Circulation: Cardiovascular Quality and Outcomes

ORIGINAL ARTICLE

Comparative Effectiveness of β-Blocker Use Beyond 3 Years After Myocardial Infarction and Long-Term Outcomes Among Elderly Patients

BACKGROUND: The benefit of β-blocker use beyond 3 years after a myocardial infarction (MI) has not been clearly determined.

METHODS AND RESULTS: Using data from the CRUSADE Registry (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) linked with Medicare claims, we studied patients ≥65 years of age with MI, discharged on β-blocker therapy and alive 3 years later without a recurrent MI to evaluate β-blocker use and dose (none, <50%, and ≥50% of the recommended target) at 3 years. Using inverse probability of treatment weighting, we then examined the adjusted association between β-blocker use (and dose) at 3 years and the cardiovascular composite of all-cause mortality, hospitalization for recurrent MI, ischemic stroke, or heart failure over the subsequent 5 years. Of the 6893 patients ≥65 years age, β-blocker use at 3 years was 72.2% (n=4980); 43% (n=2162) of these were treated with ≥50% of the target β-blocker dose. β-blocker use was not associated with a significant difference on the composite outcome (52.4% versus 55.4%, adjusted hazard ratio, 0.95; 95% CI, 0.88–1.03; *P*=0.23). Neither low dose (<50% target dose) nor high dose (≥50% target dose) β-blocker use was associated with a significant difference in risk when compared with no β-blocker use. Results were also consistent in patients with and without heart failure or systolic dysfunction (*P* interaction =0.30).

CONCLUSIONS: In this observational analysis, β-blocker use beyond 3 years post-MI, regardless of the dose achieved, was not associated with improved outcomes. The role of prolonged β-blocker use, particularly in older adults, needs further investigation.

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Key Words: heart failure ■ Medicare ■ myocardial infarction ■ probability ■ stroke

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WHAT IS KNOWN

- β-blocker therapy is recommended for at least 3 years post-myocardial infarction (MI).
- With a competing increase in noncardiovascular morbidity and mortality in older (≥65 years old) post-MI patients, the role of continued β-blocker therapy in 3-year post-MI survivors is unclear.

WHAT THE STUDY ADDS

- Nearly 3 in every 4 post-MI patients ≥65 years old initially discharged on a β-blocker and surviving to 3 years post-MI are still on β-blocker therapy at 3 years.
- In 3-year post-MI survivors ≥65 years old, no association between β-blocker use at 3 years and long-term cardiovascular outcomes is noted, including in patients with heart failure/systolic dysfunction.

High-quality clinical trial evidence exists to support the use of oral β-blocker therapy for secondary prevention following myocardial infarction (MI).[1–4] However, since these clinical trials followed patients at most for 2 to 3 years, it is unclear whether β-blockers should be continued beyond that time frame. Moreover, older, higher risk patients are typically underrepresented in clinical trials; therefore, very limited data exist to support long-term β-blocker use, particularly in a patient population more susceptible to side effects of treatment. Discrepancies in the results of several large observational analyses have introduced further ambiguity on the role of post-MI β-blocker therapy; some studies have demonstrated a strong association,[5–7] others have suggested that this association may be limited to the early postinfarct period,[8–10] and yet others have shown no association between discharge β-blocker use and long-term cardiovascular outcomes.[11,12]

Current American Heart Association/American College of Cardiology Foundation secondary prevention guidelines recommend β-blocker use up to 3 years post-MI (and considered beyond this period, class IIa) in patients with normal left ventricular systolic function.[13] Yet, how β-blockers should be managed beyond 3 years post-MI, particularly in the elderly, is unknown. To address this knowledge gap, we studied β-blocker use in post-MI patients ≥65 years of age alive at 3 years without a recurrent MI, evaluated factors associated with β-blocker use at 3 years and the association between β-blocker use and subsequent long-term cardiovascular outcomes.

METHODS

Data Source and Study Population

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedures. This is a retrospective analysis of patients with MI in the CRUSADE Registry (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines).[14] Our study population comprised patients with MI discharged alive on a β-blocker and without a recurrent MI event over the 3-year follow-up period. Three-year MI survivors in the CRUSADE Registry were then linked to Center for Medicare and Medicaid Services data to ascertain β-blocker use at the 3-year post-MI anniversary and clinical outcomes over the subsequent 5 years. The rules and process of this linkage have previously been detailed in a separate article.[15] Local institutional review board approval was obtained for collection of data on demographics, medical history, in-hospital characteristics, laboratory values, treatments and interventions, and discharge therapies.

As Center for Medicare and Medicaid Services data were available only for patients enrolled within the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines Registry between January 2, 2004, and December 31, 2006, our current study population was, therefore, limited to this period. Of the 28 562 patients with MI discharged to home on a β-blocker and eligible at discharge for Medicare parts A and B benefits, we sequentially excluded patients who died during the first 3 years (n=10 097), had a hospitalization for a recurrent MI during the first 3 years (n=1749), or discontinued Medicare coverage within 3 years of the index MI (n=2538). We then excluded patients who at 3 years were not enrolled in Medicare part D (n=7285) as Medicare part D data was fundamental to the ascertainment of 3-year β-blocker use. Our final analytic population comprised 6893 patients alive at 3 years and without a recurrent MI in the 3-year follow-up.

β-Blocker Use and Dose

β-blocker use at 3 years was ascertained using Medicare part D prescription fill data and was defined as at least 1 β-blocker fill in the 90 days before the 3-year post-MI anniversary and a ≥60 day supply filled 3 months before to 3 months after the 3-year anniversary. For this study, the target doses of commonly used β-blockers were as follows and aligned with prior studies that have evaluated β-blocker use in the post-MI setting[16,17]: metoprolol 200 mg/d; carvediolol 50 mg/d; bisoprolol 10 mg/d; atenolol 100 mg/d; propranolol 160 mg/d; labetalol 400 mg/d; nadolol 160 mg/d; nebivolol 10 mg/d; acebutolol 400 mg/d; and pindolol 20 mg/d. The daily β-blocker dose was described as a proportion of the respective target β-blocker dose and categorized into 3 β-blocker dose groups as per prior β-blocker analyses[16,17]: none, <50%, and ≥50% of the target dose. A total of 1.6% (n=80) patients did not have β-blocker dose data available and were not included in the dose-specific analysis.

Outcomes

Clinical outcomes were assessed from 3 years after the index MI. The primary outcome of interest was the cardiovascular composite of death, or hospitalization for MI, hospitalization

for ischemic stroke, or hospitalization for heart failure in the subsequent 5 years. Mortality data were derived from the Medicare denominator file; however, the cause of death was not captured. Hospitalization for MI, hospitalization for ischemic stroke, and hospitalization for heart failure were ascertained from inpatient Medicare part A data using the *International Classification of Diseases* coding algorithms described in Table I in the Data Supplement.

Statistical Analysis

We first compared baseline patient characteristics between patients who were still on or no longer on a β-blocker at 3 years post-MI. In patients on a β-blocker at 3 years, characteristics at baseline were further profiled by whether patients were on <50% or ≥50% of the target β-blocker dose. The χ^2 and Wilcoxon rank-sum tests were used to compare categorical and continuous variables, respectively. Categorical variables were reported as percentages, and continuous variables were reported as medians with 25th and 75th percentiles. We subsequently evaluated factors associated with continued β-blocker use at 3 years using a multivariable generalized estimating equation logistic regression model accounting for clustering within hospitals. A backward selection process was used to identify variables (Table II in the Data Supplement) significantly associated with β-blocker use at 3-year post-index hospitalization at a critical threshold of 0.05. The results are presented as odds ratios (ORs) with their corresponding 95% CI.

To evaluate the association between β-blocker use at 3 years and the cardiovascular composite of all-cause death, hospitalization for recurrent MI, hospitalization for ischemic stroke, or hospitalization for heart failure over the subsequent 5 years, Kaplan-Meier curves were generated and compared using the log-rank test. To account for differences in patient mix and for confounding by indication associated with the β-blocker use, inverse probability of treatment weighted analyses (with robust SE) were performed to evaluate the adjusted association between β-blocker use at 3 years and the primary composite. For this inverse probability of treatment weighted analysis, the propensity score for β-blocker use at 3 years was first computed using a multivariable logistic regression model with β-blocker use at 3 years as the dependent variable and the independent variables comprising all candidate variables potentially associated with β-blocker use at 3 years (Table II in the Data Supplement); also included in the adjustment models were statin and ACE (angiotensin-converting enzyme) inhibitor/ARB (angiotensin receptor blocker) use at 3 years. As illustrated in Figure I in the Data Supplement, standardized differences for all covariates were evaluated pre- and post-weighting, and highlight post-weighting differences of <10% for all covariates, generally suggestive of an optimal balance.[18] Using the inverse of the derived propensity score for β-blocker use as weights, a Cox proportional hazards model was then used to evaluate the adjusted association between β-blocker use at 3 years and the primary cardiovascular composite.

We then evaluated the association between β-blocker use and the individual components of the composite. For this analysis, to account for the competing risk of death, we separately generated cumulative incidence curves for each outcome. Fine and Gray regression models (with robust SE to account for patient clustering within hospitals) were then used to evaluate the unadjusted and adjusted association (inverse probability of treatment weighted as described for the primary cardiovascular composite above) between continued β-blocker use at 3 years and hospitalization for recurrent MI, hospitalization for ischemic stroke, and hospitalization for heart failure.

Adjusted hazard ratios (HR) with corresponding 95% CI and *P* values are reported by β-blocker use and β-blocker dose. We repeated the above analyses to evaluate pairwise associations between β-blocker dose (none, <50%, and ≥50% of target dose) and the 5-year composite outcome. As the association between β-blocker use and the primary composite may be modified by distinct patient subgroups, we further explored the association between β-blocker use and the primary composite in the following: (1) heart failure (includes patients with prior heart failure, heart failure during index admission or left ventricular ejection fraction ≤40%); (2) sex (female versus male); (3) MI type (ST-segment–elevation MI versus non–ST-segment–elevation MI); (4) diabetes mellitus; (5) ACE inhibitor/ARB use at 3 years; and (6) age <75 years versus ≥75 years of age.

Finally, although β-blockers as a class may be protective in patients with heart failure, only select β-blockers have been tested (carvedilol, metoprolol, bisoprolol, and nebivolol) and shown to be beneficial in patients with heart failure.[3,19–21] Therefore, we further explored whether the relationship between rehospitalization for heart failure was modified in patients using any of these 4 β-blockers compared with all other β-blockers.

All continuous variables nonlinear with respect to the outcome were fit with linear splines. The missingness rate across all variables was <2%. For continuous variables, missing values were imputed to the median of the nonmissing values; for categorical variables, missing values were set to the most frequently occurring group. This method has been well established as a reasonable choice for handling missing data when the rate of missingness is low.[22] All *P* values were 2-sided and a *P* value of <0.05 was considered significant for all analyses. All statistical analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC). The institutional review board of the Duke University approved the study protocol.

RESULTS

Among 6893 post-MI patients alive without a recurrent MI at 3 years, 4980 (72.2%) were on a β-blocker. Patients still on β-blocker at 3 years were more likely to be female, have diabetes mellitus, prior coronary artery bypass graft surgery, discharged on other evidence-based pharmacotherapies during the index MI, and seen a cardiologist within the preceding year compared with patients no longer taking β-blocker therapy (Table 1). There were no significant differences in in-hospital or postdischarge heart failure between the 2 groups. Patients who remained on a β-blocker

Table 1. Baseline Demographics, In-Hospital, and Postdischarge to 3-Year Characteristics Categorized by 3-Year β-Blocker Use

Variable*	Overall (n=6893)	β-Blocker Use at 3 Years		*P* Value
		No (n=1913)	Yes (n=4980)	
No. of patients				
Patient-level characteristics				
Age, y	75 (70–81)	75 (70–81)	75 (70–81)	0.68
Female sex	53.7	49.1	55.2	<0.01
White race	86.2	84.8	86.7	0.13
Diabetes mellitus	29.5	27.0	30.5	<0.01
BMI, kg/m^2	27.4 (24.3–31.2)	27.3 (24.2–30.8)	27.4 (24.3–31.3)	0.11
Peripheral arterial disease	10.4	9.7	10.7	0.24
Current/recent smoker	13.7	14.4	13.5	0.31
Prior MI	24.2	23.2	24.5	0.25
Prior PCI	19.6	19.0	19.9	0.44
Prior CABG	19.1	16.6	20.0	<0.01
Prior stroke	10.1	10.6	9.8	0.33
Charlson comorbidity index ≥3	30.9	32.7	30.2	0.05
Index MI characteristics				
STEMI	8.3	7.3	8.7	0.06
Heart rate (beats/min)	80 (69–96)	80 (68–96)	80 (69–96)	0.82
Systolic BP, mm Hg	146 (127–168)	146 (126–168)	147 (128–168)	0.18
In-hospital CHF	22.7	22.1	22.9	0.52
Diagnostic catheterization†	92.7	92.5	92.8	0.79
PCI	57.3	57.2	57.4	0.97
CABG	14.4	13.7	14.7	0.35
No. of diseased vessels				<0.01
None	8.5	10.8	7.7	
1	29.9	29.9	30.0	
2	28.8	29.2	28.6	
3	32.7	30.2	33.7	
Ejection fraction				0.02
>50%	55.2	58.1	54.1	
40%–50%	22.7	22.1	22.9	
25%–40%	17.7	16.1	18.4	
<25%	4.1	3.4	4.4	
Baseline troponin (×local laboratory ULN)	2.2 (0.5–9.6)	2.0 (0.5–8.7)	2.3 (0.5–10.0)	0.09
Creatinine clearance, mL/min	45.3 (33.5–59.1)	46.0 (34.2–60.0)	45.2 (33.3–58.8)	0.03
Discharge therapies				
Clopidogrel	74.9	75.0	74.9	0.85
ACE inhibitor/ARB	71.7	69.6	72.5	0.05
Statin	83.6	81.6	84.4	0.01
Discharge to 3 years				
CHF readmission	12.7	11.9	13.0	0.25
Number of days hospitalized	3 (0–10)	3 (0– 11)	3 (0–10)	0.02
Cardiologist visit <1 y	37.4	34.5	38.5	<0.01
ACE inhibitor/ARB at 3 years	54.7	35.2	62.2	<0.01
Statin at 3 years	60.1	40.0	67.8	<0.01

(*Continued*)

Table 1. Continued

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft surgery; CHF, congestive heart failure; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation MI; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation MI; and ULN, upper limit of normal.

*Continuous variables are shown as median (25th and 75th percentile) and are compared with Wilcoxon rank-sum tests; categorical variables are shown as percentages and are compared with Pearson χ^2 tests.

†Among patients without a contraindication.

were also much more likely to be taking an ACE inhibitor/ARB or a statin at 3 years than patients no longer on a β-blocker. In the multivariable model, male sex (OR, 0.73; 95% CI, 0.65–0.82) and an increase in the number of days related to all-cause hospitalization within the 3 years following index MI (OR, 0.94; 95% CI, 0.92–0.96) corelated most strongly with a lower likelihood of being on a β-blocker at 3 years, while a history of coronary artery bypass graft surgery (OR, 1.30; 95%, CI, 1.14–1.48) and cardiologist follow-up within the year preceding the 3-year post-MI anniversary (OR, 1.23; 95% CI, 1.09–1.37) were associated with a higher likelihood of being on a β-blocker at 3 years; however, the C-index of the model was only 0.57 (Table III in the Data Supplement). Of patients still on a β-blocker at 3 years, only 43% (n=2162) were treated with ≥50% of the target β-blocker dose. Compared with patients on lower β-blocker doses, patients on a higher β-blocker dose were more likely to be female, to have diabetes mellitus or prior coronary artery disease, and in-hospital or postdischarge heart failure but were less likely to undergo coronary revascularization during the index MI hospitalization (Table 2).

Outcomes by β-Blocker Use at 3 Years

The median duration of follow-up post-MI was 8 years (25th and 75th percentiles: 5.2 and 9.2 years). This allowed us to examine 5-year outcomes subsequent to the 3-year post-MI anniversary. The incidence of the composite outcome of death, hospital-

Table 2. Baseline Demographics, In-Hospital, and Postdischarge to 3-Year Characteristics in 3-Year β-Blocker Users Categorized by Dose

Variable*	Overall (n=4900)	β-Blocker Dose		*P* Value
		<50% of Target (n=2738)	≥50% of Target (n=2162)	
Demographics				
Age, y	75 (70–81)	76 (70–82)	75 (69–80)	<0.01
Female sex	55.6	53.7	58.0	<0.01
BMI, kg/m^2	27.4 (24.3–31.3)	26.9 (23.9–30.5)	28.3 (25.0–32.1)	<0.01
White race	86.6	87.0	86.2	<0.01
Risk profile				
Diabetes mellitus	30.5	26.7	35.3	<0.01
Peripheral arterial disease	10.8	10.1	11.7	0.08
Current/recent smoker	13.5	13.7	13.3	0.70
Dyslipidemia	54.9	52.2	58.2	<0.01
Prior MI	24.4	22.8	26.3	<0.01
Prior CABG	20.0	18.0	22.5	<0.01
Prior CHF	12.5	12.0	13.2	0.19
Prior stroke	9.8	9.9	9.8	0.94
Charlson comorbidity index ≥3	30.3	28.6	32.4	<0.01
Presenting characteristics				
Heart rate (beats/min)	80 (69–96)	80 (68–94)	82 (70–98)	<0.01
Systolic BP, mm Hg	147 (128–168)	144 (126–164)	150 (130–174)	<0.01
STEMI	8.7	9.3	7.9	0.08
In-hospital CHF	22.9	20.7	25.7	<0.01
Diagnostic catheterization†	92.8	93.0	92.5	0.72
PCI	57.5	60.0	54.7	<0.01
CABG	14.7	14.5	15.0	0.66
No. of diseased vessels				0.10
None	7.7	7.4	8.1	
1	29.9	31.2	28.2	
2	28.7	29.0	28.4	
3	33.7	32.5	35.3	
Ejection fraction				0.74
>50%	54.0	54.1	53.8	
40%–50%	23.0	22.8	23.2	
25%–40%	18.5	18.7	18.1	
<25%	4.3	4.1	4.7	
Baseline troponin (×local laboratory ULN)	2.3 (0.5–10.0)	2.4 (0.5–10.7)	2.0 (0.5–9.5)	0.14
Creatinine clearance, mL/min	45.2 (33.3–58.8)	45.8 (33.8–59.9)	43.9 (32.7–57.5)	<0.01
Discharge therapies				
Clopidogrel	75.1	76.3	73.7	0.05
ACE inhibitors/ARB	72.6	71.7	73.5	0.19
Statin	84.4	84.1	84.8	0.41
Discharge to 3 years				
CHF readmission	12.9	10.9	15.5	<0.01
No. of days hospitalized	3 (0–10)	3 (0–10)	3 (0–10)	0.16
Cardiologist visit <1 y	38.4	37.7	39.4	0.22
ACE inhibitors/ARB at 3 years	62.3	59.6	65.7	<0.01
Statin at 3 years	67.9	67.6	68.3	0.64

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft surgery; CHF, congestive heart failure; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation MI; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation MI; and ULN, upper limit of normal.

*Continuous variables are shown as median (25th and 75th percentile) and are compared with Wilcoxon rank-sum tests; categorical variables are shown as percentages and are compared with Pearson χ^2 tests.

†Among patients without a contraindication.

ization for recurrent MI, hospitalization for ischemic stroke, or hospitalization for heart failure was 52.4% for patients still on a β-blocker at 3 years versus 55.4% for patients no longer on a β-blocker at 3 years (*P*=0.016; Figure 1A). After multivariable risk adjustment, this association was statistically nonsignificant (HR, 0.95; 95% CI, 0.88–1.03; *P*=0.23). Similarly, no difference in the individual components of the cardiovascular composite was noted in patients on a β-blocker versus not at 3 years: all-cause mortality (adjusted HR, 0.95; [95% CI, 0.87–1.04]; *P*=0.31); hospitalization for recurrent MI: (adjusted HR, 1.03; [95% CI, 0.86–1.24]; *P*=0.74); hospitalization for ischemic stroke: (adjusted HR, 1.00; [95% CI, 0.76–1.32]; *P*=0.99); or hospitalization for heart failure: (adjusted HR, 1.01; [95% CI, 0.87–1.17]; *P*=0.92; Figure 1B through 1E).

The observed association between β-blocker use and the primary composite did not appear to be modified by any of the evaluated patient subgroups, including in patients with heart failure or systolic dysfunction during the index MI hospitalization (*P* for interaction =0.30; Figure 2). Furthermore, we observe no significant interaction on the relationship between β-blocker use and rehospitalization for heart failure by use of β-blockers established in heart failure clinical trials (carvedilol, metoprolol, bisoprolol, and nebivolol) compared with use of all other β-blockers (*P* for interaction =0.87).

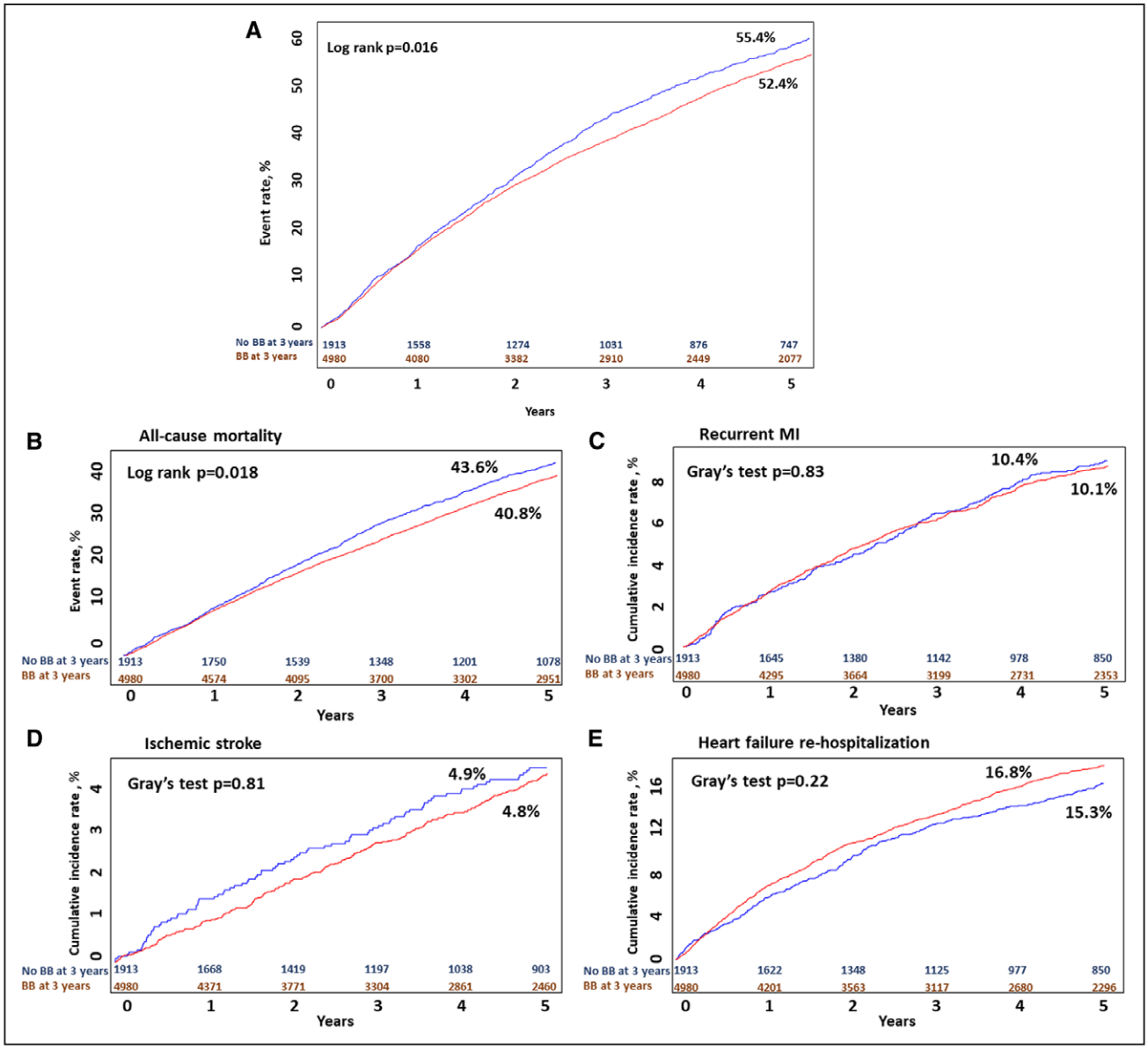

Figure 1. Association between β-blocker use at 3 years and unadjusted composite of all-cause death, hospitalization for recurrent myocardial infarction (MI), hospitalization for ischemic stroke, and hospitalization for heart failure (A), all-cause death (B), hospitalization for recurrent MI (C), hospitalization for ischemic stroke (D), and hospitalization for heart failure (E).

Outcomes by β-Blocker Dose at 3 Years

The incidence of the primary composite end point in patients not on a β-blocker, on a β-blocker at <50% target dose, or ≥50% target dose was 55.4%, 50.8%, and 54.2%, respectively. Compared with patients not on a β-blocker, patients on a β-blocker at <50% or ≥50% target dose had no significant association with the risk-adjusted primary composite: <50% β-blocker versus no β-blocker: (adjusted HR, 0.93; [95% CI, 0.85–1.02]; *P*=0.10); ≥50% β-blocker versus no β-blocker: (adjusted HR, 0.98; [95% CI, 0.89–1.07]; *P*=0.62); β-blocker at <50% versus ≥50% target dose: (adjusted HR, 0.95; [95% CI, 0.87–1.03]; *P*=0.23; Figure 3A through 3C).

DISCUSSION

This observational analysis focuses on an older aged population of patients to characterize outcomes associated with β-blocker use at 3 years after an acute MI. Our key findings include the following: First, nearly 3 in 4 older post-MI patients initially discharged on a β-blocker and alive without experiencing a recurrent MI remained on a β-blocker 3 years later; however, the majority were treated with a dose well-below target doses in the pivotal clinical trials. Second, no long-term beneficial association was noted in this nonrandomized, comparative effective analysis for continued β-blocker use beyond 3 years post-MI, regardless of the β-blocker dose

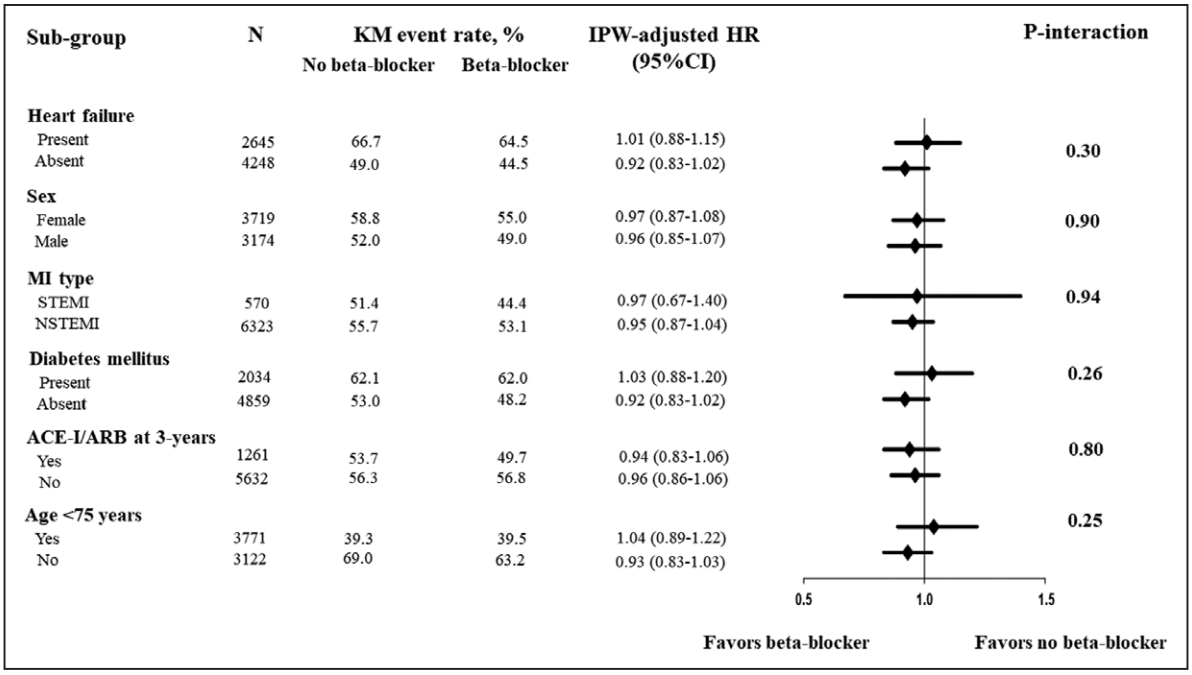

Figure 2. Comparative event rates and adjusted hazard ratios (HRs) for composite of all-cause death, hospitalization for recurrent myocardial infarction (MI), hospitalization for ischemic stroke, and hospitalization for heart failure within prespecified subgroups.
ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; KM, Kaplan-Meier; NSTEMI, non–ST-segment–elevation MI; and STEMI, ST-segment–elevation MI.

utilized. Third, our overall neutral findings remained consistent across key patient subgroups, including in patients with heart failure or systolic dysfunction at the index MI presentation.

Robust clinical trial evidence exists for risk reduction of fatal and nonfatal adverse cardiovascular events for post-MI β-blocker therapy in the immediate post-MI setting.[1,4,23,24] However, patients in these trials were followed-up on average for only about 1.5 years; yet, based on the assumption that the observed short-term benefits will similarly extend into the long-term, post-MI patients are generally treated with β-blockers into their old age. To provide longer-term follow-up data in more contemporary treated patients with MI, several registry analyses have recently compared long-term outcomes based on whether or not β-blockers were prescribed at discharge.[8,11,12,25] However, their findings have been largely discrepant and to some extent confounded by the fact that patients not being discharged on β-blockers are often sicker and more prone to adverse cardiovascular outcomes.[25,26] Additionally, modeling long-term outcomes based on β-blocker at discharge assumes that all patients discharged on a β-blocker will remain fully adherent in the long-term; long-term use of cardiovascular therapies is known to be modest and, therefore, further biases this outcome relationship. One-year β-blocker discontinuation rates of between 10% and 30% have previously been

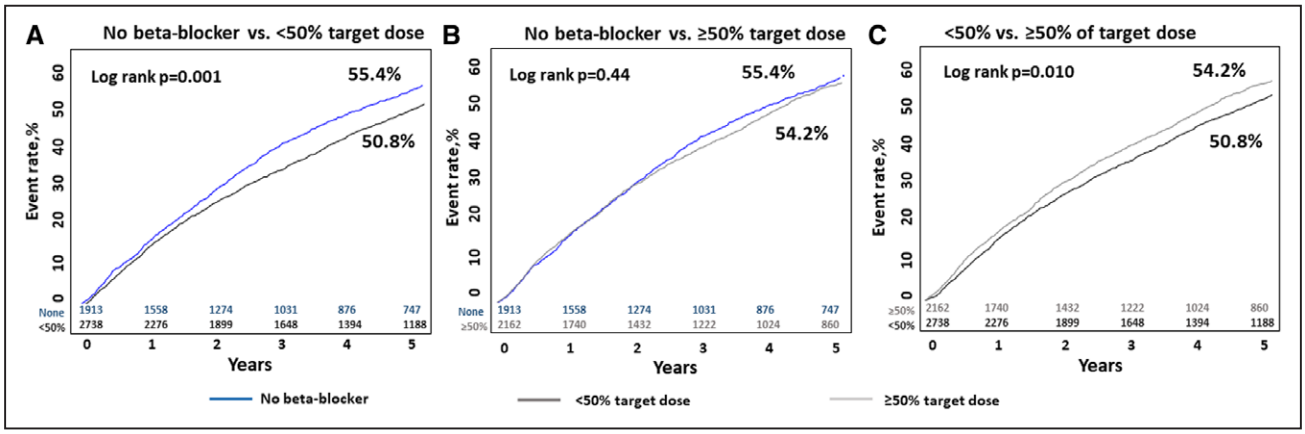

Figure 3. Association between β-blocker dose at 3 y and unadjusted composite of all-cause death, hospitalization for recurrent myocardial infarction (MI), hospitalization for ischemic stroke, and hospitalization for heart failure (A, no β-blocker vs <50% target dose; B, no β-blocker vs ≥50% target dose; and C, <50% vs ≥50% target dose).

reported,[27–29] and this estimate increasing to nearly 50% at 3 years post-MI.[28] In fact, our results suggest that of patients initially discharged on a β-blocker, nearly 3 in every 4 older post-MI patients without a recurrent event is still on a β-blocker at 3 years; surprisingly, however, in patients not on β-blocker at 3 years, we also observe a strikingly lower rate in the use of other evidence-based post-MI pharmacotherapies. The reasons for this are not entirely clear but may relate to complex and unmeasured patient comorbidity (such as decline in cognitive and physiological function, development of β-blocker contraindications) that similarly underlies our poor discriminatory ability to predict β-blocker use at 3 years (model C-index 0.57). Further credence to the high comorbidity burden in this patient population is provided by the very high mortality rates observed between discharge and 3 years and beyond 3 years. As such, these patients are at high likelihood for developing β-blocker related adverse events and in whom the reevaluation of the duration of post-MI β-blockade is even more critical.

Based on the highest quality evidence available, β-blockers are recommended for secondary cardiovascular prevention in low-risk patients for at least 3 years.[13] Acknowledging the basis for this evidence is from patients evaluated in the pre and early reperfusion era, contemporary β-blocker trials are underway (Randomized Evaluation of Decreased Usage of Beta-blockers After Myocardial Infarction (REDUCE) SWEDEHEART: URL: https://www.clincialtrials.gov. Unique identifier: NCT03278509). However, until their results become available, our study aims to address the knowledge gap on whether β-blocker use beyond 3 years is associated with a lower cardiovascular risk and particularly so in the elderly. Several possibilities explain our neutral overall, subgroup, and dose-stratified findings. First, by design, we select patients who have survived to 3 years without having experienced a recurrent ischemic event. The bias with surviving to 3 years in patients ≥65 years of age may in itself associate with improved long-term outcomes; the relevance of this selection bias becomes even more important considering that over one-third of all eligible patients in our study died within the first 3 years from hospital discharge. Second, majority of the patients with MI evaluated received revascularization during the index admission; furthermore, nearly 80% of all patients in this study had preserved or only mild systolic dysfunction (left ventricular ejection fraction ≥40%). These key favorable prognostic factors jointly reflect on an overall lower risk patient population and likely associates with improved overall long-term outcomes regardless of β-blocker use or dose at 3 years. Finally, the 5-year composite event rates in this study were >50% and largely contributed to by mortality; we were, however, unable to discern the respective associations between β-blocker use and cardiovascular or noncardiovascular mortality. β-blockers do not influence noncardiovascular deaths; since half the patients in this study were ≥75 years of age, it is plausible that the competing risk of dying from a noncardiovascular (and therefore β-blocker nonmodifiable) rather than a cardiovascular cause may be substantially greater. Our overall findings align with a recent smaller, single-center analysis from Korea, which also demonstrated no significant association between 3-year β-blocker use and all-cause or cardiovascular mortality over the subsequent 5 years.[30] Additionally, our β-blocker dose-stratified analyses expand on previous publications from a much younger post-MI population that have similarly suggested comparable cardiovascular outcomes associated with the use of high (≥50% of target) compared with low (<50% of target) β-blocker doses.[16,17]

Traditional clinical trial designs have resulted in the use of multiple therapeutic classes in post-MI patients. With the emergence of novel and more potent post-MI therapies, deprescription trials, particularly in older patients, have been proposed.[31–34] Suggestions have also been made that in the elderly, cessation rather than continued prescription of certain therapeutic classes (such as psychotropic agents) may paradoxically be associated with improved outcomes.[33,34] In this context, β-blockers are of particular relevance, as there have been concerning suggestions of harm associated with their long-term use in the elderly[35–37]; yet, very little evidence exists to guide deprescription of post-MI therapies particularly in the setting of contemporary MI care.

Our results need to be considered in the context of the following limitations. First, within the observational design of this study, selection bias, and unmeasured confounding is bound to exist, especially with the application of the inclusion criteria used to build our study cohort. For instance, the evaluated patient population consists of about 25% of the initially eligible patients with MI. This is largely because of the selection criteria applied to identify a patient population in whom most equipoise exists on whether β-blockers be continued beyond 3 years in current clinical practice. Additionally, of those excluded were one-fourth of eligible patients without Medicare part D enrollment; as these patients are likely to have confounding clinical characteristics, some degree of bias and confounding is unaccounted for. Additionally, patients studied for this analysis were selected from a specific time frame from the overall duration of the registry; therefore, the impact of this selection bias on the evaluated outcomes is unaccounted for. Furthermore, we were unable to ascertain reasons or timing of β-blocker discontinuation within the first 3 years and, therefore, plausible, that the beneficial duration of post-MI β-blockade may

be much shorter than the currently evaluated 3 years; however, given that Medicare part D only become available in the last year of our study period, the association between post-MI β-blockade and shorter treatment durations could not be evaluated in this study. Second, β-blocker use at 3 years was determined over a 180-day window around the 3-year anniversary and the long-term outcome analyses based on the intention-to-treat principle. Some patients may have discontinued, initiated, or changed β-blocker dose following our evaluation window; however, prescription patterns beyond 3 years, compared with the short-term after hospital discharge, are more likely to be stable and less prone to substantial changes. Additionally, data on heart rate/blood pressure at discharge and during follow-up were unavailable in this registry and would have provided an interesting perspective on the relationship between β-blocker therapy and the evaluated clinical outcomes in this patient population. Finally, our study population consists of post-MI patients ≥65 years of age and, therefore, not generalizable to younger 3-year post-MI survivors.

CONCLUSIONS

Nearly 3 in every 4 post-MI patients ≥65 years of age without a recurrent ischemic event is on a β-blocker at 3 years. However, in this comparative effectiveness analysis, we observed no difference in the frequency of long-term cardiovascular events with β-blocker use beyond 3 years. Randomized evidence is required to define the continued role of post-MI β-blockade beyond 3 years.

ARTICLE INFORMATION

Received August 3, 2018; accepted May 16, 2019.

The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCOUTCOMES.118.005103.

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Disclosures

None.

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