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ORIGINAL ARTICLE
Ischemic Heart Disease

Prognostic Impact of β-Blocker Dose After Acute Myocardial Infarction

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Background: The differential prognostic impact of β-blocker dose after acute myocardial infarction (AMI) has been under debate. The current study sought to compare clinical outcome after AMI according to β-blocker dose using the Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH).

Methods and Results: Of the total population of 13,104 consecutive AMI patients enrolled in the KAMIR-NIH, the current study analyzed 11,909 patients. These patients were classified into 3 groups (no β-blocker; low-dose [<25% of target dose]; and high-dose [≥25% of target dose]). The primary outcome was cardiac death at 1 year. Compared with the no β-blocker group, both the low-dose and high-dose groups had significantly lower risk of cardiac death (HR, 0.435; 95% CI: 0.363–0.521, P<0.001; HR, 0.519; 95% CI: 0.350–0.772, P=0.001, respectively). The risk of cardiac death, however, was similar between the high- and low-dose groups (HR, 1.194; 95% CI: 0.789–1.808, P=0.402). On multivariable adjustment and inverse probability weighted analysis, the result was the same.

Conclusions: The use of β-blockers in post-AMI patients had significant survival benefit compared with no use of β-blockers. There was no significant additional benefit of high-dose β-blockers compared with low-dose β-blockers, however, in terms of 1-year risk of cardiac death.

Key Words: Acute myocardial infarction; Beta-blocker; Outcome; Prognosis

Beta-blockers competitively inhibit circulatory catecholamine effects and decrease heart rate and myocardial contractility, thereby reducing myocardial oxygen demand. Previous randomized controlled trials (RCT) and observational studies reported that β-blockers improve long-term survival after acute myocardial infarction (AMI).[1–8] In this regard, β-blocker therapy has been essentially recommended after AMI in the current guidelines.[9,10] The RCT, however, did not assess the effects of different doses of β-blockers, and no large-scale studies have addressed this issue. Given that the guidelines do not refer to specific β-blockers or their doses, contemporary practice has been based on β-blocker doses evaluated in the previous trials.

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On meta-regression analysis, the clinical benefits of

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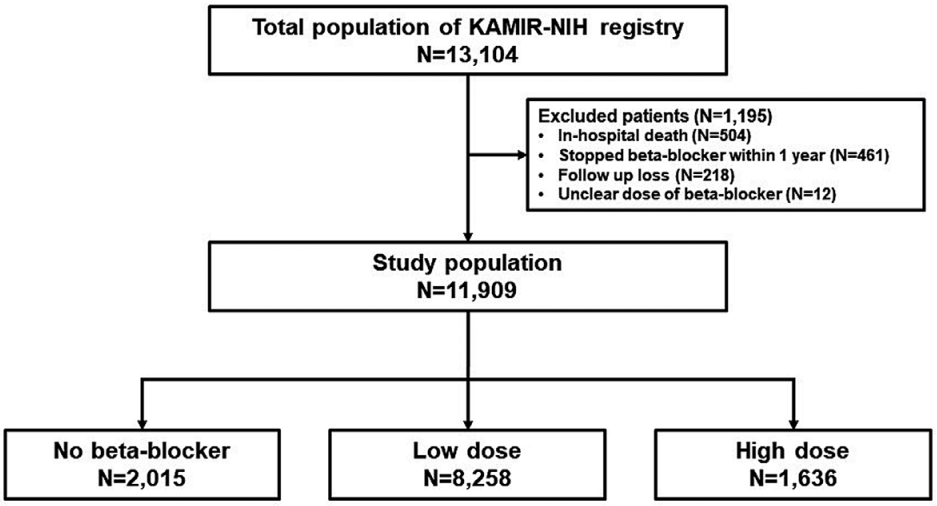

Figure 1. Subject selection. KAMIR-NIH, Korea Acute Myocardial Infarction Registry-National Institutes of Health.

β-blockers were proportional to heart rate reduction, which was dependent on β-blocker dose.[11] This infers that higher doses of β-blockers may be more beneficial than lower doses. In real-world clinical practice, however, actual β-blocker dose is significantly lower than that in RCT.[12,13] Furthermore, 2 recently published, retrospective studies, found no clear relationship between β-blocker dose and mortality after AMI.[14,15] This issue, however, has never been fully evaluated in a prospective setting, hence the clinical benefits of β-blocker under-dosing have not been clarified.

In this regard, the aim of this study was to comprehensively evaluate the differential prognostic impact of β-blockers according to treatment and maintenance doses in post-AMI patients using a large-scale, nationwide, prospective multicenter registry.

Methods

Subjects

Between November 2011 and October 2015, a total of 13,104 consecutive patients with AMI were enrolled in the Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH).[16] The KAMIR-NIH is a Korean nationwide, multicenter, prospective registry evaluating prognosis and surveillance index in post-AMI patients, utilizing 20 tertiary university hospitals capable of performing percutaneous coronary intervention (PCI). A detailed study protocol has been published previously.[16] Briefly, AMI was diagnosed on detection of increased cardiac biomarkers, preferably cardiac troponins, with at least 1 value above the 99th percentile of the upper reference limit, accompanied with at least 1 of the following: symptoms of myocardial ischemia, electrocardiogram (ECG) changes (ST elevation, left bundle branch block, ST change without ST elevation), and imaging suggestive of myocardial infarction (MI; loss of viable myocardium or new regional wall motion abnormality).[9,10,17] There was no exclusion criterion for the KAMIR-NIH other than patient refusal to enroll.

Of the 13,104 consecutive patients enrolled in the KAMIR-NIH, 504 (3.8%) died in hospital, 461 (3.5%) stopped β-blockers before 1 year, 218 (1.7%) were lost to follow-up and 12 (0.01%), whose β-blocker treatment dose was not clear, were excluded from this analysis. Finally, a total of 11,909 patients were included in this study (**Figure 1**). The study protocol was approved by the ethics committee at each participating center and was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent prior to enrollment.

Beta-Blocker Dose Classification

The type and dose of β-blocker were determined by the individual physician. For the purpose of this study, all treatment doses of β-blockers were converted to metoprolol-equivalent dose (**Supplementary Table 1**). Target dose of metoprolol was defined as 200 mg/day based on previous trials.[1,18] Beta-blocker dose was classified as low dose for <25% of metoprolol 200 mg/day, and high dose for ≥25% of metoprolol 200 mg/day.[14,15] All patients included in this study were compliant in maintaining the type and dose of β-blocker up to 1 year after discharge.

Data Collection, Follow-up, and Endpoints

For the KAMIR-NIH, data were collected by independent clinical research coordinators via Web-based case report forms in the Internet-based Clinical Research and Trial management system (iCReaT), a data management system established by the Centers for Disease Control and Prevention, Ministry of Health and Welfare, Republic of Korea (iCReaT Study No. C110016). Standardized definitions for all patient- and lesion-related variables, clinical diagnoses, and clinical events were used. For any clinical event, all relevant medical records were reviewed and adjudicated by an external clinical event adjudication committee. The primary outcome of this study was cardiac death at 1 year. All deaths were considered cardiac unless an undisputed non-cardiac cause was present.[19] Secondary outcomes of this study were MI and repeat revascularization at 1 year. MI was defined as cardiac enzyme (troponin and myocar-

Table 1. Baseline Characteristics vs. β-Blocker Dose

	No β-blocker (n=2,015)	Low dose (n=8,258)	High dose (n=1,636)	P-value
General characteristics				
Age (years)	65.6±12.8	63.3±12.4	62.5±12.7	<0.001
Male	1,469 (72.9)	6,170 (74.7)	1,228 (75.1)	0.206
BMI (kg/m^2)	23.5±3.4	24.0±3.2	24.8±3.4	<0.001
SBP (mmHg)	111.9±16.1	112.4±14.3	118.5±16.5	<0.001
DBP (mmHg)	67.0±9.9	67.7±9.6	70.9±10.9	<0.001
HR (beats/min)	71.9±13.1	70.7±10.0	71.3±10.3	<0.001
EF (%)	52.5±12.1	52.0±10.7	52.7±11.4	0.050
Clinical presentation				
STEMI	768 (38.1)	4,152 (50.3)	722 (44.1)	<0.001
NSTEMI	1,247 (61.9)	4,106 (49.7)	914 (55.9)	
Disease extent				<0.001
1-VD	780 (51.3)	3,992 (51.5)	667 (45.4)	
2-VD	441 (29.0)	2,394 (30.9)	482 (32.8)	
3-VD	299 (19.7)	1,357 (17.5)	321 (21.8)	
Killip class				<0.001
I	1,546 (76.7)	6,658 (80.6)	1,359 (83.1)	
II	175 (8.7)	721 (8.7)	111 (6.8)	
III	178 (8.8)	548 (6.6)	103 (6.3)	
IV	116 (5.8)	331 (4.0)	63 (3.9)	
Cardiovascular risk factors				
Hypertension	971 (48.2)	4,075 (49.3)	1,017 (62.2)	<0.001
DM	526 (26.1)	2,278 (27.6)	552 (33.7)	<0.001
Dyslipidemia	215 (10.7)	896 (10.9)	258 (15.8)	<0.001
Previous MI	180 (8.9)	531 (6.4)	214 (13.1)	<0.001
Previous HF	44 (2.2)	105 (1.3)	33 (2.0)	0.003
Family history	113 (5.6)	513 (6.2)	136 (8.3)	0.002
Procedures				
PCI	1,514 (75.1)	7,733 (93.6)	1,465 (89.5)	<0.001
CABG	44 (2.2)	85 (1.0)	28 (1.7)	
Conservative	457 (22.7)	440 (5.3)	143 (8.7)	
Emergency or urgent PCI	1,196 (59.4)	6,112 (74.0)	1,136 (69.4)	0.397
Medications at discharge				
β-blocker dose (mg)†		18.0±6.6	68.1±39.3	<0.001
Dual antiplatelet	1,997 (99.1)	8,256 (99.9)	1,636 (100)	<0.001
ACEI/ARB	1,099 (54.5)	7,010 (84.9)	1,386 (84.7)	<0.001
Statin	1,734 (86.1)	7,859 (95.2)	1,535 (93.8)	<0.001
CCB	503 (25.0)	317 (3.8)	188 (11.5)	<0.001

Data given as mean±SD or n (%). †Metoprolol-equivalent dose. ACEI/ARB, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; DBP, diastolic blood pressure; DM, diabetes mellitus; EF, ejection fraction; HF, heart failure; HR, heart rate; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; VD, vessel disease.

dial band fraction of creatine kinase) elevation with ischemic symptoms or ECG findings indicative of ischemia not related to the index procedure. Revascularization was considered clinically indicated in the presence of ≥50% diameter stenosis and one of the following: (1) recurrence of angina symptoms; (2) positive non-invasive test; (3) positive invasive physiologic test; or (4) ≥70% diameter stenosis, even in the absence of other criteria. All clinical outcomes were defined in keeping with the Academic Research Consortium criteria.[19,20]

Statistical Analysis

Categorical variables are presented as n (%). Continuous variables are presented as mean±SD or as median (IQR) according to distribution, determined using the Kolmogorov-Smirnov test. Chi-squared test was performed for evaluating non-random associations between categorical variables, and analysis of variance was performed for comparison of continuous variables between the groups. The analysis was performed in 2 parts. First, analysis and comparison of clinical outcomes were conducted in the original patient population. Kaplan-Meier analysis was performed to calculate cumulative incidence of clinical outcome, and the log-rank test was performed for comparison of group differences. Second, sensitivity analysis using multivariable adjusted Cox proportional hazard

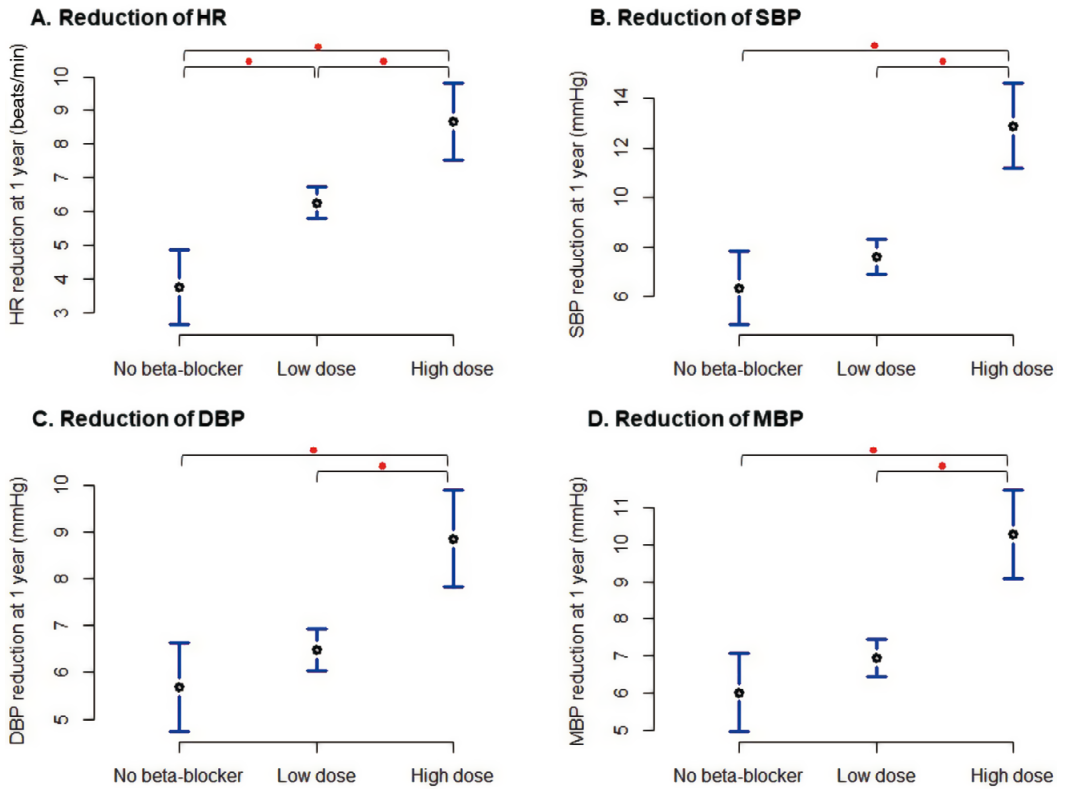

Figure 2. Reduction in (**A**) heart rate (HR), (**B**) systolic blood pressure (SBP), (**C**) diastolic blood pressure (DBP) and (**D**) mean blood pressure (MBP) at 1 year of β-blocker treatment according to β-blocker dose. *P<0.05. Data given as mean±SD.

regression, and inverse probability weighted (IPW) analysis were performed to adjust for the baseline differences between the 3 groups. All analysis was stratified by participating center. The following patient characteristics were included in the multivariable adjusted Cox proportional hazard regression model: age, sex, ST-elevation MI (STEMI), hypertension, diabetes mellitus, dyslipidemia, previous MI, previous heart failure, multivessel disease, Killip class, treatment strategy including emergency or urgent PCI, and discharge medication (dual antiplatelet therapy, angiotensin-converting enzyme inhibitor [ACEI] or angiotensin-receptor blocker [ARB], statin, and calcium channel blocker). For IPW analysis, propensity score using a logistic regression model was calculated incorporating all the measured variables. All probability values were 2-sided, and P<0.05 was considered statistically significant. Statistical package R, version 3.4.0 (Comprehensive R Archive Network) was used for statistical analysis.

Results

Baseline Characteristics

Of the 11,909 patients included in this study, 2,015 patients (16.9%) comprised the no β-blocker group; 8,258 patients (69.3%), the low-dose group; and 1,636 patients (13.7%), the high-dose group (**Figure 1**). **Table 1** lists the baseline characteristics according to β-blocker treatment dose. All variables except sex, left ventricular (LV) ejection fraction, and emergency or urgent PCI were significantly different between the 3 groups (**Table 1**). Distribution of β-blocker type was as follows: bisoprolol, 48.3%; carvedilol, 44.4%; nebivolol, 5.0%; metoprolol, 1.7%; and others, 0.6%.

Beta-Blocker Hemodynamic Effects According to Dose

Figure 2 shows hemodynamic changes at 1 year of prescribed β-blocker treatment. There was a significant dose effect of β-blockers on heart rate reduction (no β-blocker group, 3.7±20.5 beats/min; low-dose group, 6.3±18.8 beats/min and high-dose group, 8.7±19.9 beats/min; P<0.001). The effect on blood pressure reduction was significantly higher only in the high-dose group compared with the no β-blocker and the low-dose groups. The degree of blood pressure reduction was similar between the no β-blocker and the low-dose groups.

Clinical Outcome According to β-Blocker Status

Of the total patients, β-blocker therapy significantly reduced the risk of cardiac death at 1 year (**Figure 3**; **Table 2**). Cumulative incidence of cardiac death in the β-blocker group was significantly lower than in the no β-blocker group (2.6% vs. 5.7%; hazard ratio [HR], 0.449; 95% CI: 0.378–0.533, P<0.001). Multivariable adjustment and IPW analysis also showed consistent results (**Table 2**). Benefit of β-blocker use was consistently found in various subgroups including STEMI with or without LV dysfunction, non-ST-elevation MI, and β-blocker type (**Supplementary Table 2**). Conversely, the risk of MI or repeat revascularization was not significantly reduced by the β-blocker

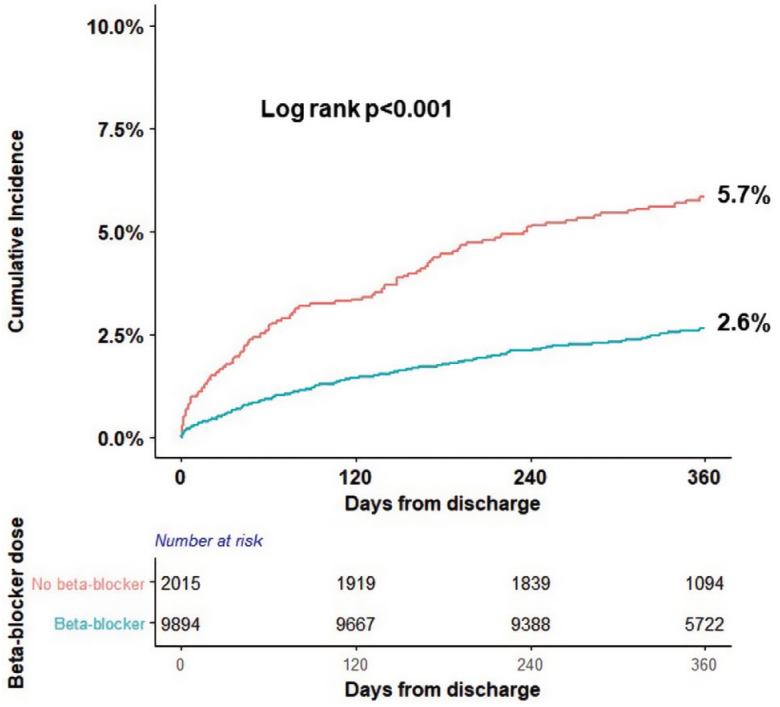

Figure 3. Cumulative incidence of cardiac death according to β-blocker status at 1 year of β-blocker treatment.

Table 2. Risk of Cardiac Death According to β-Blocker Status

	HR (95% CI), P-value
	β-blocker vs. No β-blocker
Unadjusted	0.449 (0.378–0.533), <0.001
Multivariable	0.701 (0.589–0.834), <0.001
IPW	0.755 (0.618–0.922), 0.006

HR, hazard ratio; IPW, inverse probability weighted.

therapy (**Supplementary Table 3**).

Clinical Outcomes According to β-Blocker Dose

Compared with the low-dose β-blocker group, the high-dose β-blocker group was not found to have a reduction in cardiac death (2.5% vs. 3.1%; HR, 1.194; 95% CI: 0.789–1.808, P=0.402). Similar results were also noted on multivariable adjustment and IPW analysis (**Figure 4**; **Table 3**). The lack of significant benefit of high-dose compared with low-dose β-blocker was seen consistently across the various subgroups of older age, obesity, diabetes mellitus, AMI type, LV dysfunction, concomitant use of ACEI or ARB, and β-blocker type (**Table 4**). Similarly, the risk of MI or repeat revascularization was not significantly different between the low-dose and high-dose β-blocker groups (**Supplementary Table 3**).

Discussion

This study evaluated the differential prognostic impact of β-blocker dose in post-AMI patients using a large-scale nationwide, multicenter, prospective dedicated registry for AMI, the KAMIR-NIH. The main findings are as follows. First, there was a significant dose effect of β-blocker on heart rate reduction, but blood pressure was significantly decreased only in the high-dose group. Second, compared with the no β-blocker group, the β-blocker group showed significantly lower risk of cardiac death at 1 year. Third, there was no significant benefit, however, of high-dose compared with low-dose β-blocker therapy for risk of cardiac death. Fourth, the lack of significant benefit of high-dose β-blocker, compared with low-dose β-blocker, was seen consistently in various subgroups.

Beta-Blocker Use After AMI: Current Evidence and Practice

The main effects of β-blockers on the cardiovascular system are reduction in heart rate, myocardial contractility, and blood pressure by inhibiting circulatory catecholamine effects. All of these reductions decrease myocardial oxygen demand, thereby improving myocardial ischemia. The clinical value of β-blockers has been extensively studied in previous RCT and observational studies.[1–7] From these results, current guidelines emphasize the use of β-blockers in post-MI patients who do not have a contraindication for this type of medicine.[9,10,21,22] Recent studies, however, reported no survival benefit of β-blocker therapy in contemporary AMI practice, especially in uncomplicated STEMI patients.[23–25] Therefore, the routine use of β-blocker therapy in all MI patients, especially in uncomplicated STEMI patients, is still controversial. Although the current study has indicated consistent survival benefit of β-blocker compared with the no β-blocker group, even in patients without LV dysfunction, further study is warranted to clarify the role of β-blockers in contemporary practice.

Given that the guidelines do not suggest a specific β-blocker nor a dose, current practice has been based on target doses studied in previous trials. In addition, an association has been confirmed between degree of heart rate reduction and clinical benefit of β-blockers, thereby

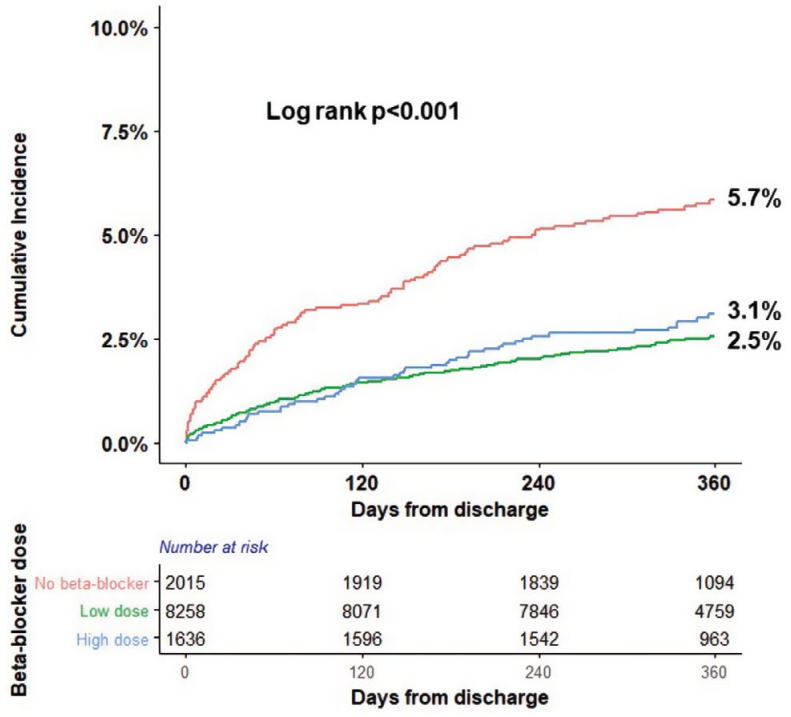

Figure 4. Cumulative incidence of cardiac death according to level of β-blocker dose at 1 year of β-blocker treatment.

Table 3. Risk of Cardiac Death According to β-Blocker Dose

	HR (95% CI), P-value		
	Low-dose vs. No β-blocker	High-dose vs. No β-blocker	High- vs. Low-dose β-blocker
Unadjusted	0.435 (0.363–0.521), <0.001	0.519 (0.350–0.772), 0.001	1.194 (0.789–1.808), 0.402
Multivariable	0.589 (0.496–0.699), <0.001	0.631 (0.415–0.959), 0.031	1.072 (0.696–1.652), 0.753
IPW	0.755 (0.620–0.920), 0.005	0.727 (0.529–0.998), 0.049	1.077 (0.635–1.827), 0.782

HR, hazard ratio; IPW, inverse probability weighted.

Table 4. Risk of Cardiac Death for High- vs. Low-Dose β-Blocker

	Unadjusted			Multivariable			IPW		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Age ≥70 years	1.379	0.998–1.906	0.051	1.174	0.843–1.637	0.343	1.222	0.790–1.892	0.367
Age <70 years	0.812	0.356–1.851	0.620	0.580	0.322–1.044	0.069	0.541	0.276–1.062	0.074
BMI ≥25 kg/m²	1.605	0.847–3.040	0.147	1.430	0.818–2.502	0.210	1.399	0.759–2.578	0.282
BMI <25 kg/m²	1.211	0.774–1.895	0.403	1.012	0.641–1.597	0.960	1.072	0.593–1.941	0.817
DM	0.969	0.605–1.552	0.895	0.795	0.537–1.177	0.252	0.931	0.568–1.526	0.778
No DM	1.307	0.823–2.078	0.257	1.369	0.836–2.239	0.212	1.200	0.651–2.213	0.559
STEMI	1.308	0.645–2.652	0.457	1.311	0.611–2.815	0.487	1.314	0.562–3.075	0.528
NSTEMI	1.082	0.766–1.528	0.657	0.969	0.686–1.369	0.860	0.958	0.623–1.474	0.847
EF ≤40%	1.137	0.682–1.897	0.623	1.151	0.692–1.915	0.589	0.982	0.569–1.696	0.949
EF >40%	1.204	0.742–1.953	0.452	1.019	0.604–1.721	0.943	1.124	0.749–1.684	0.573
ACEI/ARB	1.138	0.694–1.869	0.608	0.998	0.609–1.637	0.995	1.097	0.600–2.005	0.764
No ACEI/ARB	1.395	0.679–2.865	0.365	1.224	0.595–2.522	0.583	1.012	0.493–2.076	0.974
Lipid-soluble β-blocker	1.194	0.789–1.809	0.402	1.050	0.709–1.555	0.808	1.077	0.635–1.827	0.782
Carvedilol	1.250	0.699–2.235	0.452	0.978	0.581–1.646	0.932	1.014	0.514–2.001	0.969
Bisoprolol	2.015	1.458–2.785	<0.001	1.609	0.888–2.913	0.117	1.837	0.994–3.393	0.052

Abbreviations as in Tables 1,2.

inferring that high-dose β-blockers may be more beneficial than low-dose β-blockers.[1,11] In real world practice, however, most patients have been prescribed relatively low doses of β-blockers at discharge, and the target dose of β-blockers was achieved in only 32% of patients during follow-up.[13] The reasons for β-blocker under-dosing were intolerable subjective symptoms, such as depression, headache or fatigue; hypotension; bradycardia; atrioventricular block; and combined airway disease.[13]

Recently, 2 retrospective studies were performed to assess the effects of β-blocker dose on clinical outcomes after AMI. Goldberger et al evaluated 6,682 consecutive AMI patients and reported that β-blockers significantly decreased the risk of all-cause death, regardless of β-blocker dose, but that higher doses of β-blocker were not associated with further decreased risk of all-cause mortality at 2 years compared with low doses.[14] Allen et al also evaluated the relationship between β-blocker dose and clinical outcome in 5,287 AMI patients and reported that the rates for major adverse cardiac events between high- and low-dose β-blockers were similar.[15] Although previous studies included relatively large populations and adjusted baseline characteristics using adequate statistical methods, these were retrospective studies, which were not free from bias, leaving the clinical benefit of β-blocker under-dosing under debate.

Beta-Blocker Dose and Clinical Outcome

In comparing the hemodynamic changes, the effect of β-blockers on heart rate reduction was prominent, not only in the low-dose but also in the high-dose β-blocker groups. Although the hemodynamic effects of β-blockers were significantly different between the low- and high-dose β-blocker groups, the rate of cardiac death was similar between the 2 groups. Furthermore, the lack of benefit in the high-dose group was seen consistently in various subgroups such as older age, obesity, diabetes mellitus, AMI type, LV dysfunction, combined use of ACEI/ARB, and β-blocker type. Although study-level meta-regression analysis has shown a significant association between lowered heart rate and decreased cardiac mortality,[11] we could not find an increased benefit of high-dose β-blocker therapy for 1-year cardiac mortality in the present study, despite significant heart rate reduction. The previous meta-regression should be interpreted with caution, given that patient-level confounders could not be adjusted for in the study-level meta-regression. Considering that the current study evaluated consecutive, prospectively enrolled patients with similar sample size, the current results should be considered more robust.

Some possible explanations can be considered to explain the lack of increased benefit of high-dose β-blocker therapy despite significant hemodynamic changes. First, there is a possible threshold in β-blocker effective dose instead of target dose from previous trials. Second, other mechanisms for the benefit of β-blockers other than hemodynamic effects can be considered. Beta-blockers also have anti-arrhythmic, antioxidative, anti-inflammatory, and neurohormonal regulatory effects.[25–27] These actions of β-blockers, beyond the hemodynamic changes, can affect cardiac remodeling, reduce the incidence of fatal arrhythmia after AMI, and improve clinical outcomes after AMI.[25–27] Given that the current study was not randomized, the possibility of unmeasured confounders should be considered even with the multiple sensitivity analysis. Nevertheless, previous observational studies, including the current one, consistently showed insufficient evidence to support the increased benefit of higher dose β-blocker therapy.[14,15] Further study is warranted to clarify this issue.

Clinical Implications

This study evaluated the largest AMI population from a nationwide dedicated multicenter registry. Even after adjusting for multiple patient-level confounders, β-blockers produced significant survival benefit compared with no β-blockers. High-dose β-blockers, however, did not have an increased benefit compared with low-dose β-blockers, despite significant hemodynamic changes. These results are important for daily routine practice, given that most AMI patients are taking under-dosed β-blockers compared with previous RCT. Considering that the β-blocker dose in the present low-dose group was relatively much lower than that used in the previous trials, further study to confirm the optimal β-blocker dose for improved clinical outcome is warranted.

Study Limitations

This study had several limitations. First, the inherent limitation of a non-randomized controlled study should be considered. Although we performed multiple sensitivity analyses, the possibility of unobserved confounders should be considered. Second, multiple types of β-blockers were used in the current study and we converted the dose of all types of β-blockers to a metoprolol-equivalent dose. A total of 92.7% of patients in the β-blocker group, however, took carvedilol or bisoprolol, and subgroup analyses according to these types of β-blocker showed the same results.

Conclusions

The use of β-blockers in post-AMI patients produced significant survival benefit compared with no use of β-blockers. There was no significant additional benefit, however, of high-dose compared with low-dose β-blocker therapy in terms of 1-year cardiac death.

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Disclosures

The authors declare no conflicts of interest.

References

1. Hjalmarson A, Elmfeldt D, Herlitz J, Holmberg S, Malek I, Nyberg G, et al. Effect on mortality of metoprolol in acute myocardial infarction: A double-blind randomised trial. *Lancet* 1981; **2:** 823–827.
2. Goldstein S. Propranolol therapy in patients with acute myocardial infarction: The Beta-Blocker Heart Attack Trial. *Circulation* 1983; **67:** I53–I57.
3. 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:** 1589–1595.
4. Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta blockade after myocardial infarction: Systematic review and meta regression analysis. *BMJ* 1999; **318:** 1730–1737.
5. 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:** 489–497.
6. Krumholz HM, Radford MJ, Wang Y, Chen J, Heiat A,

Marciniak TA. National use and effectiveness of beta-blockers for the treatment of elderly patients after acute myocardial infarction: National Cooperative Cardiovascular Project. *JAMA* 1998; **280:** 623–629.
7. Soumerai SB, McLaughlin TJ, Spiegelman D, Hertzmark E, Thibault G, Goldman L. Adverse outcomes of underuse of beta-blockers in elderly survivors of acute myocardial infarction. *JAMA* 1997; **277:** 115–121.
8. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: The CAPRICORN randomised trial. *Lancet* 2001; **357:** 1385–1390.
9. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; **64:** e139–e228.
10. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, 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. *Circulation* 2013; **127:** e362–e425.
11. 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:** 3012–3019.
12. Goldberger JJ, Bonow RO, Cuffe M, Dyer A, Rosenberg Y, O'Rourke R, et al. Beta-blocker use following myocardial infarction: Low prevalence of evidence-based dosing. *Am Heart J* 2010; **160:** 435–442.e431.
13. Arnold SV, Spertus JA, Masoudi FA, Daugherty SL, Maddox TM, Li Y, et al. Beyond medication prescription as performance measures: Optimal secondary prevention medication dosing after acute myocardial infarction. *J Am Coll Cardiol* 2013; **62:** 1791–1801.
14. Goldberger JJ, Bonow RO, Cuffe M, Liu L, Rosenberg Y, Shah PK, et al. Effect of beta-blocker dose on survival after acute myocardial infarction. *J Am Coll Cardiol* 2015; **66:** 1431–1441.
15. Allen JE, Knight S, McCubrey RO, Bair T, Muhlestein JB, Goldberger JJ, et al. Beta-blocker dosage and outcomes after acute coronary syndrome. *Am Heart J* 2017; **184:** 26–36.
16. Kim JH, Chae SC, Oh DJ, Kim HS, Kim YJ, Ahn Y, et al. Multicenter cohort study of acute myocardial infarction in Korea: Interim analysis of the Korea Acute Myocardial Infarction Registry-National Institutes of Health Registry. *Circ J* 2016; **80:** 1427–1436.
17. Hwang D, Kim HK, Lee JM, Choi KH, Kim J, Rhee TM, et al. Effects of statin intensity on clinical outcome in acute myocardial infarction patients. *Circ J* 2018; **82:** 1112–1120.
18. The MIAMI Trial Research Group. Metoprolol in acute myocardial infarction (MIAMI): A randomised placebo-controlled international trial. *Eur Heart J* 1985; **6:** 199–226.
19. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: A case for standardized definitions. *Circulation* 2007; **115:** 2344–2351.
20. Stefanini GG, Serruys PW, Silber S, Khattab AA, van Geuns RJ, Richardt G, et al. The impact of patient and lesion complexity on clinical and angiographic outcomes after revascularization with zotarolimus- and everolimus-eluting stents: A substudy of the RESOLUTE All Comers Trial (a randomized comparison of a zotarolimus-eluting stent with an everolimus-eluting stent for percutaneous coronary intervention). *J Am Coll Cardiol* 2011; **57:** 2221–2232.
21. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; **33:** 2569–2619.
22. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016; **37:** 267–315.
23. Chen ZM, Pan HC, Chen YP, Peto R, Collins R, Jiang LX, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: Randomised placebo-controlled trial. *Lancet* 2005; **366:** 1622–1632.
24. Bangalore S, Makani H, Radford M, Thakur K, Toklu B, Katz SD, et al. Clinical outcomes with beta-blockers for myocardial infarction: A meta-analysis of randomized trials. *Am J Med* 2014; **127:** 939–953.
25. Galli A, Lombardi F. Postinfarct left ventricular remodelling: A prevailing cause of heart failure. *Cardiol Res Pract* 2016; **2016:** 2579832.
26. Kopecky SL. Effect of beta blockers, particularly carvedilol, on reducing the risk of events after acute myocardial infarction. *Am J Cardiol* 2006; **98:** 1115–1119.
27. Bhatt AS, Ambrosy AP, Velazquez EJ. Adverse remodeling and reverse remodeling after myocardial infarction. *Curr Cardiol Rep* 2017; **19:** 71.

Supplementary Files

Please find supplementary file(s);
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