basic demographic, historical, and hospitalization information, as well as information regarding the index MI, was collected. Discharge beta-blocker type and dose were recorded. All data were collected at the site, and deidentified patient information was entered in a Web-based electronic data capture system.

BETA-BLOCKER DOSING. Beta-blocker type and dose were chosen by the managing physician. For the purposes of the present study, target doses for the most commonly used beta-blockers were as follows: metoprolol 200 mg/day (13,14); carvedilol 50 mg/day (15) (Coreg CR [GlaxoSmithKline Pharmaceuticals, Philadelphia, Pennsylvania]-equivalent dose 80 mg/day); propranolol 180 mg/day (16); timolol 20 mg/day (17); bisoprolol 10 mg/day (18); and atenolol 100 mg/day (19). On the basis of the dose administered, a proportion of the target dose was calculated (administered/target dose) only for patients taking 1 of these beta-blockers. Beta-blocker doses were divided into 5 pre-specified groups: no beta-blocker, >0% to 12.5%, >12.5% to 25%, >25% to 50%, and >50% of the target dose.

STUDY ENDPOINT. The pre-specified endpoint for this study was time to all-cause mortality with survival right-censored at 2 years. Vital status was assessed by use of chart review, the Social Security Administration's Death Master File, or direct communication with the patient/family. Per protocol, vital status was assessed 1 and 2 years after MI. Follow-up using the Social Security Administration's Death Master File incorporated a 6-month delay to account for the lag time in recording deaths. A longer term follow-up (>3 years) was available, particularly for sites that participated in the original registry.

STATISTICAL ANALYSIS. Patient characteristics were summarized as mean ± SD or count (%). Differences among groups were compared by using chi-square tests for categorical variables and analysis of variance for continuous variables. Distribution-free rank sum tests were used for variables that deviated from normality. The median (interquartile range) was used to summarize these variables. The Kaplan-Meier method was used to calculate 1-, 2-, and 3-year survival in each study group.

Pre-specified analysis of the effect of the 5 pre-specified groups on 2-year survival was tested