ORIGINAL RESEARCH

Benefit of Vasodilating β-Blockers in Patients With Acute Myocardial Infarction After Percutaneous Coronary Intervention: Nationwide Multicenter Cohort Study

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Background—Although current guidelines recommend β-blocker after acute myocardial infarction (MI), the role of β-blocker has not been well investigated in the modern reperfusion era. In particular, the benefit of vasodilating β-blocker over conventional β-blocker is still unexplored.

Methods and Results—Using nation-wide multicenter Korean Acute Myocardial Infarction Registry data, we analyzed clinical outcomes of 7127 patients with acute MI who underwent successful percutaneous coronary intervention with stents and took β-blockers: vasodilating β-blocker (n=3482), and conventional β-blocker (n=3645). In the whole population, incidence of cardiac death at 1 year was significantly lower in the vasodilating β-blocker group (vasodilating β-blockers versus conventional β-blockers, 1.0% versus 1.9%; *P*=0.003). In 2882 pairs of propensity score–matched population, the incidence of cardiac death was significantly lower in the vasodilating β-blocker group (1.1% versus 1.8%; *P*=0.028). Although incidences of MI (1.1% versus 1.5%; *P*=0.277), any revascularization (2.8% versus 3.0%; *P*=0.791), and hospitalization for heart failure (1.4% versus 1.9%; *P*=0.210) were not different between the 2 groups, incidences of cardiac death or MI (2.0% versus 3.1%; *P*=0.010), cardiac death, MI, or hospitalization for heart failure (3.0% versus 4.5%; *P*=0.003), cardiac death, MI, or any revascularization (3.9% versus 5.3%; *P*=0.026), and cardiac death, MI, any revascularization, or hospitalization for heart failure (4.8% versus 6.5%; *P*=0.011) were significantly lower in the vasodilating β-blocker group.

Conclusions—Vasodilating β-blocker therapy resulted in better clinical outcomes than conventional β-blocker therapy did in patients with acute MI in the modern reperfusion era. Vasodilating β-blockers could be recommended preferentially to conventional ones for acute MI patients. **(*J Am Heart Assoc*. 2017;6:e007063. DOI: 10.1161/JAHA.117.007063.)**

Key Words: acute myocardial infarction • beta-blocker • cohort study • prognosis • propensity score

β-blocker therapy after acute myocardial infarction (AMI) decreases myocardial oxygen demand, inhibits fatal arrhythmias, and improves ventricular remodeling.[1] Because of these beneficial features, β-blockers have long been regarded as a first-line treatment option in patients with AMI. The current American College of Cardiology

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Accompanying Tables S1 through S3 and Figure S1 are available at http://jaha.ahajournals.org/content/6/10/e007063/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Vasodilating β-blocker therapy in acute myocardial infarction patients was associated with significantly lower risk of cardiac death or other composite events, compared with conventional β-blocker therapy in the modern reperfusion era.

What Are the Clinical Implications?

- Current recommendations for β-blocker therapy in acute myocardial infarction patients are largely based on the studies performed in the prereperfusion era.
- With future large-scale randomized controlled trials, guidelines for acute myocardial infarction would be revised to recommend vasodilating β-blockers as a first-line choice over conventional β-blockers.

Foundation/American Heart Association guideline for ST-segment elevation myocardial infarction (STEMI) and non-ST-elevation acute coronary syndromes recommends β-blockers be initiated and continued for all patients without contraindications as a Class I recommendation.[2,3] However, this recommendation is based on outdated studies in the prereperfusion era. In the reperfusion era, there are only limited and controversial data for β-blockers.[4,5] For this reason, the current European Society of Cardiology guideline no longer recommends β-blockers for all STEMI patients without contraindications as a Class I recommendation, but instead as a Class IIa recommendation.[6] Of note, β-blockers are not all the same. In particular, β-blockers can be classified into vasodilating β-blockers, such as carvedilol and nebivolol, and conventional β-blockers, such as bisoprolol and metoprolol, depending on their vasodilating properties. Conventional β-blockers possess some distinct characteristics: central blood pressure elevation and metabolic derangement.[7–9] However, vasodilating β-blockers do not share these potentially harmful characteristics.[10,11] Vasodilating β-blockers improves coronary flow reserve, maintain cardiac index, reduce peripheral vascular resistance, less impact on insulin sensitivity, and improves dyslipidemia.[12,13] Accordingly, vasodilating β-blockers may be associated with better long-term outcomes, although few clinical trials have been performed for this comparison. In particular, there has been so far no study which evaluates the differential efficacy of vasodilating over conventional β-blockers in patients with AMI. In this study, we therefore sought to assess the efficacy of vasodilating β-blockers in AMI in the modern reperfusion era, compared with that of conventional β-blockers.

Methods

Study Population and Study Design

This study analyzed the data from the Korean Acute Myocardial Infarction Registry, which is a nation-wide multicenter registry of patients with AMI in Korea as previously described.[14] From November 2011 to November 2015, 13 019 consecutive patients with AMI were enrolled in this registry. Among these, we excluded the patients: (1) who died in hospital (n=503); (2) who were discharged without hope (n=50); (3) who were not prescribed any β-blocker at discharge (n=2040); (4) who were prescribed a β-blockers different from the following (carvedilol, nebivolol, bisoprolol, and metoprolol) at discharge (n=84); (5) who did not revisit the hospital after discharge (n=1332); (6) whose prescribed β-blocker was changed to a different class β-blocker (from vasodilating to conventional, or vice versa) or stopped β-blocker during follow-up (n=841); (7) who did not undergo coronary angiography (n=76); (8) who had no significant lesion on coronary angiography (n=449); (9) who underwent coronary artery bypass graft (n=85); (10) who underwent thrombolysis (n=17); (11) who failed percutaneous coronary intervention (PCI) (n=14); or (12) who underwent only plain old balloon angioplasty (n=477). Therefore, 7127 patients were included in this study (Figure 1). Subjects were divided into a vasodilating β-blocker group (carvedilol, n=3198; nebivolol, n=284) and a conventional β-blocker group (bisoprolol, n=3516; metoprolol, n=129), according to the type of β-blocker prescribed at discharge and maintained during follow-up. Because there were few patients (n=84) who were prescribed other β-blockers, such as atenolol, amosulalol, arotinolol, betaxolol, and propranolol, and many were changed to other β-blockers during follow-up, those patients were excluded in the analysis. Because we aimed to evaluate long-term efficacy of vasodilating β-blocker and in-hospital death was mainly affected by patients' initial presentation rather than which kinds of β-blocker was used, patients who died during index hospitalization were excluded. Among the 503 patients who died in-hospital, only 44 patients took the lowest dose of β-blockers (conventional β-blocker, n=27; vasodilating β-blocker, n=17) during hospitalization because most of them were in a cardiogenic shock state. Our study was conducted according to the Declaration of Helsinki. The study protocol was approved by the institutional review board of all centers, and written informed consent was obtained from all patients. Of the 7127 study patients, 5655 (79.35%) completed 1-year follow-up.

PCI Procedure

Coronary interventions were performed according to current standard procedural guidelines. All patients received a

300-mg loading dose of aspirin and a 300- to 600-mg loading dose of clopidogrel, a 60-mg loading dose of prasugrel, or a 180-mg loading dose of ticagrelor before PCI, unless they had previously received these antiplatelet drugs. During the PCI, anticoagulation with weight-adjusted unfractionated heparin was performed. The treatment strategy, use of glycoprotein IIb/IIIa receptor inhibitors or intravascular ultrasound, and choice of the specific type of drug-eluting stent were left to the operator's discretion. Coronary flow pre-PCI and post-PCI was evaluated according to the Thrombolysis in Myocardial Infarction grading system. Coronary lesions were classified according to the American College of Cardiology/American Heart Association classification system.

Definitions and Outcomes

All deaths were considered to be associated with cardiac problems, unless a definite noncardiac cause could be established. Recurrent myocardial infarction (MI) were recurrent symptoms of ischemia with new electrocardiographic changes compatible with MI or elevated cardiac enzymes at least 2-fold above the normal limit. Any revascularization was defined as revascularization on either target or nontarget vessels with PCI or coronary artery bypass graft. The primary outcome was cardiac death at 1 year. Secondary outcomes were recurrent MI, any revascularization, hospitalization for heart failure (HF), composite of cardiac death or MI, composite of cardiac death, MI, or hospitalization for HF, composite of cardiac death, MI, or any revascularization, and composite of cardiac death, MI, any revascularization or hospitalization for HF at 1 year. Clinical follow-up was routinely performed at 6 and 12 months by visiting the hospital and whenever any clinical event occurred. Clinical events were not centrally adjudicated in this registry. The patient's physician identified all events and the principal investigator of each hospital confirmed them.

Statistical Analysis

Results are expressed as the mean±SD for continuous variables and as percentage for categorical variables. Continuous variables were analyzed with the *t* test or Mann–Whitney *U* test. Categorical data were analyzed with Pearson's chi-square test. Survival curves for study end points were constructed using Kaplan–Meier estimates and compared with the log-rank test. The Cox proportional hazard model was used to compare the hazard ratio (HR) for each end point in the use of vasodilating β-blockers and use of conventional β-blockers. To adjust potential confounders, we did multivariable Cox regression analysis. Chi-square statistics and −2log likelihood were used to find suitable variables for the multivariable model. Log minus log plot was drawn to check proportional assumption of Cox proportional hazard model, and there was no violation of proportional assumption. We also checked multicollinearity of variables, and there was no multicollinearity between variables included in the model. In the multivariable Cox regression analysis age, sex, hypertension, diabetes mellitus, dyslipidemia, HF, cerebrovascular disease, current or ex-smoking, chronic kidney disease over stage 3, left main or left anterior descending as infarct-related artery, multivessel disease, left ventricular ejection fraction, STEMI or non-STEMI, use of renin-angiotensin system blockade, and use of statin were included as covariates that were significant on univariable analysis and those that are generally considered clinically relevant.

Because β-blocker strategy was not randomized, a propensity score was used to adjust selection or predisposition bias. The propensity score was estimated using multiple logistic regression analysis, with all variables shown in Table S1. According to propensity score, patients were selected by 1:1 matching without replacement by greedy algorithm and nearest available pair matching methods. A calliper width of 0.1 SD of the logit of the estimated propensity score was used for matching. The covariate balance achieved by propensity score matching was assessed by calculating the absolute standardized differences in covariates between the 2 groups. All analyses were 2-tailed, and clinical significance was defined as $P<0.05$. All statistical analyses were performed with the statistical package SPSS (V.20.0; IBM Co, Armonk, NY) and R programming language (V.2.12.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

Whole population

Baseline clinical characteristics are shown in Table S1. The overall mean age of study patients was 62.7±12.4 years. Males were 5405 (75.8%) patients and STEMI were 3790 (53.2%) patients. Among 7127 eligible patients, 3482 (48.9%) took vasodilating β-blockers, whereas 3645 (51.1%) took conventional β-blockers. There were significant differences in baseline characteristics between the 2 groups. As shown in Table S1, 2 groups were a little bit different from one another in terms of frequency in sex, smoker, comorbidities (diabetes mellitus, hypertension, chronic kidney disease), medications, STEMI, and degree of left ventricular (LV) function. However, there was no significant difference between the 2 groups in angiographic and procedural characteristics (Table S2).

Propensity score–matched population

A total of 2882 matched pairs of patients were created after performing propensity score matching for all patients. The

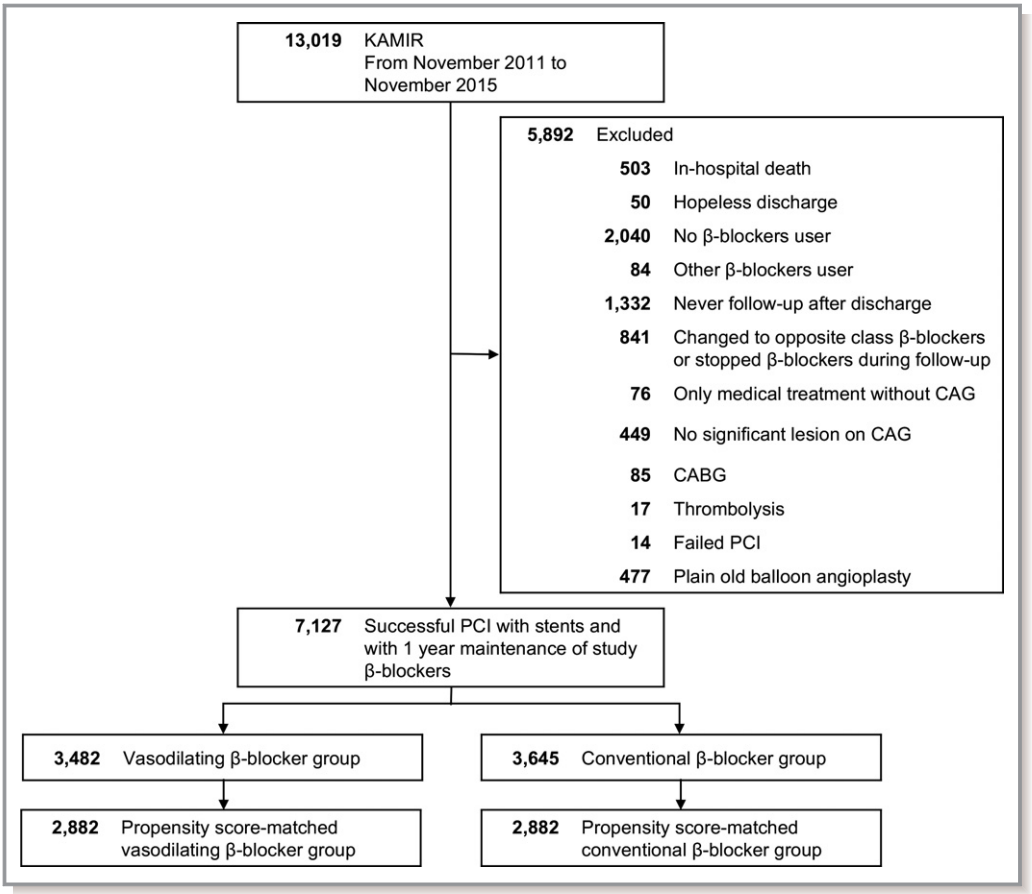

Figure 1. Flow chart of group distribution for analysis. The propensity score was estimated with all variables shown in Table 1. CABG indicates coronary artery bypass graft; CAG, coronary angiography; KAMIR, Korean Acute Myocardial Infarction Registry; PCI, percutaneous coronary intervention.

C-statistic for the propensity score model was 0.524, suggesting that use of conventional or vasodilating β-blockers were relatively random. The *P* value of Hosmer–Lemeshow goodness of fit for the propensity score model was 0.824. There was no significant difference in baseline characteristics between the 2 groups, and absolute standardized differences were <10.0% in all covariates in the propensity-matched patients. The baseline characteristics of propensity-matched patients are shown in Tables 1 and 2.

Clinical Outcomes

Whole population

Median follow-up duration was 371 days (interquartile range, 258–400). In survival analysis, the incidence of cardiac death was significantly lower in the vasodilating β-blocker group (vasodilating β-blockers versus conventional β-blockers, 1.0% versus 1.9%; log rank, *P*=0.003; Figure S1 and Table S3). In secondary outcomes of each component, the incidences of MI (1.1% versus 1.6%; log rank, *P*=0.146), any revascularization (3.0% versus 3.0%; log rank, *P*=0.783), or hospitalization for HF (1.7% versus 2.1%; log rank, *P*=0.279) were not different between the 2 groups. However, the composite rates of cardiac death, or MI (2.0% versus 3.3%; log rank, *P*=0.001), cardiac death, MI, or hospitalization for HF (3.2% versus 4.8%; log rank, *P*=0.002), cardiac death, MI, or any revascularization (4.1% versus 5.3%; log rank, *P*=0.041), or cardiac death, MI, any revascularization, or hospitalization for HF (5.2% versus 6.7%; log rank, *P*=0.022) were significantly lower in the vasodilating β-blocker group (Figure S1 and Table S3). On multivariable Cox regression analysis, the use of vasodilating β-blockers was an independent predictor of cardiac death at 1 year (adjusted HR, 0.65; 95% confidence interval [CI], 0.43–0.98; *P*=0.039) after adjustment of potential confounding factors (Table S3). Among factors that were used in multivariable Cox regression analysis, the independent predictors for cardiac death at 1 year besides vasodilating β-blockers were age (HR, 1.06 per 1-year older; 95% CI, 1.04–1.09), HF (HR, 3.47; 95% CI, 1.49–8.08), chronic kidney disease over stage 3 (HR, 2.07; 95% CI, 1.33–3.21), LVEF (HR, 0.96 per 1% higher; 95% CI, 0.95–0.98), and non-STEMI (HR, 1.59; 95% CI, 1.05–2.42).

Table 1. Baseline Clinical Characteristics of Propensity Score–Matched Population According-Treatment At Discharge

Variables	Vasodilating β-Blockers (n=2882)	Conventional β-Blockers (n=2882)	*P* Value	Standardized Difference
Demographics				
Age, mean (SD), y	62.4 (12.4)	62.5 (12.4)	0.684	1.1
Male (%)	2208 (76.6)	2207 (76.7)	0.975	0.1
Coronary risk factors (%)				
Diabetes mellitus	739 (25.6)	760 (26.4)	0.528	1.7
Hypertension	1428 (49.5)	1451 (50.3)	0.545	1.6
Dyslipidemia	321 (11.1)	318 (11.0)	0.900	0.3
Current or ex-smoking	1807 (62.7)	1783 (61.9)	0.514	1.7
Chronic kidney disease	427 (14.8)	435 (15.1)	0.768	0.8
Family history of CAD	202 (7.0)	198 (6.9)	0.836	0.6
Previous medical history (%)				
History of CVA	163 (5.7)	169 (5.9)	0.734	0.9
History of MI	148 (5.1)	147 (5.1)	0.952	0.2
History of angina	193 (6.7)	188 (6.5)	0.791	0.7
History of PCI	206 (7.1)	202 (7.0)	0.837	0.5
History of CABG	14 (0.5)	13 (0.5)	0.847	0.4
History of heart failure	26 (0.9)	24 (0.8)	0.776	0.7
Clinical characteristics at presentation and in-hospital (%)				
Killip class ≥III on admission	251 (8.7)	254 (8.8)	0.889	0.4
STEMI	1567 (54.4)	1533 (53.2)	0.369	2.4
Mean (SD) left ventricular ejection fraction	52.1 (10.4)	52.4 (10.2)	0.267	2.9
Medication at discharge (%)				
Aspirin	2877 (99.8)	2880 (99.9)	0.257	2.2
Clopidogrel	2209 (76.6)	2230 (77.4)	0.511	1.7
Prasugrel	407 (14.1)	423 (14.7)	0.548	1.6
Cilostazol	296 (10.3)	307 (10.7)	0.636	1.3
Tichlopidine	6 (0.2)	7 (0.2)	0.781	0.8
Ticagrelor	671 (23.3)	630 (21.9)	0.196	3.3
RAS blockade	2510 (87.1)	2549 (88.4)	0.117	3.7
Statins	2762 (95.8)	2768 (96.0)	0.689	1.1

Figures are numbers (percentage) of patients, unless stated otherwise. CABG indicates coronary artery bypass graft; CVA, cerebrovascular accident; MI, myocardial infarction; PCI, percutaneous coronary intervention; RAS, renin-angiotensin system; STEMI, ST-segment elevation MI.

Propensity-matched patients

In a 1:1 propensity score–matched population, cardiac death within 1 year occurred significantly less frequently in the vasodilating β-blocker group (1.1% versus 1.8%; log rank, *P*=0.028; number needed to treat [NNT]=142.9) as in the whole population (Figure 2 and Table 3). In secondary outcomes of each component, the difference between the 2 groups was not statistically significant in the incidences of MI (1.1% versus 1.5%; log rank, *P*=0.277), any revascularization (2.8% versus 3.0%; log rank, *P*=0.791), or hospitalization for HF (1.4% versus 1.9%; log rank, *P*=0.210), although each incidence was numerically lower in the vasodilating β-blocker group. However, the composite incidences of cardiac death, or MI (2.0% versus 3.1%; log rank, *P*=0.010; NNT=90.9), cardiac death, MI, or hospitalization for HF (3.0% versus 4.5%; log rank, *P*=0.003; NNT=66.7), cardiac death, MI, or any revascularization (3.9% versus 5.3%; log rank, *P*=0.026; NNT=71.4), or cardiac death, MI, any revascularization, or hospitalization for HF (4.8% versus 6.5%; log rank, *P*=0.011; NNT=58.8) were significantly lower in the vasodilating β-blocker group (Figure 2 and Table 3). On multivariable Cox regression analysis, vasodilating β-blocker use was an

Table 2. Angiographic and Procedural Characteristics of Propensity Score–Matched Population According-Treatment at Discharge

Variables	Vasodilating β-Blockers (n=2882)	Conventional β-Blockers (n=2882)	*P* Value	Standardized Difference
Glycoprotein IIb/IIIa inhibitor	417 (14.5)	417 (14.5)	1.000	0.0
LM or LAD infarct-related artery	1453 (50.4)	1457 (50.6)	0.916	0.3
ACC/AHA B2/C lesion	2509 (87.1)	2508 (87.0)	0.969	0.1
Preprocedural TIMI flow grade 0 to 1	1642 (57.0)	1626 (56.4)	0.671	1.1
Postprecedural TIMI flow grade 3	2817 (97.7)	2813 (97.6)	0.727	0.9
Mean (SD) maximal stent diameter (mm)	3.18 (0.45)	3.18 (0.45)	0.953	0.2
Mean (SD) total stent length (mm)	29.5 (14.2)	29.7 (14.1)	0.590	1.4
Multivessel coronary artery disease	1456 (50.5)	1440 (50.0)	0.673	1.1
Vasopressor	138 (4.8)	137 (4.8)	0.951	0.2
Intra-aortic balloon pump	65 (2.3)	61 (2.1)	0.719	0.9
Temporary pacemaker	110 (3.8)	108 (3.7)	0.890	0.4
Defibrillator/cardioversion	83 (2.9)	83 (2.9)	1.000	0.0

Figures are numbers (percentage) of patients unless stated otherwise. ACC/AHA indicates American College of Cardiology/American Heart Association; LAD, left anterior descending; LM, left main; TIMI, thrombolysis in myocardial infarction.

independent predictor of cardiac death at 1 year (adjusted HR, 0.63; 95% CI; 0.41–0.98; *P*=0.042) after adjustment of the same covariates in the whole population (Table 3). Among the factors used in multivariable Cox regression analysis, the independent predictors of cardiac death at 1 year besides use of vasodilating β-blockers were age (HR, 1.07 per 1 year older; 95% CI, 1.04–1.09), HF (HR, 3.93; 95% CI, 1.68–9.23), chronic kidney disease over stage 3 (HR, 2.10; 95% CI, 1.29–3.42), left ventricular ejection fraction (HR, 0.97 per 1% higher; 95% CI, 0.95–0.99), and non-STEMI (HR, 1.91; 95% CI, 1.20–3.03).

Subgroup Analysis of Cardiac Death

To determine whether the outcomes according to vasodilating β-blocker therapy in the propensity-matched population were consistent, we calculated unadjusted HR for cardiac death in various subgroups. There were no significant interactions between the use of vasodilating β-blockers and cardiac death in any of the subgroup (Figure 3). Of note, the beneficial effect of vasodilating β-blockers was not affected by the mode of MI (STEMI or NSTEMI) or the presence of LV dysfunction.

Discussion

This study was based on a nation-wide multicenter registry and showed that the use of vasodilating β-blockers was associated with better 1-year cardiac mortality in patients with AMI who underwent PCI than use of nonvasodilating β-blockers. Our study results were consistent across univariable, multivariable, and propensity-matched analysis. Furthermore, these beneficial effects of vasodilating β-blockers were consistently observed across various subgroups. The C-statistic of multivariable cox model for cardiac death was 0.65 (95% CI, 0.58–0.72; *P*<0.001).

Although β-blocker therapy has long been regarded as the standard of care for patients with AMI, this notion is largely based on the studies performed in the prereperfusion era. One study performed in 1985 showed that timolol in patients surviving AMI reduced the mortality and rate of reinfarction in a 17-month follow-up.[15] The BHAT (β-Blocker Heart Attack Trial) in 1982 demonstrated that treatment with propranolol was associated with improved survival.[16] In the MIAMI (Metoprolol in Acute Myocardial Infarction) trial in 1985, treatment with metoprolol for 15 days resulted in mortality reduction for high-risk patients.[17] In the ISIS-1 (First International Study of Infarct Survival) trial, atenolol therapy for 7 days showed mortality benefits.[18] A meta-analysis in 1999 that mostly included studies in the prereperfusion era demonstrated that long-term β-blocker therapy for more than 6 months was associated with mortality reduction.[19] However, in the reperfusion era, few randomized, controlled trials have considered this issue. In the CAPRICORN (Carvedilol Post-Infarct Survival Control in LV Dysfunction) trial in 2001, 1959 patients with MI who had LV dysfunction were treated with a titrated dose of carvedilol.[5] Almost half of the enrolled patients underwent thrombolysis or primary angioplasty. At a median follow-up of 1.3 years, incidences of all-cause mortality (HR, 0.77; 95% CI, 0.60–0.98) and nonfatal MI (HR, 0.59; 95% CI, 0.39–0.90) were significantly reduced. In contrast, the COMMIT (Clopidogrel and

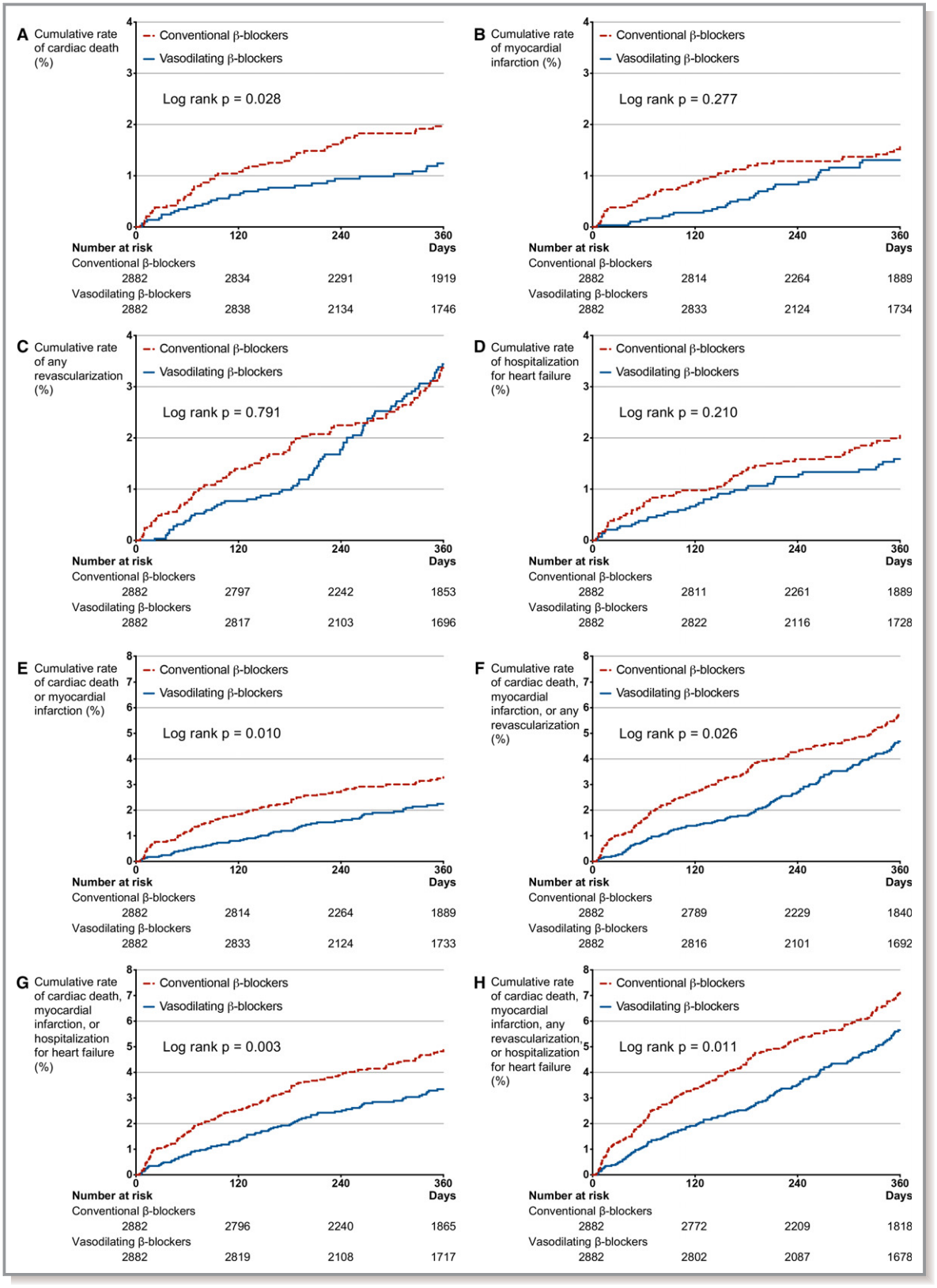

Figure 2. Kaplan–Meier curves for 1-year clinical outcomes in vasodilating versus conventional β-blocker groups in propensity-matched population. A, Cardiac death. B, Myocardial infarction. C, Any revascularization. D, Hospitalization for heart failure. E, Composite of cardiac death or myocardial infarction. F, Composite of cardiac death, myocardial infarction, or any revascularization. G, Composite of cardiac death, myocardial infarction, or hospitalization for heart failure. H, Composite of cardiac death, myocardial infarction, any revascularization, or hospitalization for heart failure.

Table 3. Clinical Outcomes in Propensity Score-Matched Population According-Treatment at Discharge and During Follow-up

	Vasodilating β-Blockers (n=2882)	Conventional β-Blockers (n=2882)	Adjusted* HR (95% CI)	*P* Value
Cardiac death	32 (1.1)	53 (1.8)	0.63 (0.41–0.98)	0.042
Myocardial infarction	32 (1.1)	42 (1.5)	0.76 (0.48–1.20)	0.241
Any revascularization	80 (2.8)	86 (3.0)	0.95 (0.70–1.29)	0.743
Hospitalization for HF	41 (1.4)	54 (1.9)	0.75 (0.50–1.13)	0.173
Cardiac death or MI	57 (2.0)	89 (3.1)	0.66 (0.47–0.92)	0.014
Cardiac death or MI or hospitalization for HF	86 (3.0)	131 (4.5)	0.67 (0.51–0.88)	0.004
Cardiac death or MI or any revascularization	113 (3.9)	152 (5.3)	0.76 (0.59–0.97)	0.025
Cardiac death or MI or any revascularization or hospitalization for HF	139 (4.8)	188 (6.5)	0.75 (0.60–0.93)	0.009

Figures are numbers (percentage) of patients and hazard ratios (95% confidence interval). HF indicates heart failure; HR, hazard ratio; MI, myocardial infarction.
*Adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, cerebrovascular disease, current or ex-smoking, chronic kidney disease over stage 3, LM or LAD as infarct related artery, multivessel disease, left ventricular ejection fraction, ST elevation MI or non-ST-elevation MI, use of renin-angiotensin system blockade, statin.

Metoprolol in Myocardial Infarction Trial) in 2005, 45 852 patients with AMI were treated with the full dose of metoprolol.[4] More than half of all patients received thrombolysis. During mean follow-up of 15 days, metoprolol therapy resulted in 5 fewer patients with reinfarction, and 5 fewer with ventricular fibrillation, at the expense of 11 more with cardiogenic shock per 1000 treated. There was no difference in death between metoprolol and placebo groups. Bangalore et al conducted an interesting meta-analysis.[20] Of note, the researchers excluded the trials dealing with patients with LV dysfunction, such as the CAPRICORN trial in their analysis, because they considered that the efficacy of β-blockers was already established in that cohort. The meta-analysis of 48 randomized trials in the prereperfusion era demonstrated mortality reduction by β-blockers. However, the analysis of 12 randomized trials in the reperfusion era, each of which had a small sample size (except for the COMMIT trial), showed no difference in mortality with use of β-blockers. Rather, β-blockers increased the risk of HF or cardiogenic shock in the reperfusion era. In contrast, recent registry data showed that β-blocker therapy decreased all-cause or cardiac mortality at a median 1-year follow-up in STEMI patients undergoing primary PCI,[21] or at 3-year follow-up in AMI patients undergoing PCI who had preserved LV function.[22] In summary, there is a paucity of randomized controlled trials regarding the efficacy and safety of β-blockers for AMI patients in the modern reperfusion era. If it exists, the impact on clinical outcomes of β-blocker therapy is controversial. The effects on central blood pressure and metabolic derangement attributed to conventional β-blockers may plausibly explain the adverse outcomes of β-blocker therapy. Conventional β-blockers, such as metoprolol and bisoprolol, elevate central blood pressure, in contrast to other classes of antihypertensive drugs.[7] However, vasodilating β-blockers, such as carvedilol and nebivolol, decrease central blood pressure and arterial stiffness.[8] Furthermore, vasodilating β-blockers, in contrast to conventional β-blockers, do not worsen glycemic and lipid control.[9] Based on these beneficial mechanisms, the potential superiority of vasodilating to conventional β-blockers can be surmised. However, because of lack of sufficient clinical data, even the current hypertension guidelines do not provide a favorable recommendation specific to vasodilating compared with conventional β-blockers.[23,24]

To the best of our knowledge, our study is the first to address the efficacy of vasodilating, compared with conventional, β-blockers in patients with AMI. In this study, vasodilating β-blocker therapy significantly reduced the rate of cardiac death, and numerically decreased the incidence of MI and hospitalization for heart failure. This study was performed in a population that underwent PCI. In other words, this study demonstrated better clinical efficacy for vasodilating β-blockers in patients with AMI in the modern reperfusion era. Furthermore, the results were not affected by subgroups: Vasodilating β-blockers were associated with better clinical outcomes not only in patients with LV dysfunction, as in the CAPRICORN trial, but also in those without LV dysfunction, as in the COMMIT trial. Whether patients had STEMI or non-STEMI also did not change the results.

Limitations

Our study has some potential limitations. First, this study is based on nonrandomized observational registry data. Although we performed a propensity score–matched analysis to adjust potential confounding factors, other unmeasured variables

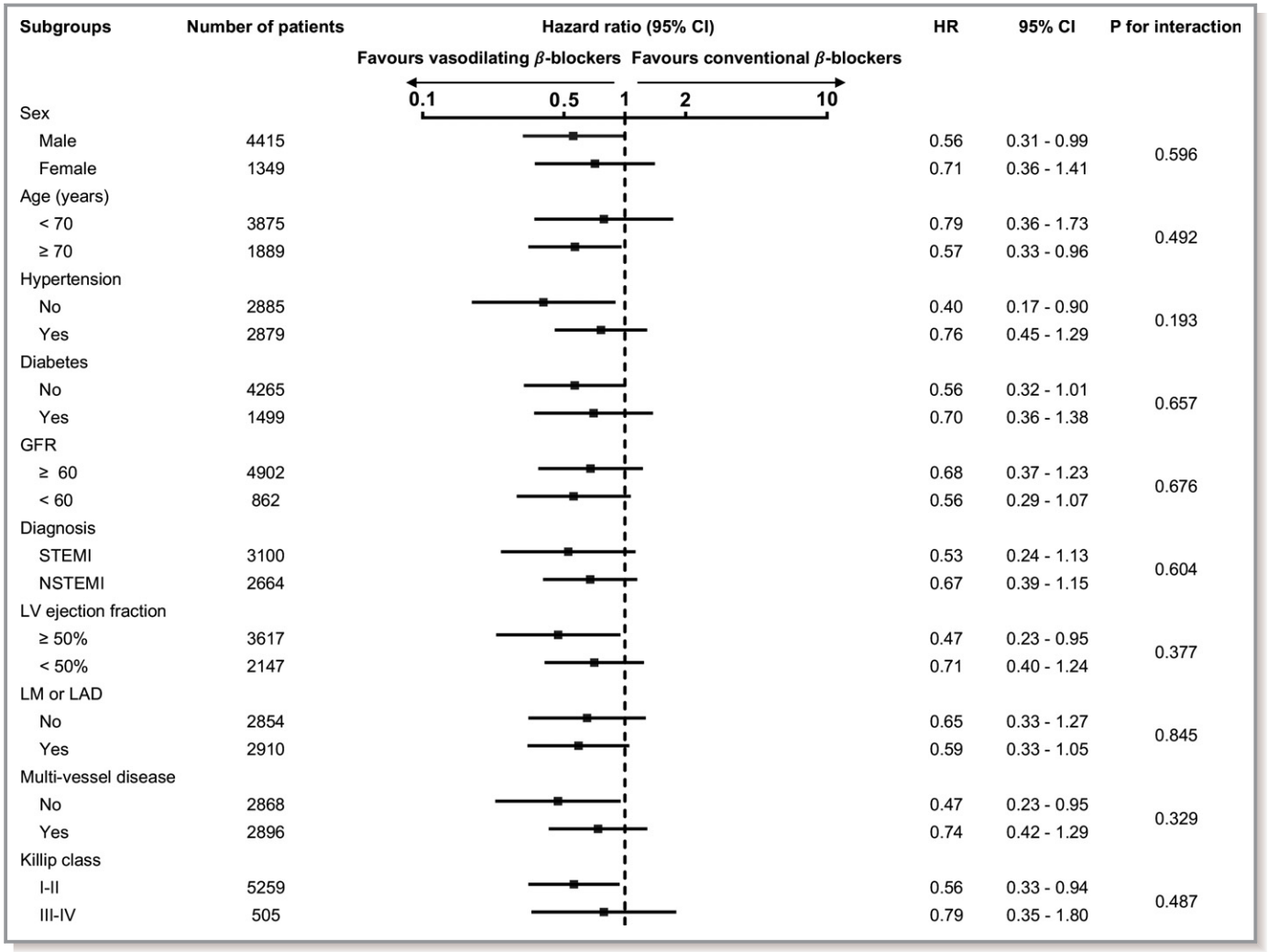

Figure 3. Comparative unadjusted hazard ratios of cardiac death for subgroups in propensity-matched populations using vasodilating β-blockers and conventional β-blockers. CI indicates confidence interval; GFR, glomerular filtration rate (mg/dL); HR, hazard ratio; LAD, left anterior descending artery; LM, left main; LV, left ventricle; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

could not be corrected. In particular, we did not have information on why physicians prescribed a certain β-blocker. Second, we did not have data regarding the dosage of β-blockers administered to patients. However, because of the nature of a "real-world" registry in which the dose was determined at the physician's discretion, we believe that the maximal tolerable dosages were administered to patients depending on their status. Therefore, the fact that vasodilating β-blockers at common dosages resulted in better outcomes has important clinical implications. Furthermore, we surmise that the contrasting results between the COMMIT and CAPRICORN trials may provide valuable insights into the dosage and titration of β-blockers in patients with AMI. In the COMMIT trial,[4] a fixed full dose of metoprolol was administered to all patients (15 mg intravenously, and subsequently 200 mg per day orally). In contrast, in the CAPRICORN trial,[5] the dose of carvedilol was carefully titrated to maximal tolerable dose over 4 to 6 weeks (from 6.25 mg twice-daily, and progressively up to a maximum 25 mg twice-daily). We believe that these differences in dosage and titration strategy may plausibly explain the worse outcomes with β-blocker therapy in the COMMIT trial, and better outcomes in the CAPRICORN trial. Maximal tolerable dose, but not full dose, of β-blockers may be sufficient to obtain good clinical results. Another important difference between the 2 trials is that conventional β-blocker was used in the COMMIT trial, and vasodilating β-blocker in the CAPRICORN trial. Third, we excluded patients who died in-hospital and discharged without hope, so early effect of β-blockers in patients with AMI is not assessed in this analysis. Fourth, most of the conventional β-blockers in this study were bisoprolol; however, in some countries, especially in United States, bisoprolol is rarely used in clinical practice. Therefore,

there is a limitation in direct application of our study in general clinical practice. Fifth, a follow-up at 1 year may not be long enough to observe differences in efficacy between vasodilating and conventional β-blockers. However, given that the beneficial mechanisms of vasodilating β-blockers, such as the effects on central blood pressure and metabolic derangement, may have a slowly progressing impact on patients, longer-term follow-up may result in much better outcomes with vasodilating β-blocker therapy compared with the results for 1-year follow-up in the current study.

Conclusions

Our study shows that vasodilating β-blocker therapy in patients with AMI who underwent successful PCI is associated with better clinical outcomes than conventional β-blocker therapy. This is a hypothesis-generating study to justify large-scale, randomized trials confirming the benefit of vasodilating β-blockers in patients with AMI in the reperfusion era.

Appendix

Contributors of the Korea Acute Myocardial Infarction Registry (KAMIR) include Tae Hoon Ahn, MD, Youngkeun Ahn, MD, Kwang Soo Cha, MD, In-Ho Chae, MD, Jei Keon Chae, MD, Shung Chull Chae, MD, Myeong Chan Cho, MD, Hyeon-Cheol Gwon, MD, Jin-Yong Hwang, MD, Myung Ho Jeong, MD, Seung Jae Joo, MD, Chong Jin Kim, MD, Doo-il Kim, MD, Hyo-Soo Kim, MD, Kwon-Bae Kim, MD, Young Jo Kim, MD, Dong Joo Oh, MD, Seok Kyu Oh, MD, In-Whan Seong, MD, Ki-Bae Seung, MD, and Jung-Han Yoon, MD.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Baseline clinical characteristics of whole population according to treatment at discharge and during follow up. Figures are numbers (percentage) of patients unless stated otherwise.

Variables	Vasodilating β-blockers (n=3482)	Conventional β-blockers (n=3645)	*P* Value	Standardized Difference
Demographics				
Age, mean (SD), years	62.2 (12.4)	63.2 (12.3)	0.001	9.0
Male (%)	2691 (77.3)	2714 (74.5)	0.005	7.2
Coronary risk factors (%)				
Diabetes mellitus	878 (25.2)	1076 (29.5)	<0.001	10.9
Hypertension	1715 (49.3)	1893 (51.9)	0.024	6.1
Dyslipidemia	410 (11.8)	379 (10.4)	0.064	3.7
Current or Ex-smoking	2168 (63.6)	2152 (60.0)	0.002	7.6
Chronic kidney disease	505 (14.5)	642 (17.6)	<0.001	9.0
Family history of CAD	230 (6.8)	232 (6.5)	0.589	1.8
Previous medical history (%)				
History of CVA	193 (5.6)	238 (6.6)	0.079	3.8
History of MI	189 (5.4)	195 (5.3)	0.884	0.8
History of Angina	239 (6.9)	239 (6.6)	0.605	1.3
History of PCI	259 (7.4)	274 (7.5)	0.899	1.3

History of CABG	25 (0.7)	13 (0.4)	0.036	4.0
History of heart failure	32 (0.9)	29 (0.8)	0.566	0.6
Clinical characteristics at presentation and In-hospital (%)				
Killip class ≥ Ⅲ on admission	289 (8.3)	397 (10.9)	<0.001	10.5
STEMI	1957 (56.2)	1833 (50.3)	<0.001	12.4
Mean (SD) left ventricular ejection fraction	51.6 (10.5)	52.8 (10.4)	<0.001	11.3
Medication at discharge (%)				
Aspirin	3475 (99.8)	3643 (99.9)	0.082	3.4
Clopidogrel	2649 (76.1)	2917 (80.0)	<0.001	9.0
Prasugrel	462 (13.3)	501 (13.7)	0.556	2.3
Cilostazol	318 (9.1)	557 (15.3)	<0.001	21.6
Tichlopidine	6 (0.2)	11 (0.3)	0.263	1.7
Ticagrelor	891 (25.6)	691 (19.0)	<0.001	15.2
RAS blockade	2905 (83.4)	3269 (89.7)	<0.001	15.9
Statins	3344 (96.0)	3440 (94.4)	0.001	9.7

SD indicates standard deviation; CVA, cerebrovascular accident; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; STEMI, ST segment elevation MI; RAS, renin-angiotensin system

Table S2. Angiographic and procedural characteristics of whole population according to treatment at discharge and during follow up. Figures are numbers (percentage) of patients unless stated otherwise.

Variables	Vasodilating β-blockers (n=3482)	Conventional β-blockers (n=3645)	*P* Value	Standardized Difference
Glycoprotein Ⅱb/Ⅲa inhibitor	499 (14.3)	530 (14.5)	0.801	1.6
LM or LAD infarct-related artery	1711 (50.9)	1811 (49.7)	0.320	3.2
ACC/AHA B2/C lesion	3017 (86.7)	3138 (86.2)	0.549	0.4
Pre-procedural TIMI flow grade 0-1	1988 (57.1)	2073 (57.0)	0.892	0.5
Post-precedural TIMI flow grade 3	3398 (97.6)	3554 (97.5)	0.818	0.1
Mean (SD) maximal stent diameter (mm)	3.17 (0.44)	3.18 (0.45)	0.489	1.8
Mean (SD) total stent length (mm)	29.3 (14.0)	29.9 (14.5)	0.085	4.7
Multi-vessel coronary artery disease	1784 (51.2)	1812 (49.7)	0.198	3.3
Vasopressor	164 (4.7)	202 (5.5)	0.112	4.4
Intra-aortic balloon pump	88 (2.5)	71 (1.9)	0.098	3.7
Temporary pacemaker	134 (3.8)	134 (3.7)	0.703	0.9
Defibrillator/cardioversion	100 (2.9)	100 (2.7)	0.743	1.0

SD indicates standard deviation; LM, left main; LAD, left anterior descending; ACC/AHA, American College of Cardiology/American Heart Association; TIMI, thrombolysis in myocardial infarction

Table S3. Clinical outcomes in whole population according to treatment at discharge and during follow-up. Figures are numbers (percentage) of patients and hazard ratios (95% confidence interval).

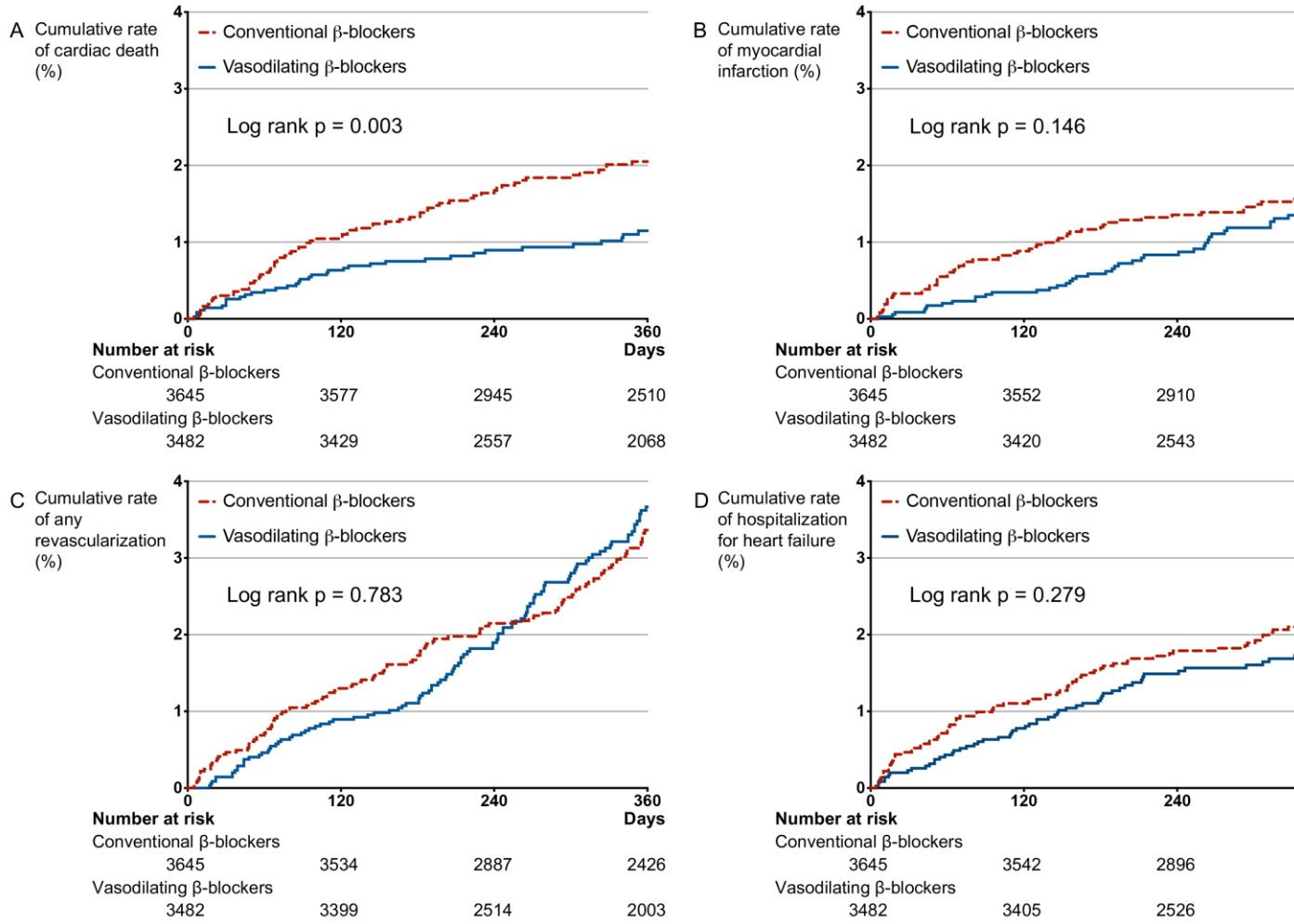
	Vasodilating β-blockers (n=3482)	Conventional β-blockers (n=3645)	Adjusted* HR (95% CI)	*P* Value
Cardiac death	36 (1.0)	70 (1.9)	0.65 (0.43-0.98)	0.039
Myocardial infarction	40 (1.1)	58 (1.6)	0.80 (0.53-1.22)	0.304
Any revascularization	103 (3.0)	109 (3.0)	0.99 (0.75-1.32)	0.959
Hospitalization for HF	58 (1.7)	75 (2.1)	0.79 (0.55-1.13)	0.196
Cardiac death or MI	69 (2.0)	119 (3.3)	0.70 (0.51-0.95)	0.022

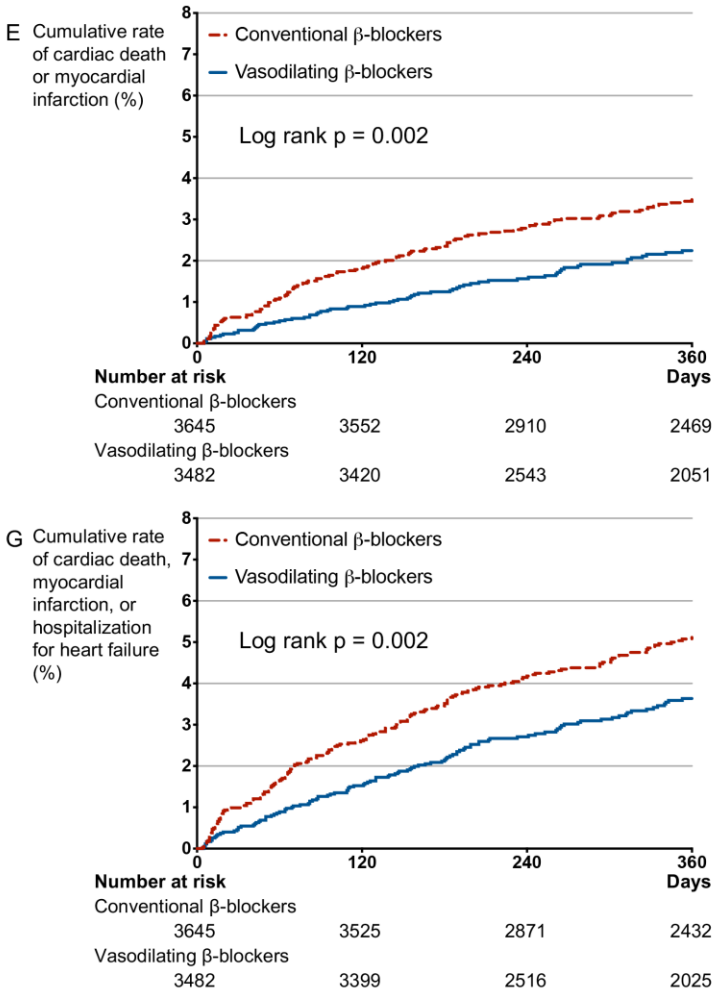
Cardiac death or MI or hospitalization for HF	113 (3.2)	175 (4.8)	0.72 (0.56-0.92)	0.008
Cardiac death or MI or any revascularization	142 (4.1)	193 (5.3)	0.80 (0.64-1.01)	0.059
Cardiac death or MI or any revascularization or hospitalization for HF	180 (5.2)	243 (6.7)	0.80 (0.65-0.98)	0.028

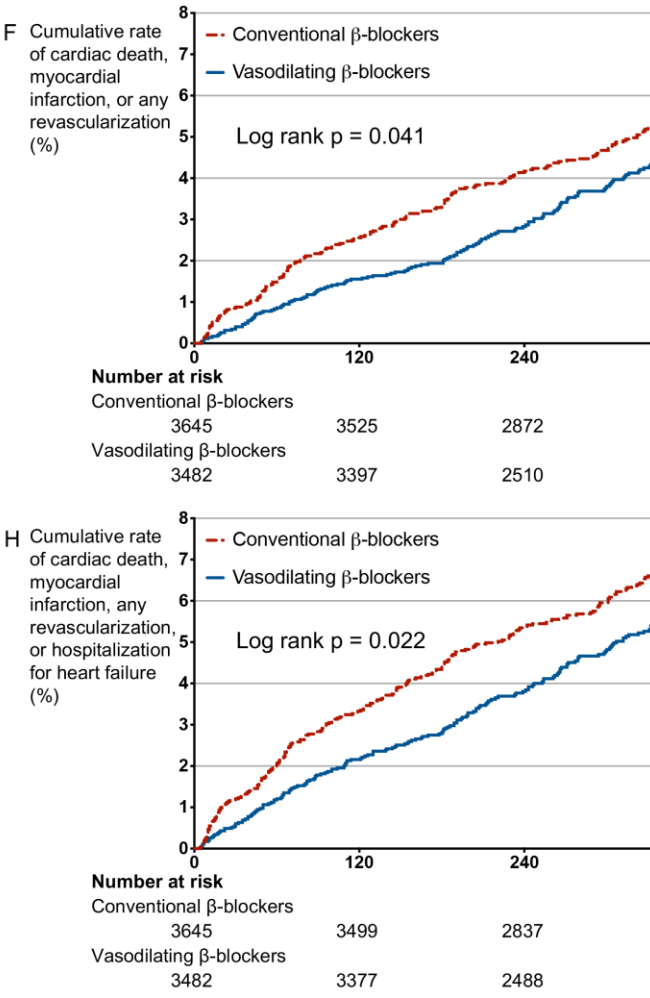
HR indicates hazard ratio; MI, myocardial infarction; HF, heart failure

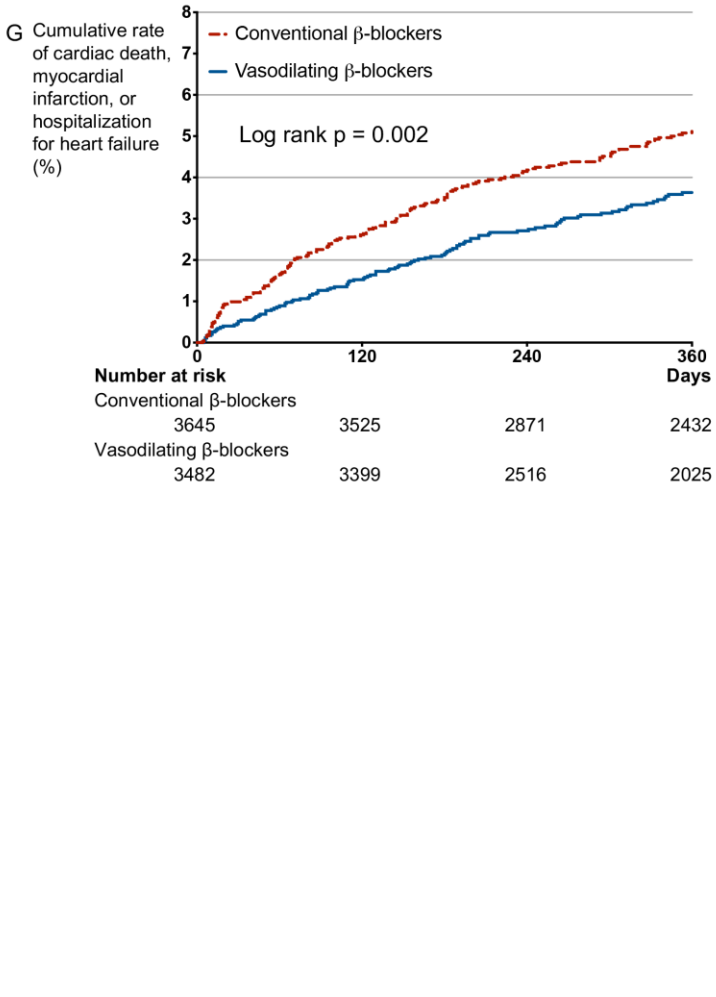
*Adjusted for age, sex, hypertension, diabetes, dyslipidemia, heart failure, cerebrovascular disease, current or ex-smoking, chronic kidney disease over stage 3, LM or LAD as infarct related artery, multi vessel disease, left ventricular ejection fraction, ST elevation MI or Non-ST elevation MI, use of renin angiotensin system blockade, statin.

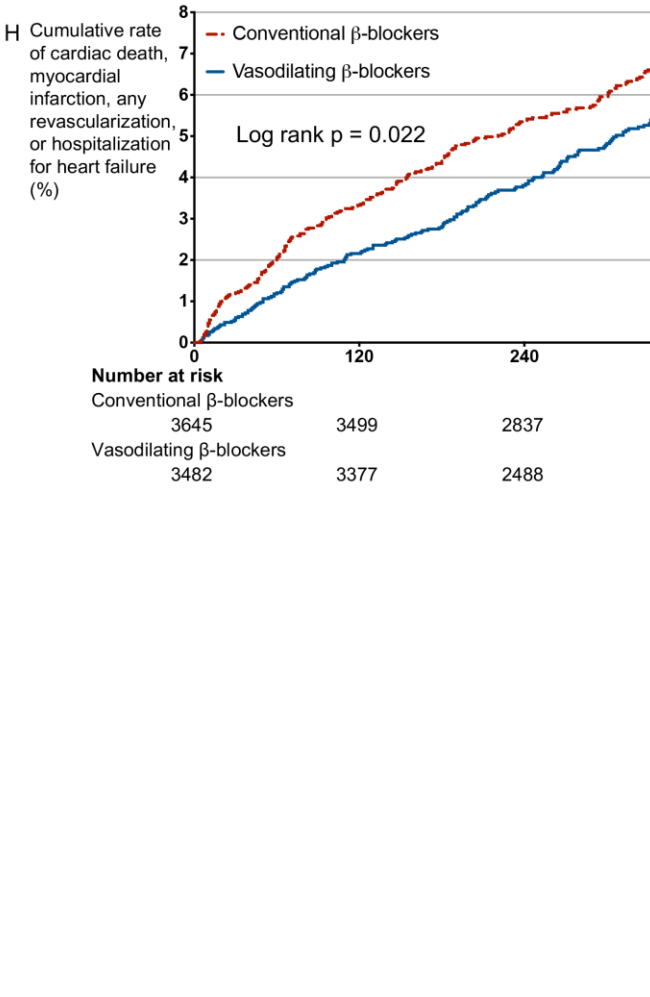
Figure S1. Kaplan-Meier curves for one year clinical outcomes in vasodilating vs. conventional β-blocker groups in the whole population. (**A**) Cardiac death, (**B**) Myocardial infarction, (**C**) Any revascularization, (**D**) Hospitalization for heart failure, (**E**) Composite of cardiac death or myocardial infarction, (**F**) Composite of cardiac death, myocardial infarction, or any revascularization, (**G**) Composite of cardiac death, myocardial infarction, or hospitalization for heart failure. (**H**) composite of cardiac death, myocardial infarction, any revascularization, or hospitalization for heart failure.




E
Cumulative rate of cardiac death or myocardial infarction (%)
Conventional β-blockers
Vasodilating β-blockers
Log rank p = 0.002
0
1
2
3
4
5
6
7
8
0
120
240
360
Days
Number at risk
Conventional β-blockers
3645
3552
2910
2469
Vasodilating β-blockers
3482
3420
2543
2051


F
Cumulative rate of cardiac death, myocardial infarction, or any revascularization (%)
Conventional β-blockers
Vasodilating β-blockers
Log rank p = 0.041
0
1
2
3
4
5
6
7
8
0
120
240
Number at risk
Conventional β-blockers
3645
3525
2872
Vasodilating β-blockers
3482
3397
2510


G
Cumulative rate of cardiac death, myocardial infarction, or hospitalization for heart failure (%)
Conventional β-blockers
Vasodilating β-blockers
Log rank p = 0.002
0
1
2
3
4
5
6
7
8
0
120
240
360
Days
Number at risk
Conventional β-blockers
3645
3525
2871
2432
Vasodilating β-blockers
3482
3399
2516
2025


H
Cumulative rate of cardiac death, myocardial infarction, any revascularization, or hospitalization for heart failure (%)
Conventional β-blockers
Vasodilating β-blockers
Log rank p = 0.022
0
1
2
3
4
5
6
7
8
0
120
240
Number at risk
Conventional β-blockers
3645
3499
2837
Vasodilating β-blockers
3482
3377
2488