JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
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

Jeffrey J. Goldberger, MD, MBA,* Robert O. Bonow, MD,* Michael Cuffe, MD,† Lei Liu, PhD,‡ Yves Rosenberg, MD, MPH,§ Prediman K. Shah, MD,‖ Sidney C. Smith, Jr, MD,¶ Haris Subačius, MA,* on behalf of the OBTAIN Investigators

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

From the *Center for Cardiovascular Innovation and the Division of Cardiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; †Hospital Corporation of America, Brentwood, Tennessee; ‡Department of Preventive Medicine, Northwestern University, Chicago, Illinois; §Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; ‖Cedars-Sinai Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California; and the ¶Heart and Vascular Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina. This research was supported by grant 5U01HL080416 from the National Heart, Lung, and Blood Institute of the National Institutes of Health. The views expressed in this manuscript are the authors' and do not necessarily reflect those of the National Institutes of Health or the Department of Health and Human Services. Dr. Liu is a consultant to Celladon, Outcome Research Solutions, and Zensun. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

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.

SEE PAGE 1442

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

by comparing Kaplan-Meier survival curves with a log-rank test. Cox proportional hazards regression was used to test for the independent effects of beta-blocker dosing on survival. The following pre-specified patient characteristics were used in multivariable adjustment: age, sex, white race, Hispanic ethnicity, cardiac enzymes, left ventricular ejection fraction, diabetes, hypertension, hypercholesterolemia, ST-segment elevation MI, thrombolytic therapy, primary percutaneous coronary intervention, length of stay, and other discharge medications (aspirin, angiotensin-converting enzyme [ACE] inhibitors/angiotensin receptor blockers, and statins). A pre-specified secondary analysis was performed comparing the outcomes for low-dose (≤25%) and high-dose (≥50%) beta-blocker therapy.

Further sensitivity analyses of the effect of the 4 beta-blocker doses on outcome included evaluation of 3-year outcomes. Multivariable analysis included an expanded set of all covariates listed in **Table 1**, including use of carvedilol versus metoprolol. Random effects (shared frailty model) were also included for each of the recruiting hospitals to better model differences in mortality among them. Quadratic and cubic polynomial terms for continuous predictors were included to account for potential nonlinearity.

Propensity score analysis was also performed as an alternative adjustment for patient differences in the 4 beta-blocker dose groups. To calculate the propensity score, we used mixed effects linear regression with random effects of the recruiting centers, continuous discharge beta-blocker dose (percentage of target dose) as a dependent variable, and the expanded control variable set reported in **Table 1** (including quadratic and cubic polynomial terms for continuous predictors). Thus, the propensity scores represent the predicted discharge beta-blocker dose, given the extended set of patient characteristics. The propensity score was used as a control variable in the proportional hazards frailty regression model. Further details are provided in the Online Appendix.

All tests were 2-tailed, and a conventional 5% significance level was used. A gatekeeper hypothesis strategy for type I error control was used for pre-specified study endpoints; alpha levels were to be adjusted for subsequent tests if the gatekeeper null hypothesis was rejected. Analyses were performed by using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The registry included 7,057 patients. In-hospital mortality was 4.7%, and 43 patients were lost to follow-up. **Table 1** displays baseline characteristics of the 6,682 patients discharged alive, stratified according to beta-blocker use. The mean age across groups was 63 to 65 years, with male predominance. Small to moderate group differences were noted for most characteristics.

Discharge therapy included beta-blockers (91.5%), aspirin (92.6%), ACE inhibitors/angiotensin receptor blockers (66.3%), and statins (86.3%). There were 567 patients (8.5%) discharged without beta-blocker therapy. Reasons provided for not administering beta-blockers included low blood pressure (26%), conduction system disease (16%), pulmonary disease (17%), heart failure (9%), drug use (5%), debilitation (5%), and other (22%).

Beta-blockers administered at discharge included metoprolol (67.7%), carvedilol (24.3%), atenolol (3.8%), bisoprolol (2.8%), propranolol (0.2%), and others (1.1%). Of the patients discharged on a beta-blocker, 24.0%, 37.2%, 25.5%, and 13.4% received >0% to 12.5%, >12.5% to 25%, >25% to 50%, and >50% of the target dose, respectively. The mean administered dose was 38.1% of the target dose. Median follow-up was 2.1 years (interquartile range: 2.0 to 2.5 years). At last follow-up (n = 3,581), 52.4%, 20.2%, and 20.2% were taking the same, a higher, or a lower dose, respectively, with a 3.8% discontinuation rate and a 3.4% initiation rate in patients not discharged on beta-blockers. From discharge to 1 year, of the patients treated with >12.5% to 25% of the target dose, only 4% were subsequently in the >50% of the target dose group. Of the patients treated with >50% of the target dose, only 12% were subsequently treated with ≤25% of the target dose. In this cohort, beta-blocker therapy was associated with an unadjusted 51% (adjusted 45%; 95% confidence interval [CI]: 33% to 55%) lower mortality compared with no beta-blocker therapy.

At 2 years, there were a total of 831 deaths (post-discharge mortality of 12.4%). The **Central Illustration** (panel A) displays the Kaplan-Meier curves for the primary analysis. **Tables 2** and **3** provide the hazard ratios (HRs) relative to no beta-blocker use and to the >50% target dose. Multivariable analysis identified that all tested parameters were independently related to survival (**Table 4**). After the pre-specified multivariable adjustment, relative to the >50% target dose, mortality did not differ for the >0% to 12.5% and >25% to 50% doses, and was borderline statistically significant in those taking >12.5% to 25% of the target dose but not after multivariable adjustment with the extended set of covariates.

The Kaplan-Meier curves for low-dose (≤25%) versus high-dose (≥50%) beta-blocker therapy (**Central Illustration**, panel B) show a significantly lower

TABLE 1 Characteristics of the Study Population and Mortality According to Beta-Blocker Dose

	Discharge Beta-Blocker		p Value	Beta-Blocker Dose (% of the Target Dose)				p Value	
	No, n = 567 (8.5%)	Yes, n = 6,115 (91.5%)	No Versus Yes	>0%-12.5%, n = 1,448 (21.7%)	>12.5%-25%, n = 2,247 (33.6%)	>25%-50%, n = 1,541 (23.1%)	>50%, n = 809 (12.1%)	Among 5 Doses	Among 4 Beta-Blocker Doses
Patient characteristics									
Age, yrs	65.1 ± 14.7	63.7 ± 13.5	0.03	64.5 ± 13.6	62.6 ± 13.6	64.0 ± 13.3	64.2 ± 13.1	<0.0001	0.0001
Male	349 (61.6)	4,195 (68.6)	0.0006	971 (67.1)	1,555 (69.2)	1,056 (68.5)	570 (70.5)	0.004	0.35
Race			0.16					0.002	0.002
White	438 (77.2)	4,851 (79.3)	0.24	1,164 (80.4)	1,792 (79.8)	1,220 (79.2)	617 (76.3)	0.13	0.12
Black	69 (12.2)	654 (10.7)	0.28	116 (8.0)	226 (10.1)	185 (12.0)	120 (14.8)	<0.0001	<0.0001
Asian	6 (1.1)	150 (2.5)	0.04	39 (2.7)	51 (2.3)	37 (2.4)	22 (2.7)	0.24	0.82
American Indian	3 (0.5)	26 (0.4)	0.73	6 (0.4)	11 (0.5)	8 (0.5)	1 (0.1)	0.68	0.52
Pacific Islander	2 (0.4)	13 (0.2)	0.37	4 (0.3)	4 (0.2)	3 (0.2)	1 (0.1)	0.87	0.87
Unknown	50 (8.8)	428 (7.0)	0.11	120 (8.3)	164 (7.3)	91 (5.9)	49 (6.1)	0.04	0.05
Other	1 (0.2)	7 (0.1)	0.51	1 (0.1)	1 (0.0)	3 (0.2)	1 (0.1)	0.66	0.52
Hispanic	33 (6.4)	441 (7.7)	0.27	126 (9.5)	176 (8.4)	87 (6.0)	49 (6.3)	0.002	0.002
BMI, kg/m^2	28.0 ± 6.8	29.2 ± 6.5	<0.0001	28.1 ± 6.0	29.2 ± 6.3	29.6 ± 6.8	30.4 ± 6.9	<0.0001	<0.0001
Medical history									
Diabetes	152 (26.9)	1,985 (32.5)	0.006	399 (27.6)	688 (30.7)	533 (34.6)	336 (41.6)	<0.0001	<0.0001
Hypertension	357 (63.1)	4,177 (68.4)	0.01	857 (59.2)	1,465 (65.3)	1,131 (73.4)	666 (82.4)	<0.0001	<0.0001
Hyperlipidemia	276 (48.8)	3,336 (54.6)	0.008	723 (49.9)	1,154 (51.4)	893 (58.0)	523 (64.8)	<0.0001	<0.0001
Previous MI	115 (20.3)	1,277 (20.9)	0.74	250 (17.3)	411 (18.3)	378 (24.6)	217 (26.9)	0.0000	<0.0001
CHF history	70 (12.4)	635 (10.4)	0.14	135 (9.3)	177 (7.9)	174 (11.3)	137 (17.0)	<0.0001	<0.0001
CABG history	69 (12.2)	815 (13.3)	0.44	143 (9.9)	238 (10.6)	240 (15.6)	178 (22.0)	<0.0001	<0.0001
ESRD	21 (3.7)	204 (3.3)	0.64	37 (2.6)	66 (2.9)	51 (3.3)	45 (5.6)	0.002	0.0009
CVA/TIA	58 (10.2)	640 (10.5)	0.86	133 (9.2)	199 (8.9)	183 (11.9)	115 (14.2)	<0.0001	<0.0001
COPD	102 (18.0)	618 (10.1)	<0.0001	150 (10.4)	222 (9.9)	150 (9.7)	83 (10.3)	<0.0001	0.94
Current smoker	206 (36.9)	1,997 (33.1)	0.08	486 (33.9)	804 (36.2)	482 (32.0)	211 (26.5)	<0.0001	<0.0001
ICD*	18 (3.2)	208 (3.4)	0.78	41 (2.8)	66 (2.9)	57 (3.7)	44 (5.4)	0.009	0.004
MI characteristics									
STEMI	201 (35.4)	2,691 (44.0)	0.0001	717 (49.6)	1,002 (44.6)	651 (42.3)	297 (36.7)	<0.0001	<0.0001
Anterior	60 (29.9)	904 (33.6)	0.28	247 (34.4)	311 (31.0)	231 (35.5)	108 (36.4)	0.17	0.16
Inferior/posterior	114 (56.7)	1,356 (50.4)	0.08	362 (50.5)	524 (52.3)	329 (50.5)	127 (42.8)	0.02	0.04
Thrombolytic therapy	25 (12.4)	365 (13.6)	0.65	79 (11.0)	146 (14.6)	105 (16.1)	32 (10.8)	0.03	0.02
Primary PCI	147 (73.1)	2,241 (83.3)	0.0002	630 (87.9)	864 (86.3)	526 (80.8)	203 (68.4)	<0.0001	<0.0001
In-hospital revascularization (nonprimary PCI and CABG)	41 (20.4)	444 (16.5)	0.15	105 (14.6)	149 (14.9)	115 (17.7)	71 (23.9)	0.001	0.001
Diagnostic angiography	18 (9.0)	132 (4.9)	0.02	25 (3.5)	41 (4.1)	37 (5.7)	28 (9.4)	<0.0001	0.0004
NSTEMI	366 (64.6)	3,424 (56.0)	0.0001	731 (50.5)	1,245 (55.4)	890 (57.8)	512 (63.3)	<0.0001	<0.0001
Thrombolytic therapy	14 (3.8)	95 (7.5)	0.25	22 (3.0)	38 (3.1)	20 (2.2)	14 (2.7)	0.62	0.70
Primary PCI	126 (34.4)	1,409 (41.2)	0.01	334 (45.7)	565 (45.4)	333 (37.5)	159 (31.1)	<0.0001	<0.0001
In-hospital revascularization (nonprimary PCI and CABG)	84 (23.0)	1,106 (32.3)	0.0002	233 (31.9)	409 (32.9)	292 (32.8)	164 (32.0)	0.006	0.96
Diagnostic angiography	72 (19.7)	508 (14.8)	0.01	97 (13.3)	168 (13.5)	143 (16.1)	91 (17.8)	0.008	0.05
Admission SBP, mm Hg	133.3 ± 31.2	141.0 ± 29.7	<0.0001	135.8 ± 27.5	140.1 ± 28.6	142.9 ± 30.6	148.7 ± 32.5	<0.0001	<0.0001
Admission heart rate, beats/min	82.9 ± 23.4	82.9 ± 21.2	0.94	81.3 ± 20.1	81.3 ± 20.2	84.2 ± 22.0	87.5 ± 23.6	<0.0001	<0.0001
Heart failure on admission	71 (12.5)	616 (10.1)	0.07	167 (11.5)	179 (8.0)	150 (9.7)	112 (13.8)	<0.0001	<0.0001
LVEF	48.8 ± 14.5	46.7 ± 12.8	0.001	45.3 ± 13.6	47.6 ± 12.4	46.4 ± 12.6	47.2 ± 12.8	<0.0001	<0.0001
Troponin, ng/ml	4.8 (1.3-21.6)	7.2 (2-28.1)	<0.0001	12 (2.9-42.5)	7.2 (1.9-28.8)	6.2 (1.9-22.4)	4.3 (1.3-17.7)	<0.0001	<0.0001
LOS, days	5 (3-9)	5 (4-8)	0.11	5 (4-8)	4 (3-7)	5 (4-8)	6 (4-10)	<0.0001	<0.0001

Continued on the next page

mortality with low-dose therapy compared with high-dose therapy (HR: 0.758; 95% CI: 0.651 to 0.883; p = 0.0004). After multivariable adjustment (Table 4), there was lower mortality (HR: 0.857; 95% CI: 0.734 to 1.002; p = 0.05) with low- versus high-dose therapy but not after multivariable adjustment with the extended set of covariates (Table 2).

TABLE 1 Continued

	Discharge Beta-Blocker		p Value	Beta-Blocker Dose (% of the Target Dose)				p Value	
	No, n = 567 (8.5%)	Yes, n = 6,115 (91.5%)	No Versus Yes	>0%-12.5%, n = 1,448 (21.7%)	>12.5%-25%, n = 2,247 (33.6%)	>25%-50%, n = 1,541 (23.1%)	>50%, n = 809 (12.1%)	Among 5 Doses	Among 4 Beta-Blocker Doses
Discharge medications									
Beta-blocker dose, % target				12.0 ± 1.7	25.0 ± 0.4	49.1 ± 3.2	100.3 ± 29.0		<0.0001
Mode (% taking mode dose)				12.5 (92.4)	25 (99.6)	50 (93.1)	100 (59.8)		
Metoprolol				923 (63.7)	1,645 (73.2)	1,052 (68.3)	522 (64.5)		<0.0001
Carvedilol				505 (34.9)	468 (20.8)	340 (22.1)	174 (21.5)		<0.0001
ASA	477 (84.1)	5,708 (93.3)	<0.0001	1,352 (93.4)	2,099 (93.4)	1,450 (94.1)	745 (92.1)	<0.0001	0.33
ACE-I/ARB	282 (49.7)	4,150 (67.9)	<0.0001	899 (62.1)	1,541 (68.6)	1,084 (70.3)	581 (71.8)	<0.0001	<0.0001
Statin	404 (71.8)	5,363 (87.8)	<0.0001	1,246 (86.2)	2,003 (89.2)	1,330 (86.4)	726 (89.7)	<0.0001	0.004
Clopidogrel	333 (58.7)	4,432 (72.5)	<0.0001	1,034 (71.4)	1,654 (73.6)	1,118 (72.6)	573 (70.8)	<0.0001	0.34
Dual antiplatelet	314 (55.4)	4,246 (69.4)	<0.0001	997 (68.9)	1,580 (70.3)	1,074 (69.7)	546 (67.5)	<0.0001	0.47
Mortality									
1 yr (Kaplan-Meier %)	97 (17.1)	473 (7.7)	<0.0001	117 (8.1)	142 (6.4)	136 (8.9)	69 (8.6)	<0.0001	0.02
2 yrs (Kaplan-Meier %)	123 (21.7)	708 (11.7)	<0.0001	165 (11.5)	212 (9.5)	197 (12.9)	118 (14.7)	<0.0001	0.0002
3 yrs (Kaplan-Meier %)	133 (25.4)	795 (15.7)	<0.0001	191 (16.2)	237 (12.2)	219 (17.6)	131 (20.6)	<0.0001	<0.0001

Values are mean ± SD, n (%), or median (interquartile range). *Includes patients with pre-admission ICD and those discharged with an ICD.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASA = aspirin; BMI = body mass index; CABG = coronary artery bypass graft surgery; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; ESRD = end-stage renal disease; ICD = implantable cardioverter-defibrillator; LOS = length of stay; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack.

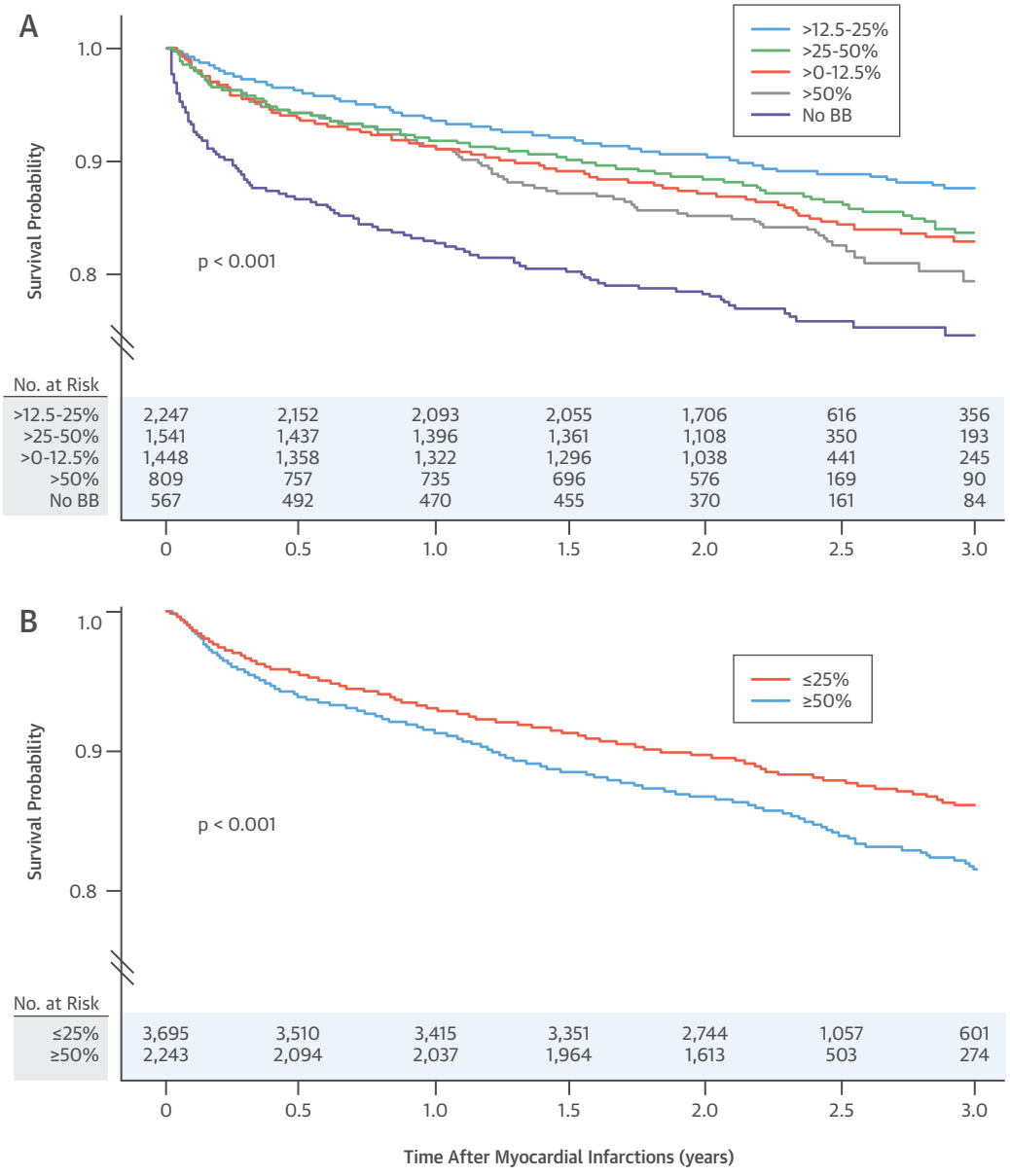
Table 3 presents the multivariable HRs with extended follow-up to 3 years (using the pre-specified multivariable analysis) and the analyses focusing on the 4 beta-blocker dose groups using multivariable analysis with the expanded set of covariates (Table 5) and the propensity score analysis. Relative to the >50% dose group, there were no significant differences between the >0% to 12.5% and >25% to 50% dose groups. Although there were lower HRs in the >12.5% to 25% dose group, these findings were not consistently significant across all analyses. Because the >12.5% to 25% group was the largest and experienced the lowest mortality, the HRs relative to the >12.5% to 25% dose group were analyzed (Figure 1). Increased HRs were noted in the >0% to 12.5% dose group (expanded multivariable HR: 1.092; 95% CI: 0.896 to 1.331; p = 0.38; propensity score HR: 1.394; 95% CI: 1.148 to 1.692; p = 0.0008) and the >25% to 50% dose group (expanded multivariable HR: 1.176; 95% CI: 0.973 to 1.420; p = 0.09; propensity score HR: 1.248; 95% CI: 1.035 to 1.505; p = 0.02).

Subgroup analyses were performed for patients taking metoprolol versus carvedilol, for those with ST-segment elevation MI versus non-ST-segment elevation MI, patients with left ventricular ejection fraction above or below 40%, and patients who were or were not revascularized during their admission (primary percutaneous coronary intervention, later percutaneous coronary intervention, or surgery). There was a significant interaction with the effect of beta-blocker dose only for revascularization (p = 0.037). In patients undergoing revascularization, the HRs compared with the >50% dose were 0.649 (95% CI: 0.472 to 0.891), 0.546 (95% CI: 0.403 to 0.740), and 0.768 (95% CI: 0.563 to 1.048) for the >0% to 12.5%, >12.5% to 25%, and >25% to 50% doses, respectively. In nonrevascularized patients, these effects were less pronounced (HR: 1.294; 95% CI: 0.940 to 1.782; HR: 0.963; 95% CI: 0.709 to 1.308; HR: 1.223; 95% CI: 0.901 to 1.660) for the >0% to 12.5%, >12.5% to 25%, and >25% to 50% doses.

DISCUSSION

The present study was designed to evaluate whether higher dose beta-blocker therapy is associated with increased survival compared with lower doses in patients discharged from the hospital after MI. Contrary to our hypothesis, improved outcome with higher dose beta-blocker therapy (specifically the target beta-blocker doses used in previous randomized clinical trials) was not observed. Although baseline differences in the treatment groups preclude a definitive determination of the dose-response relationship between beta-blocker dose and mortality post-MI, the lowest observed mortality was at 25% of the target dose (i.e., metoprolol 50 mg/day). However, there was no consistent statistically significant reduction in mortality with this dose with the various analyses used to adjust for baseline differences among the groups. In relation to these

CENTRAL ILLUSTRATION **Beta-Blockers After MI: Unadjusted Kaplan-Meier Survival Curves for the 5 Discharge Doses Analyzed and Low- and High-Dose Beta-Blocker Therapy**



Goldberger, J.J. et al. J Am Coll Cardiol. 2015; 66(13):1431–41.

Kaplan-Meier survival curves for **(A)** the primary (unadjusted) analysis comparing the 5 discharge doses (no beta-blocker and >0% to 12.5%, >12.5% to 25%, >25% to 50%, and >50% of the target dose) of beta-blockers and **(B)** the secondary (unadjusted) analysis comparing low-dose (≤25% of the target dose) versus high-dose (≥50% of the target dose) beta-blocker therapy. BB = beta-blocker; MI = myocardial infarction.

findings, the existing evidence base from randomized clinical trials incorporated primarily target doses and provided no information regarding the dose-response of post-MI beta-blocker therapy on subsequent survival. Thus, the present registry data remain consistent with prior clinical trials that reported a benefit of full-dose beta-blocker therapy. However, they raise the question of whether lower

TABLE 2 Univariable and Multivariable Adjusted HRs for the Primary 5-Dose Analysis and the Secondary Analysis Comparing Low (≤25% of Target Dose) Versus High (≥50% of Target Dose) Dose on the Basis of the Pre-Specified Analyses and Using the Extended Set of Covariates

	Pre-Specified Analyses						Extended Multivariable Analysis		
	Univariable			Multivariable					
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
Primary analysis									
Versus no beta-blocker									
>0%-12.5% (n = 1,448)	0.486	0.385-0.614	<0.0001	0.530	0.418-0.673	<0.0001	0.576	0.379-0.877	0.01
>12.5%-25% (n = 2,247)	0.395	0.316-0.493	<0.0001	0.492	0.392-0.617	<0.0001	0.562	0.374-0.843	0.005
>25%-50% (n = 1,541)	0.547	0.437-0.685	0.0009	0.593	0.471-0.746	<0.0001	0.649	0.435-0.970	0.04
>50% (n = 809)	0.626	0.487-0.806	0.002	0.615	0.475-0.797	0.0002	0.666	0.440-1.007	0.05
Versus >50%									
>0%-12.5%	0.776	0.612-0.983	0.05	0.862	0.677-1.098	0.23	0.865	0.667-1.123	0.28
>12.5%-25%	0.630	0.503-0.789	<0.0001	0.799	0.635-1.005	0.05	0.843	0.664-1.071	0.16
>25%-50%	0.873	0.695-1.097	0.49	0.963	0.765-1.213	0.75	0.975	0.769-1.237	0.84
Secondary analysis									
≤25% versus ≥50%	0.758	0.651-0.883	0.0004	0.857	0.734-1.002	0.05	0.889	0.754-1.048	0.16

CI = confidence interval; HR = hazard ratio.

doses may result in equivalent outcomes compared with the target dose. These data support the need for further testing to determine optimal dosing of beta-blockers after MI.

Because there are several potential explanations for the results, these intriguing findings from the registry require careful explication. First, it remains possible, although unlikely, that target dose beta-blocker therapy is still associated with better survival than lower doses; this would be possible in this registry if some unmeasured confounder(s) were unequally represented in the target and lower dose groups, making the former a substantially higher risk group than the low-dose group in which accounting for this parameter would substantially alter (reverse) the estimates of the adjusted survival. It is more feasible that further adjusting for other unmeasured confounders would show that there is no strong dose dependence of beta-blocker effect. In other words, once a threshold dose is achieved, further increments in the dose do not provide further benefit. In addition, the registry data are consistent with a greater benefit at lower doses than the target doses used in the clinical trials, but this claim would need to be tested prospectively. Finally, it is conceivable that there is no single optimal dose for all post-MI patients, with some patients benefiting from lower doses and some patients requiring higher doses. Because the trial hypothesis was that higher doses would be associated with improved outcomes, an a priori noninferiority analysis was not proposed to show noninferiority of the >12.5% to 25% target dose. Although it would not be appropriate to conduct noninferiority testing with a margin determined in a post-hoc manner, our post-hoc calculations showed that the noninferiority margin which would change the conclusion regarding noninferiority of the >12.5% to 25% target dose would have to be relatively small. Further studies will need to determine whether fixed target dosing for all post-MI patients or individualized dosing on the basis of patient or MI characteristics will optimize outcomes.

TABLE 3 Sensitivity Analyses Showing Adjusted HRs for 3-Year Mortality Compared With the >50% of Target Dose Group Using the Pre-Specified MV Analysis, and the MV Analysis With the Extended Set of Covariates and Propensity Score Analysis for the 4 Beta-Blocker Dose Groups

	Pre-Specified MV Analysis			Extended MV Analysis			Propensity Score Analysis		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
>0%-12.5%	0.886	0.705-1.114	0.30	0.937	0.730-1.202	0.61	1.163	0.910-1.486	0.23
>12.5%-25%	0.792	0.638-0.984	0.04	0.866	0.688-1.091	0.22	0.834	0.664-1.047	0.12
>25%-50%	0.964	0.775-1.120	0.74	1.016	0.809-1.275	0.89	1.041	0.832-1.302	0.73

MV = multivariable; other abbreviations as in Table 2.

TABLE 4 HRs and 95% CIs From MV Analysis of 2-Year Mortality in the 2 Pre-Specified Analyzed Cohorts According to Predictor

	5 Discharge Doses		≤25% Versus ≥50% of Target Dose	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Beta-blocker dose	See Table 2	<0.001	0.857 (0.734–1.002)	0.05
Age	1.054 (1.048–1.060)	<0.0001	1.057 (1.050–1.064)	<0.0001
ln(troponin)	1.070 (1.023–1.119)	0.003	1.068 (1.018–1.121)	0.008
LVEF	0.980 (0.975–0.986)	<0.0001	0.981 (0.975–0.987)	<0.0001
ln(LOS) (days)	1.320 (1.188–1.467)	<0.0001	1.312 (1.167–1.476)	<0.0001
Male	1.240 (1.070–1.436)	0.004	1.213 (1.031–1.427)	0.02
White race	0.822 (0.698–0.969)	0.02	0.824 (0.688–0.988)	0.04
Hispanic ethnicity	0.678 (0.496–0.926)	0.02	0.665 (0.479–0.924)	0.02
Diabetes	1.453 (1.256–1.680)	<0.0001	1.550 (1.320–1.820)	<.0001
Hypertension	1.313 (1.090–1.581)	0.004	1.275 (1.037–1.568)	0.02
Hyperlipidemia	0.815 (0.706–0.940)	0.005	0.811 (0.693–0.949)	0.009
STEMI	0.694 (0.575–0.837)	0.0001	0.690 (0.561–0.848)	0.0004
Thrombolytic therapy	0.646 (0.445–0.937)	0.02	0.587 (0.381–0.905)	0.02
Primary PCI	0.614 (0.516–0.731)	<0.0001	0.596 (0.492–0.721)	<0.0001
ASA	0.599 (0.494–0.727)	<0.0001	0.677 (0.539–0.849)	0.001
ACE-I/ARB	0.763 (0.662–0.878)	0.0002	0.810 (0.693–0.947)	0.008
Statin	0.752 (0.633–0.892)	0.001	0.818 (0.671–0.998)	0.05

Predictors were: 1) the 5 pre-specified dose groups (none, >0% to 12.5%, >12.5% to 25%, >25% to 50%, and >50% of the target dose); and 2) the low-dose (≤25% of target dose) and high-dose (≥50% of the target dose) groups. HRs for continuous variables are associated with 1 unit increase in the measure.

Abbreviations as in Tables 1 and 2.

TABLE 5 HRs and 95% CIs From the Multivariable Analysis With the Extended Set of Covariates of 3-Year Mortality in the 4 Treated Beta-Blocker Dose Groups

	HR (95% CI)	p Value
Beta-blocker dose	See Table 2	
Age	1.529 (1.044–2.240)	0.03
Age (quadratic)	0.994 (0.989–1.000)	0.05
Age (cubic)	1.000 (1.000–1.000)	0.04
ln(troponin) (cubic)	1.006 (0.999–1.013)	0.09
ln(LOS)	2.838 (0.578–13.937)	0.20
Male	1.374 (1.170–1.615)	0.0001
Diabetes	1.370 (1.163–1.614)	0.0002
Hypertension	1.219 (0.999–1.487)	0.05
STEMI	0.842 (0.666–1.065)	0.15
Thrombolytic therapy	0.739 (0.498–1.098)	0.13
Primary PCI	0.580 (0.474–0.710)	<0.0001
ASA	0.784 (0.625–0.984)	0.04
ACE-I/ARB	0.878 (0.754–1.023)	0.10
Statin	0.778 (0.632–0.958)	0.02
History of MI	1.200 (1.015–1.419)	0.03
History of CABG	1.285 (1.073–1.538)	0.006
In-hospital revascularization	0.526 (0.431–0.641)	<0.0001
History of COPD	1.708 (1.411–2.066)	<0.0001
History of ESRD	2.366 (1.836–3.049)	<0.0001
History of CHF	1.327 (1.104–1.595)	0.003
History of CVA/TIA	1.256 (1.048–1.504)	0.01
ICD	1.360 (1.006–1.840)	0.05
BMI	0.745 (0.617–0.899)	0.002
BMI (quadratic)	1.007 (1.002–1.013)	0.01
BMI (cubic)	1.000 (1.000–1.000)	0.03

The 4 treated beta-blocker dose groups were as follows: >0% to 12.5%, >12.5% to 25%, >25% to 50%, and >50% of the target dose.

BMI = body mass index; other abbreviations as in Tables 1 and 2.

A variety of data support the biologic plausibility for the lack of a uniform improved survival with target dose versus low-dose beta-blocker therapy post-MI. Because most of the randomized clinical trial data for the beneficial effects of beta-blocker therapy were derived before thrombolysis, primary angioplasty, and routine use of aspirin, statins, and ACE inhibitors, the benefit of beta-blockers in the modern era has often been questioned. Meta-analyses including >50,000 patients from the early randomized trials of post-MI beta-blocker therapy (1,2) demonstrated 19% to 23% reductions in mortality. The more contemporary CAPRICORN (Effect of Carvedilol on Outcome After Myocardial Infarction in Patients With Left Ventricular Dysfunction) (15) randomized trial of carvedilol in post-MI patients with a left ventricular ejection fraction ≤40% also demonstrated a 23% reduction in all-cause mortality. Notably, in CAPRICORN, 74% of patients achieved the target dose and an additional 11% achieved 50% of the target dose. Large-scale observational studies (3–5) from Medicare databases documented the benefits of beta-blocker therapy in an era of rampant underuse. The largest contemporary trial, COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) (20), randomized 45,852 patients with suspected acute MI to receive metoprolol (initially intravenous followed by 200 mg orally daily) versus placebo and noted no reduction in mortality at 28 days. A 2014 meta-analysis (21) comparing the effect of beta-blockers on mortality after MI in the pre- versus post-reperfusion eras noted no benefit in the post-reperfusion era. Finally, a contemporary observational report identified a 15% reduction in mortality with beta-blocker therapy after MI (22). The changes in the therapeutic landscape of MI care and the variable reported outcomes provide further rationale to re-explore the effect of beta-blocker treatment and dosing on outcomes after MI.

Several studies (8,9) have noted beta-blocker underdosing relative to clinical trial doses. There are scant data overall and no randomized clinical trial data addressing whether this represents an acceptable or "poor" clinical practice. A 1998 retrospective cohort study (23) of 1,165 post-MI patients, of whom 365 were treated with beta-blockers, is the only previous study evaluating the effect of dose on outcome. Unadjusted mortality at a mean follow-up of approximately 2 years in those treated with ≥50%

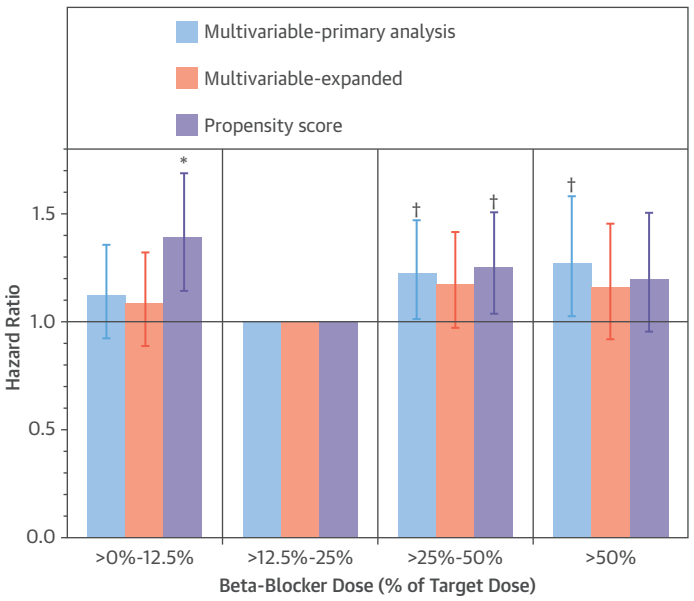
and <50% of the target dose was 6.9% and 3.4%, respectively. Multivariable analysis demonstrated a 67% reduction in cardiovascular mortality associated with low-dose beta-blockers. Interestingly, a study of 208 post-MI patients (24), of whom 154 were treated with a mean beta-blocker dose of 34% of the target dose, demonstrated a 60% reduction in all-cause mortality at a mean follow-up of 58.5 months. Because no previous randomized clinical trials evaluated whether low-dose or target dose beta-blocker therapy results in improved outcomes after MI, the OBTAIN registry establishes clinical equipoise for this issue and justifies further evaluation.

Dose-dependent effects of beta-blockers in the setting of heart failure have been examined, with somewhat inconsistent results (25–27). Whereas some trials (26,27) have shown a direct relationship of dose to survival, a meta-analysis (28) found no significant difference in mortality reduction between the trials in which patients received ≥50% of the target dose versus low doses (relative risk: 0.74 and 0.78, respectively); a relationship to heart rate reduction was noted. Although there may be some commonality of purpose in the use of beta-blockers post-MI and in heart failure, it is also possible that the dose-response relationships are different, reflecting important variations in underlying global and regional autonomic abnormalities (particularly in the degree of sympathoexcitation) between the 2 conditions. Furthermore, it is possible that the dose-response relationships for the beneficial effects of beta-blockers, even among subgroups of patients with MI, may be flatter than the dose-response relationships for adverse effects, including those that might affect the conduction system or cause metabolic adverse effects (e.g., hyperlipidemia, insulin resistance) (29).

The predominant mechanisms of the benefit for beta-blocker therapy after MI are reductions in ischemia, reinfarction, and sudden death. In the era of revascularization, aspirin, and statin use, it is plausible that the contribution of beta-blocker therapy to reductions in ischemia and reinfarction are not as prominent as when the initial beta-blocker clinical trials were performed. In fact, a 41% reduction in sudden death was reported in a pooled analysis of 5 studies evaluating trials of metoprolol post-MI, accounting for virtually all the difference in total mortality between the patients receiving metoprolol and placebo (30). Although it is possible that this benefit plays an even more prominent role in the modern era of post-MI treatment, it is also interesting to note that the presenting rhythms for out-of-hospital cardiac arrest have undergone transformation over the last decades, with a decline in ventricular fibrillation and an increase in pulseless electrical activity/asystole (31). The natural history of this change is uncertain but may reflect, at least in part, the use of beta-blockers. Of particular interest is a report that noted an adjusted odds ratio of 5 for beta-blocker use among out-of-hospital cardiac arrest survivors presenting with pulseless electrical activity versus ventricular fibrillation (32). The potential importance of bradyarrhythmias was further highlighted in the CARISMA (Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction) study (33), in which post-MI patients with a left ventricular ejection fraction <40% received an implantable cardiac monitor. At the 2-year follow-up, 17% of patients had either high-degree atrioventricular block, significant sinus bradycardia, or sinus arrest.

Personal factors that might influence the optimal beta-blocker dose include individual risk on the basis of patient and MI characteristics, genetic polymorphisms, and observed beta-blocker effect. For example, the OACIS (Osaka Acute Coronary Insufficiency Study) registry (34) noted improved survival with beta-blocker therapy after ST-segment elevation MI only in the higher risk subgroup. Some data

FIGURE 1 Adjusted Hazard Ratios for 3-Year Survival With Multivariable Analyses and Propensity Score Analysis Relative to the >12.5% to 25% of Target Dose Group



Adjusted hazard ratios for 3-year survival with multivariable analysis incorporating the prespecified variable set, multivariable analysis incorporating the expanded variable set, and propensity score analysis comparing mortality with each beta-blocker dose versus the mortality observed in the >12.5% to 25% of the target dose group. *$p < 0.03$. †$p < 0.001$.

suggest that beta-adrenergic receptor polymorphisms influence outcomes in acute coronary syndromes and heart failure (35-38), but the dose-response effect is unknown. Furthermore, genetic polymorphisms may affect beta-blocker metabolism and concentration (39,40). A number of analyses have suggested that mortality reduction post-MI is related more to the degree of heart rate reduction than to the type of beta-blocker (10,11). Whether these factors can allow for optimal titration of beta-blocker dose for an individual post-MI patient requires further study.

There are several reasons for the current high rate of low-dose beta-blocker therapy post-MI. This may represent either physician or patient inertia. Some patients may not be able to tolerate higher doses for hemodynamic reasons or due to noncardiac adverse effects or a more severe medical condition. Finally, advanced conduction system or myocardial disease may also preclude dose up-titration. There is no a priori reason for these factors to bias toward greater benefit with lower doses.

STUDY LIMITATIONS. An important caveat for the current findings is that they do not represent randomized clinical trial results. As such, multiple beta-blockers were used, and the doses were indexed to doses used in clinical trials. Although this method does not assure equivalent effects, it should be noted that 93% of the treated patients in this registry received either metoprolol or carvedilol, which was accounted for in the sensitivity analyses. In addition, the survival analysis was indexed to the discharge beta-blocker dose. Although dose changes do occur over time, only a minority of patients had their doses up-titrated. Being a registry, there was also nonuniform distribution of risk factors among groups. In addition, the specific rationale for the individual dosing regimens is unknown. Thus, the multivariable/propensity score analyses may have incompletely adjusted for these differences, and there may be unmeasured covariates, such as the extent of coronary artery disease or follow-up heart rate and blood pressure, which could affect the findings. However, multivariable adjustment and propensity score analyses consistently showed no greater benefit with full-dose beta-blocker therapy, contrary to the original hypothesis. Thus, despite these limitations, it is apparent that there is a need to stimulate further randomized trials of post-MI beta-blocker therapy from their currently dormant state.

CONCLUSIONS

Current practice is characterized by the use of low-dose beta-blocker therapy post-MI. To date, no data support this practice, as all the randomized clinical trials used higher target doses. Because these trials did not include dose titration studies, the present findings are not in conflict with the randomized clinical trial data. Importantly, further research is needed to establish optimal (personalized) beta-blocker dosing after MI.

ACKNOWLEDGMENT The authors thank Daya Alexander for her special contributions to the conduct and management of this study.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Jeffrey J. Goldberger, Northwestern University Feinberg School of Medicine, Division of Cardiology, 676 North Saint Clair, Arkes 600, Chicago, Illinois 60611. E-mail: j-goldberger@northwestern.edu.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Therapy with beta-adrenergic antagonist drugs is recommended for patients after MI, but the most commonly prescribed doses are one-quarter of the dose evaluated in the randomized clinical trials that demonstrated efficacy, and optimum doses have not been validated.

TRANSLATIONAL OUTLOOK: Additional research is needed to compare various doses of beta-blockers in survivors of MI and to identify factors that influence optimum dose selection.

REFERENCES

1. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction. An overview of results from randomized controlled trials. JAMA 1993;270:1589–95.

2. Freemantle N, Cleland J, Young P, et al. β blockade after myocardial infarction: systematic review and meta regression analysis. BMJ 1999;318:1730–7.

3. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. N Engl J Med 1998;339:489–97.

4. Krumholz HM, Radford MJ, Wang Y, et al. National use and effectiveness of β-blockers for the treatment of elderly patients after acute myocardial infarction: National Cooperative Cardiovascular Project. JAMA 1998;280:623–9.

5. Soumerai SB, McLaughlin TJ, Spiegelman D, et al. Adverse outcomes of underuse of β-blockers in elderly survivors of acute myocardial infarction. JAMA 1997;277:115–21.

6. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on

Practice Guidelines. J Am Coll Cardiol 2013;61:e78–140.

7. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol 2007;50:652–726.

8. Arnold SV, Spertus JA, Masoudi FA, et al. Beyond medication prescription as performance measures: optimal secondary prevention medication dosing after acute myocardial infarction. J Am Coll Cardiol 2013;62:1791–801.

9. Goldberger JJ, Bonow RO, Cuffe M, et al., PACE-MI Investigators. β-blocker use following myocardial infarction: low prevalence of evidence-based dosing. Am Heart J 2010;160:435–42.

10. Cucherat M. Quantitative relationship between resting heart rate reduction and magnitude of clinical benefits in post-myocardial infarction: a meta-regression of randomized clinical trials. Eur Heart J 2007;28:3012–9.

11. Kjekshus JK. Importance of heart rate in determining beta-blocker efficacy in acute and long-term acute myocardial infarction intervention trials. Am J Cardiol 1986;57:43F–9.

12. Goldberger JJ, Bonow RO, Cuffe M, et al. Post-myocardial infarction β-blocker therapy: the bradycardia conundrum. Rationale and design for the Pacemaker & β-Blocker Therapy Post-MI (PACE-MI) trial. Am Heart J 2008;155:455–64.

13. The MIAMI Trial Research Group. Metroprolol in Acute Myocardial Infarction (MIAMI): a randomized placebo-controlled international trial. Eur Heart J 1985;6:199–226.

14. Hjalmarson A, Elmfeldt D, Herlitz J, et al. Effect on mortality of metoprolol in acute myocardial infarction: a double-blind randomised trial. Lancet 1981;2:823–7.

15. The CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet 2001;357:1385–90.

16. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. JAMA 1982;247:1707–14.

17. Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981;304:801–7.

18. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomised trial. Lancet 1999;353:9–13.

19. Viskin S, Kitzis I, Lev E, et al. Treatment with beta-adrenergic blocking agents after myocardial infarction: from randomized trials to clinical practice. J Am Coll Cardiol 1995;25:1327–32.

20. Chen ZM, Pan HC, Chen YP, et al., for the COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1622–32.

21. Bangalore S, Makani H, Radford M, et al. Clinical outcomes with β-blockers for myocardial infarction: a meta-analysis of randomized trials. Am J Med 2014;127:939–53.

22. Andersson C, Shilane D, Go AS, et al. β-blocker therapy and cardiac events among patients with newly diagnosed coronary heart disease. J Am Coll Cardiol 2014;64:247–52.

23. Barron HV, Viskin S, Lundstrom RJ, et al. β-blocker dosages and mortality after myocardial infarction: data from a large health maintenance organization. Arch Intern Med 1998;158:449–53.

24. Siu CW, Pong V, Jim MH, et al. β-blocker in post-myocardial infarct survivors with preserved left ventricular systolic function. Pacing Clin Electrophysiol 2010;33:675–80.

25. Wikstrand J, Hjalmarson A, Waagstein F, et al., for the MERIT-HF Study Group. Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in metoprolol CR/XL randomized intervention trial in chronic heart failure (MERIT-HF). J Am Coll Cardiol 2002;40:491–8.

26. Metra M, Torp-Pedersen C, Swedberg K, et al. Influence of heart rate, blood pressure, and beta-blocker dose on outcome and the differences in outcome between carvedilol and metoprolol tartrate in patients with chronic heart failure: results from the COMET trial. Eur Heart J 2005;26:2259–68.

27. Dobre D, van Veldhuisen DJ, Mordenti G, et al., for the SENIORS Investigators. Tolerability and dose-related effects of nebivolol in elderly patients with heart failure: data from the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial. Am Heart J 2007;154:109–15.

28. McAlister FA, Wiebe N, Ezekowitz JA, et al. Meta-analysis: β-blocker dose, heart rate reduction, and death in patients with heart failure. Ann Intern Med 2009;150:784–94.

29. Fonseca VA. Effects of beta-blockers on glucose and lipid metabolism. Curr Med Res Opin 2010;26:615–29.

30. Olsson G, Wikstrand J, Warnold I, et al. Metoprolol-induced reduction in postinfarction mortality: pooled results from five double-blind randomized trials. Eur Heart J 1992;13:28–32.

31. Hulleman M, Berdowski J, de Groot JR, et al. Implantable cardioverter-defibrillators have reduced the incidence of resuscitation for out-of-hospital cardiac arrest caused by lethal arrhythmias. Circulation 2012;126:815–21.

32. Youngquist ST, Kaji AH, Niemann JT. Beta-blocker use and the changing epidemiology of out-of-hospital cardiac arrest rhythms. Resuscitation 2008;76:376–80.

33. Bloch Thomsen PE, Jons C, Raatikainen MJ, et al., for the Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) Study Group. Long-term recording of cardiac arrhythmias with an implantable cardiac monitor in patients with reduced ejection fraction after acute myocardial infarction: the Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) study. Circulation 2010;122:1258–64.

34. Nakatani D, Sakata Y, Suna S, et al., for the Osaka Acute Coronary Insufficiency Study (OACIS) Investigators. Impact of beta blockade therapy on long-term mortality after ST-segment elevation acute myocardial infarction in the percutaneous coronary intervention era. Am J Cardiol 2013;111:457–64.

35. Liu WN, Fu KL, Gao HY, et al. β1 adrenergic receptor polymorphisms and heart failure: a meta-analysis on susceptibility, response to β-blocker therapy and prognosis. PLoS One 2012;7:e37659.

36. Lanfear DE, Jones PG, Marsh S, et al. β_2-adrenergic receptor genotype and survival among patients receiving β-blocker therapy after an acute coronary syndrome. JAMA 2005;294:1526–33.

37. Cresci S, Dorn GW II, Jones PG, et al. Adrenergic-pathway gene variants influence beta-blocker-related outcomes after acute coronary syndrome in a race-specific manner. J Am Coll Cardiol 2012;60:898–907.

38. Aleong RG, Sauer WH, Robertson AD, et al. Adrenergic receptor polymorphisms and prevention of ventricular arrhythmias with bucindolol in patients with chronic heart failure. Circ Arrhythm Electrophysiol 2013;6:137–43.

39. Koytchev R, Alken RG, Vlahov V, et al. Influence of the cytochrome P4502D6*4 allele on the pharmacokinetics of controlled-release metoprolol. Eur J Clin Pharmacol 1998;54:469–74.

40. Ismail R, Teh LK. The relevance of CYP2D6 genetic polymorphism on chronic metoprolol therapy in cardiovascular patients. J Clin Pharm Ther 2006;31:99–109.

KEY WORDS adrenergic beta-antagonists, follow-up studies, registries, survival analysis

APPENDIX For a complete list of study investigators and additional information on propensity score adjustment, please see the online version of this article.