Optimal Dose and Type of β-blockers in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

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The clinical benefit of β-blockers in modern reperfusion era is not well determined. We investigated the impact of β-blockers in acute coronary syndrome (ACS) after percutaneous coronary intervention. From the Grand-DES registry, a patient-level pooled registry consisting of 5 Korean multicenter prospective drug-eluting stent registries, a total of 6,690 ACS patients were included. Prescription records of dose and type of β-blockers were investigated trimonthly from discharge. Patients were categorized by the mean value of doses during the follow-up (≥50% [high-dose], ≥25% to <50% [medium-dose], and <25% [low-dose] of the full dose that was used in each randomized clinical trial) and vasodilating property of β-blockers. Three-year cumulative risk of all-cause death, cardiac death, and myocardial infarction were assessed. Patients receiving β-blockers were associated with a lower risk of all-cause and cardiac death compared with those not receiving β-blockers (adjusted hazard ratio [aHR] 0.29, 95% confidence interval [CI] 0.24 to 0.35 for all-cause death; aHR 0.27, 95% CI 0.21 to 0.34 for cardiac death). Medium-dose β-blocker group was associated with a lower risk of cardiac death compared with high- and low-dose β-blocker groups (aHR 0.49, 95% CI 0.25 to 0.96, for high-dose; aHR 0.46, 95% CI 0.29 to 0.74, for low-dose). Patients receiving vasodilating β-blockers were associated with a lower risk of cardiac death compared with those receiving conventional β-blockers (aHR 0.58, 95% CI 0.40 to 0.84). In conclusion, β-blocker therapy was associated with better clinical outcomes in patients with ACS, especially with medium-dose and vasodilating β-blockers. **(Am J Cardiol 2020;137:12−19)**

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This study was funded by Chong Kun Dang Inc. (Seoul, Republic of Korea) (Grant number 0620173860). The funding agencies had no role in study design, analysis, interpretation of data, the writing of the manuscript or in the decision to submit the article for publication.

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There are several key questions to be answered regarding β-blocker therapy in patients with acute coronary syndrome (ACS). First, is β-blocker therapy still beneficial for patients with ACS in the modern reperfusion era? The role of β-blockers in ACS was mostly established in old studies of the prereperfusion era, but is controversial in the modern reperfusion era.[1,2] Second, what is the optimal dose of β-blockers for patients with ACS? Theoretically, the dose of β-blockers should be titrated to so-called full doses, targeted in randomized trials to establish their benefits. However, because of potential adverse hemodynamic effects of β-blockers, doses of clinically used β-blockers are substantially lower than full doses.[3] Third, are the effects of vasodilating β-blockers on patients with ACS different from those of conventional β-blockers? Previously, we found a better clinical outcome associated with vasodilating β-blockers compared with conventional β-blockers in patients with acute myocardial infarction (MI).[4] However, this study needs validation in other study groups and for longer-term follow-up. Here, we investigated the effect of β-blocker therapy in relation to different doses and types on clinical outcomes in ACS patients.

Methods

The detailed methods are available in Supplementary Appendix. In brief, the study population was derived from

0002-9149/
https://doi.org/10.1016/j.amjcard.2020.09.044

the Grand Drug-Eluting Stent (Grand-DES) registry (NCT03507205), a patient-level pooled registry including 5 independent multicenter prospective DES registries in South Korea which were hosted by Seoul National University Hospital. The study protocol was approved by the ethics committee of each participating center and conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent.

To overcome the intrinsic limitation of previous studies[3,5] which categorized patients based on a β-blocker dose obtained at a single time point (e.g., at discharge or after percutaneous coronary intervention [PCI]), we thoroughly reviewed prescription records of β-blockers with doses and types for each patient at a 3-month interval after discharge. Among the total population (n = 17,286), we excluded patients without available data regarding the β-blocker use (n = 5,799), those with noncontinuous prescription of β-blockers (n = 1,722), and those with stable chest pain at initial presentation. We defined patients with noncontinuous use of β-blockers as those who had no prescriptions of β-blockers at any point in the 3-month time intervals we reviewed until the last follow-up date after discharge. Finally, a total of 6,690 patients with ACS were included for analysis (Figure 1). We calculated daily dose of β-blockers by multiplying the daily frequency (times per day), and amount (milligram per each administration) of the β-blockers. The daily dose was translated into % of full dose used in previous randomized trials: metoprolol 200 mg/day,[6] carvedilol 50 mg/day,[2] propranolol 160 mg/day,[7] bisoprolol 10 mg/day,[8] atenolol 100 mg/day,[9] nebivolol 10 mg/day,[10] betaxolol 40 mg/day,[11] and bevantolol 200 mg/day.[12] Then, each translated % during the whole follow-up period was averaged. Finally, patients were categorized into 3 groups according to these mean values of β-blocker doses: "low-dose" (<25% of full dose), "medium-dose" (≥25% to <50%), and "high-dose" (≥50%) β-blocker groups. Patients were also categorized into 2 groups according to the vasodilating property of β-blockers: "vasodilating β-blockers" (carvedilol, nebivolol, betaxolol, and bevantolol) and "conventional β-blockers" (bisoprolol, metoprolol, atenolol, and propranolol).

The primary outcomes were all-cause death, cardiac death, and MI. Patients were longitudinally followed from discharge to the date of an outcome event or death, or the end of follow-up, whichever came first. We used Cox proportional-hazard regression modeling to estimate the hazard ratios (HRs) for the clinical outcomes according to (1) β-blocker use, (2) different dose categories, and (3) different types of β-blockers. HRs were estimated after balancing the differences in baseline characteristics between the study groups using the inverse probability weighted analysis. Also, HRs for the clinical outcomes were estimated after adjustment for competing risk of death. To assess whether the effect of β-blocker therapy differs after stabilization of the index event, we conducted additional landmark analysis at post discharge 30 days. Kaplan-Meier curves were used

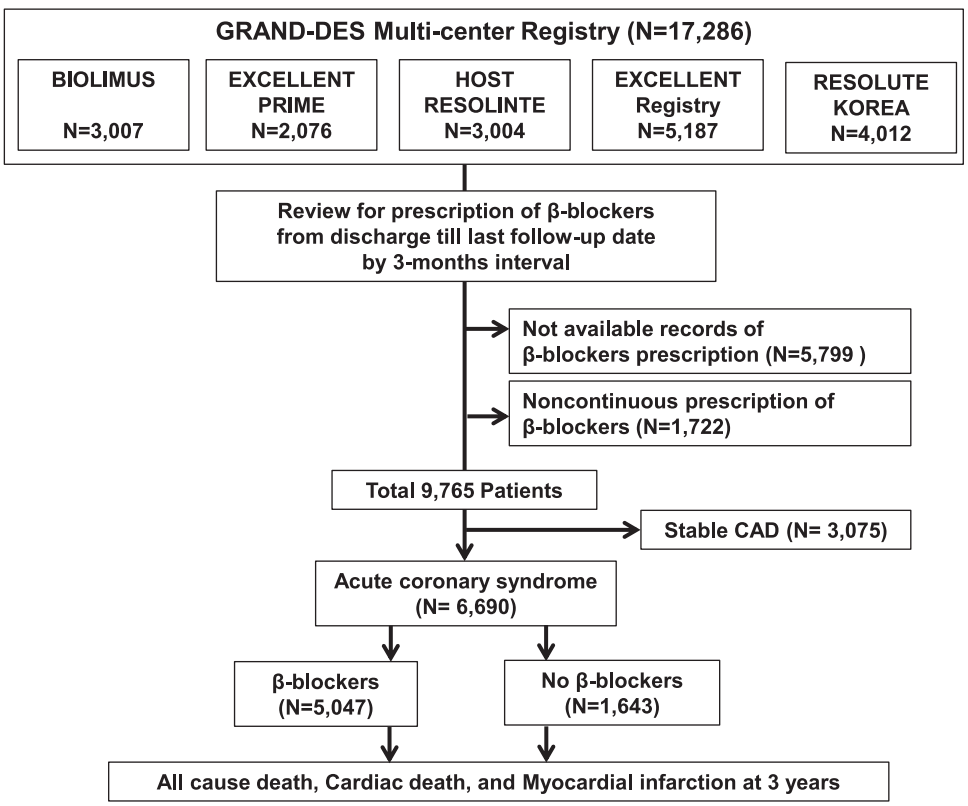

Figure 1. Study flow. A total of 17,286 patients with CAD who had undergone PCI were screened for inclusion from Grand-DES multicenter registry. We excluded patients without records of β-blocker prescription during the follow-up, those with noncontinuous β-blocker use, and those with initial clinical presentation as stable CAD. Patients were classified based on the prescription of β-blockers. CAD = coronary artery disease, DES = drug-eluting stent, PCI = percutaneous coronary intervention

to estimate the distribution of the time to the occurrence of clinical outcomes according to the study groups with differences in the event-free rate evaluated using the Log-rank test. Further subgroup analysis for the association of β-blocker use and different dose categories with cardiac death was conducted according to the presence of cardiovascular risk factors and initial diagnosis. We also analysed the data of β-blocker doses collected at a 3-month interval using time-varying Cox regression analysis to consider the actual doses and their variations throughout the follow-up period. Regarding the β-blocker types, the HRs were estimated (1) with exclusion of patients whose β-blocker was changed to the opposite class (i.e., from vasodilating to conventional, or conventional to vasodilating) during follow-up (n = 524) or (2) using time-varying Cox regression analysis considering type change during the follow-up period. All probability values were 2-sided, and p-values <0.05 were considered statistically significant. SPSS version 21.0 (SPSS Inc., Chicago, Illinois) and R version 3.4.3 (R Development Core Team, Vienna, Austria) were used for statistical analyses.

Results

A total of 5,047 (75%) patients received β-blockers after PCI, and the most frequently used β-blocker was carvedilol (Table 1). Patients receiving β-blockers were associated with a lower risk of all-cause death and cardiac death, compared with those not receiving β-blockers (Table 2, Figure 2, and Online Figure 1). The results were concordant after the adjustment for competing risk of death (Online Table 1). We also analyzed the data after excluding 3 β-blockers (atenolol, bevantolol, and betaxolol) of which survival benefits after MI have not been

Table 1
Baseline characteristics of study population

Variable	Beta Blockers		p
	YES (n = 5,047)	NO (n = 1,643)	
Age (Years)	63.0 ± 11.4	64.9 ± 11.0	<0.001
> 65	2,402 (47.6%)	885 (53.9%)	<0.001
Men	3,590 (71.1%)	1,145 (69.7%)	0.274
Body mass index > 30 kg/m^2	234 (4.6%)	55 (3.3%)	0.025
Follow-up duration (days)	1,126 (1,107−1,144)	1,125 (1,095-1,139)	<0.001
Previous myocardial infarction or revascularization	782 (15.5%)	324 (19.7%)	<0.001
Congestive heart failure or left ventricular ejection fraction < 40%	441 (8.7%)	113 (6.9%)	0.018
Diabetes mellitus	1,651 (32.7%)	534 (32.5%)	0.880
Hypertension	2,897 (57.4%)	920 (56.0%)	0.329
Chronic kidney disease	210 (4.2%)	70 (4.3%)	0.887
Stroke	378 (7.5%)	132 (8.0%)	0.487
Peripheral arterial disease	68 (1.3%)	38 (2.3%)	0.009
Current smoker	1,865 (37.0%)	522 (31.8%)	<0.001
Dyslipidemia	2,067 (41.0%)	618 (37.6%)	0.017
Initial systolic blood pressure < 90 mm Hg	76 (1.6%)	34 (2.2%)	0.092
Initial pulse rate < 60 bpm	623 (12.9%)	248 (16.2%)	0.001
Initial diagnosis for acute myocardial infarction	2,799 (55.5%)	512 (31.2%)	<0.001
Initial diagnosis for ST-segment elevation myocardial infarction	1,447 (28.7%)	237 (14.4%)	<0.001
Cardiogenic shock	32 (0.6%)	24 (1.5%)	0.003
Multi-vessel coronary disease	3,037 (60.2%)	944 (57.4%)	0.146
Left main narrowing	291 (5.8%)	130 (7.9%)	0.002
Type B2/C lesion	4,110 (81.4%)	1,258 (76.6%)	<0.001
2nd generation drug-eluting stent	4,141 (82.0%)	1,372 (83.5%)	0.192
Stent diameter	3.08 ± 0.44	3.06 ± 0.46	0.067
Total stent length	39.3 ± 25.5	37.4 ± 25.9	0.007
Medications			
Aspirin	5,031 (99.7%)	1,624 (98.8%)	<0.001
Clopidogrel	4,921 (97.5%)	1,593 (97.0%)	0.265
Angiotensin-converting enzyme inhibitors / angiotensin II receptor blockers	3,821 (75.7%)	900 (54.8%)	<0.001
Statins	4,545 (90.1%)	1,362 (82.9%)	<0.001
β-blockers			
Atenolol	130 (2.6%)	-	-
Betaxolol	51 (1.0%)	-	-
Bevantolol	20 (0.4%)	-	-
Bisoprolol	1,714 (34.0%)	-	-
Carvedilol	2,630 (52.1%)	-	-
Metoprolol	219 (4.3%)	-	-
Nebivolol	216 (4.3%)	-	-
Propranolol	67 (1.3%)	-	-

Values given as mean ± standard deviation, median (interquartile range, 25th and 75th percentile), or number (percentage), unless otherwise indicated.

Table 2
Comparison of clinical outcomes according to β-blocker therapy

Outcome	β-blockers (n = 5,047)	No β-blockers (n = 1,643)	Adjusted Hazard Ratio* (95% Confidence Interval)	p
All death	202 (4.0%)	189 (11.5%)	0.29 (0.24−0.35)	<0.001
Cardiac death	114 (2.3%)	115 (7.0%)	0.27 (0.21−0.34)	<0.001
Myocardial infarction	70 (1.4%)	22 (1.3%)	0.79 (0.51−1.22)	0.287

Values given as number (percentage), unless otherwise indicated.
* Adjusted variable: see methods.

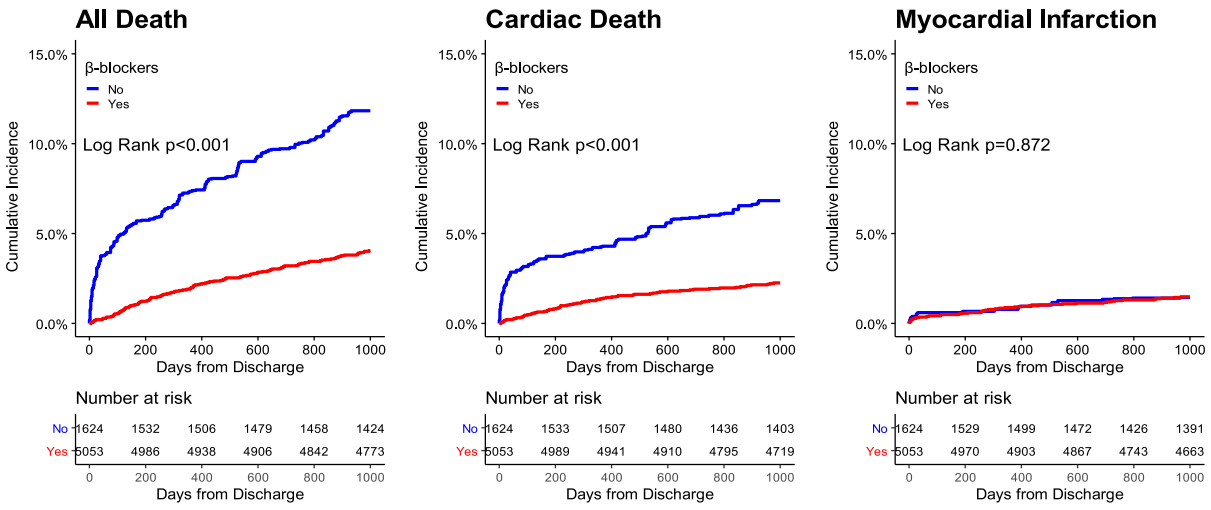

Figure 2. Cumulative risk of clinical outcomes according to β-blocker therapy. Patients receiving β-blockers showed a lower risk of all-cause death and cardiac death, compared with those not receiving β-blockers.

confirmed by randomized trials, and found consistent result (Online Table 2). In landmark analysis, the benefits of β-blockers were maintained after stabilization of the index event (Online Figure 2). There was an increasing association of β-blocker therapy with a lower risk of cardiac death, which was highest in patients with ST-segment elevated MI (Figure 3).

The patients were categorized into 3 groups according to the mean value of the β-blocker doses during follow-up: low-, medium-, and high-dose groups as 2,713 (54%), 1,722 (35%), and 562 (11%) patients, respectively (Table 3). Online Figure 3 shows the temporal trends of the β-blocker doses. The proportion of patients whose β-blocker doses were consistently maintained within each category during the follow-up was only 55% (51%, 54%, and 80% for low-, medium-, and high-dose categories, respectively). The medium-dose group was associated with a lower risk of cardiac death, compared with the high-dose group (Table 4, Figure 4, and Online Figure 4). The medium-dose group was also associated with a lower risk of all-cause and cardiac death, compared with the low-dose group. The results were consistent after the adjustment for competing risk of

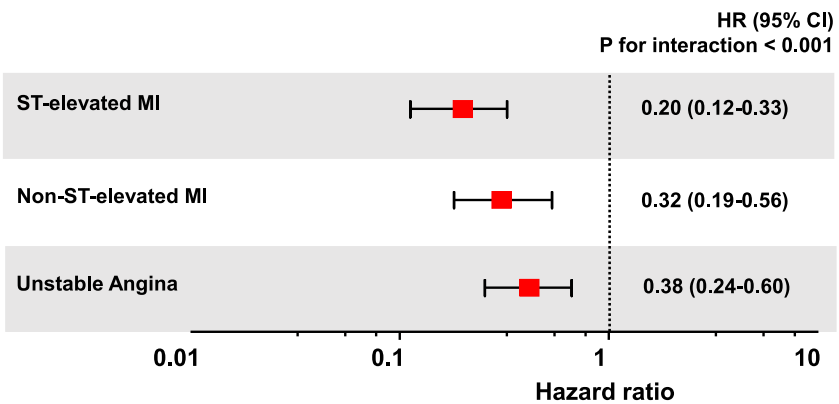

Figure 3. Subgroup analysis for the effect of β-blockers in risk reduction for cardiac death according to initial diagnosis. There was an increasing association of β-blocker therapy with a lower risk of cardiac death, which was highest in patients with ST-segment elevated MI. CI = confidence interval, HR = hazard ratio, MI = myocardial infarction.

Table 3
Baseline characteristics of patients according to β-blocker doses

Variable	High-dose (n = 562)	Medium- dose (n = 1,772)	Low- dose (n = 2,713)	No β-blockers (n = 1,643)	p
Age (Years)	63.3 ± 10.7	62.7 ± 11.2	63.1 ± 11.7	64.9 ± 11.0	<0.001
> 65	287 (51.1%)	825 (46.6%)	1,290 (47.5%)	885 (53.9%)	<0.001
Men	367 (65.3%)	1,239 (69.9%)	1,984 (73.1%)	1,145 (69.7%)	0.001
Body mass index > 30 kg/m^2	47 (8.4%)	98 (5.5%)	89 (3.3%)	55 (3.3%)	<0.001
Previous myocardial infarction or revascularization	136 (24.2%)	299 (16.9%)	347 (12.8%)	324 (19.7%)	<0.001
Congestive heart failure or left ventricular ejection fraction < 40%	41 (7.3%)	138 (7.8%)	262 (9.7%)	113 (6.9%)	0.006
Diabetes mellitus	242 (43.1%)	583 (32.9%)	826 (30.4%)	534 (32.5%)	<0.001
Hypertension	447 (79.5%)	1,107 (62.5%)	1,343 (49.5%)	920 (56.0%)	<0.001
Chronic kidney disease	49 (8.7%)	68 (3.8%)	93 (3.4%)	70 (4.3%)	<0.001
Stroke	52 (9.3%)	148 (8.4%)	178 (6.6%)	132 (8.0%)	0.042
Peripheral arterial disease	9 (1.6%)	26 (1.5%)	33 (1.2%)	38 (2.3%)	0.044
Current smoker	164 (29.2%)	635 (35.8%)	1,066 (39.3%)	522 (31.8%)	<0.001
Dyslipidemia	244 (43.4%)	702 (39.7%)	1,121 (41.3%)	618 (37.6%)	0.034
Initial systolic blood pressure < 90 mm Hg	7 (1.3%)	19 (1.1%)	50 (1.9%)	34 (2.2%)	0.070
Initial pulse rate < 60 bpm	74 (13.8%)	201 (11.8%)	348 (13.4%)	248 (16.2%)	0.004
Initial diagnosis for acute myocardial infarction	222 (39.5%)	875 (49.4%)	1,702 (62.7%)	512 (31.2%)	<0.001
Initial diagnosis for ST-segment elevation myocardial infarction	89 (15.8%)	431 (24.4%)	927 (34.2%)	237 (14.4%)	<0.001
Cardiogenic shock	3 (0.5%)	11 (0.6%)	18 (0.7%)	24 (1.5%)	0.016
Multi-vessel coronary disease	393 (70.0%)	1,072 (60.5%)	1,572 (58.0%)	844 (57.4%)	<0.001
Left main narrowing	41 (7.3%)	112 (6.3%)	138 (5.1%)	130 (7.9%)	0.002
Type B2/C lesion	443 (78.8%)	1,402 (79.1%)	2,265 (83.5%)	1,258 (76.6%)	<0.001
2nd generation drug-eluting stent	439 (78.1%)	1,389 (78.4%)	2,213 (85.3%)	1,372 (83.5%)	<0.001
Stent diameter	3.04 ± 0.40	3.10 ± 0.44	3.07 ± 0.44	3.06 ± 0.46	0.002
Total stent length	41.0 ± 26.3	39.2 ± 25.2	39.1 ± 25.5	37.5 ± 25.7	0.020

Values given as mean ± standard deviation or number (percentage), unless otherwise indicated.

Table 4
Comparison of clinical outcomes according to different doses of β-blockers

Outcome	High-dose (n = 562)	Medium-dose (n = 1,772)	Low-dose (n = 2,713)	Medium vs High Adjusted Hazard Ratio* (95% Confidence Interval)	p	Medium vs Low Adjusted Hazard Ratio* (95% Confidence Interval)	p
All death	29 (5.2%)	48 (2.7%)	125 (4.6%)	0.65 (0.40−1.07)	0.124	0.59 (0.42−0.82)	0.005
Cardiac death	18 (3.2%)	22 (1.2%)	74 (2.7%)	0.49 (0.25−0.96)	0.039	0.46 (0.29−0.74)	0.002
Myocardial infarction	13 (2.3%)	21 (1.2%)	36 (1.3%)	1.05 (0.46−2.39)	0.999	1.02 (0.61−1.70)	0.794

Values given as number (percentage), unless otherwise indicated.
* Adjusted variable: see methods.

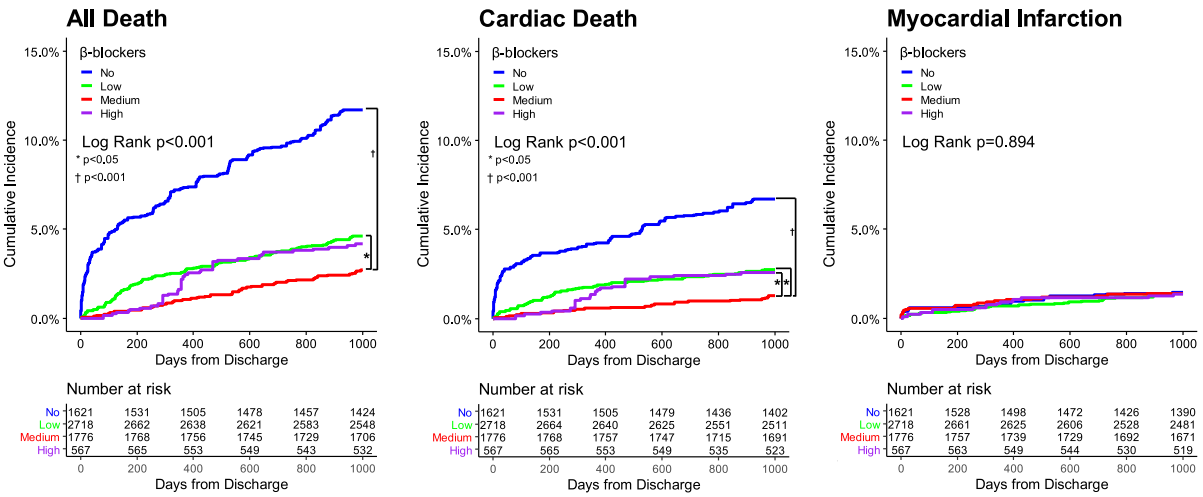

Figure 4. Cumulative risk of clinical outcomes according to different doses of β-blockers. Medium-dose β-blocker group was associated with a lower risk of all-cause death and cardiac death, compared with high or low-dose β-blocker group.

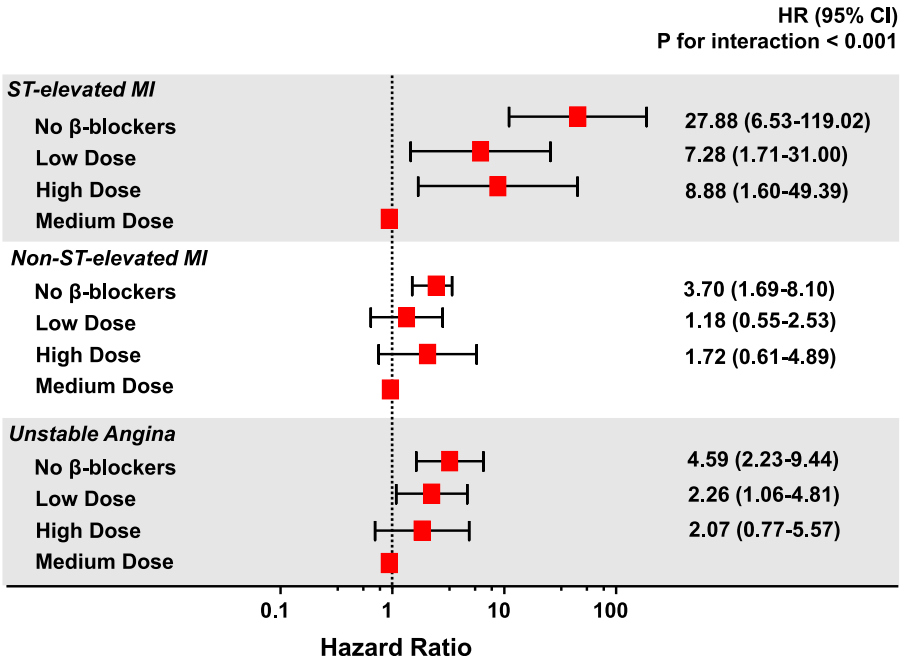

Figure 5. Subgroup analysis for the effect of *β*-blocker doses in risk reduction for cardiac death according to initial diagnosis. Medium-dose *β*-blocker group was associated with a lower risk of cardiac death, compared with other dose categories and with no *β*-blocker group. It was more noticeable in patients with ST-segment elevation MI. CI = confidence interval, HR = hazard ratio, MI = myocardial infarction.

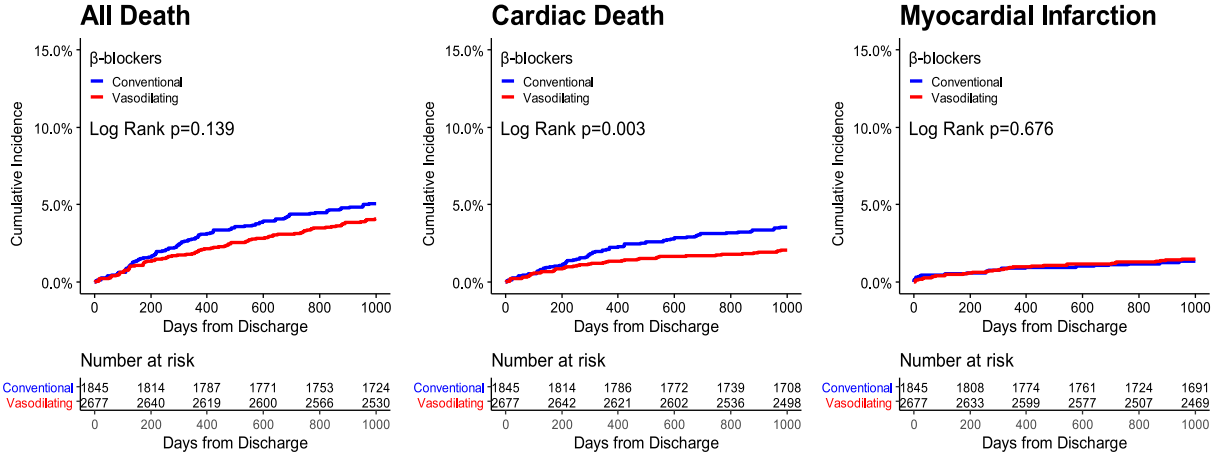

Figure 6. Cumulative risk of clinical outcomes according to vasodilating property of *β*-blockers. Vasodilating *β*-blocker group was associated with a lower risk of cardiac death compared with conventional *β*-blocker group.

death (Online Table 1), or with time-varying Cox regression analysis (Online Table 3). In subgroup analysis, medium-dose group showed a lowest risk of cardiac death across various subgroups (Online Table 4, and Figure 5).

When *β*-blockers were classified by their vasodilating property, 2,677 (59%) patients received vasodilating *β*-blockers continuously (Online Table 5). Vasodilating *β*-blocker group was associated with a lower risk of cardiac death compared with conventional *β*-blocker group (Online Table 6, Figure 6, and Online Figure 5). The results were consistent after the adjustment for competing risk of death (Online Table 1) or with time-dependent analysis (Online Table 3). A higher proportion of the vasodilating *β*-blocker group received low dose *β*-blockers compared with conventional *β*-blocker group (61% vs 46%) (Online Figure 6), suggesting that the differences in outcomes between the vasodilating and conventional *β*-blocker groups were not attributable to dose, but to type of *β*-blockers.

Discussion

The main findings of this study are as follows: (1) *β*-blockers were still associated with a lower risk of clinical outcomes in patients with ACS in the modern reperfusion era. (2) Medium-dose *β*-blockers were associated with a lower risk of clinical outcomes in patients with ACS who underwent PCI. (3) Vasodilating *β*-blockers were associated with a lower risk of clinical outcomes in patients with ACS who underwent PCI, compared with conventional *β*-blockers.

The role of β-blockers in ACS has been questioned in the modern reperfusion era. A recent meta-analysis showed no mortality benefit of β-blockers in MI.[13] However, the result was mainly driven by the effect of the COMMIT trial showing no survival benefit with metoprolol, a conventional β-blocker, administrated at a fixed full dose within 24 hours after MI. This meta-analysis did not include the CAPRICORN trial demonstrating mortality benefit with carvedilol, a vasodilating β-blocker, of which dose was titrated slowly over 4 to 6 weeks, targeting a maximal tolerable dose. Some registry data reported no benefit of β-blockers in acute MI,[14−16] suggesting that the benefit of β-blockers would be attenuated by contemporary treatment strategies in ischemic heart disease. However, the study population was relatively small, and the dose or type of β-blockers was not considered in these studies.[14−16] Furthermore, β-blockers were still related to better outcomes in subgroups with high risk profiles,[15] or those with LV dysfunction.[16] In contrast, several registries in the reperfusion era demonstrated survival benefit of β-blockers in acute MI.[17,18] One of the important limitations of the previous reports was that the study population was classified based on the β-blocker use at a single time point, usually at discharge. In contrast, our study thoroughly collected the prescription records every 3 months. The results of our study add to the evidence supporting the benefits of β-blockers in patients with ACS in the modern reperfusion era. Particularly, our study provides expanding evidence because it included not only patients with ST-segment elevated MI but also patients with other ACS presentations, that is, non-ST-segment elevated MI and unstable angina.

Current guidelines do not refer to doses of β-blockers in patients with ACS. Previous studies found a quantitative relationship between heart rate and mortality reduction in post-MI patients,[19,20] which may support the importance of full-dose medication. However, β-blockers have inherent limitations, including adverse effects and non-ideal tolerability. Thus, substantially lower doses of β-blockers have been widely used in the clinical practices. One prospective registry analyzed the 2-year risk of all-cause death in patients with acute MI classified by β-blocker doses at discharge (>0% to 12.5%, >12.5% to 25%, >25% to 50%, and >50% of the full dose).[3] Interestingly, the risk was lowest in >12.5% to 25% dose group. This finding is comparable with our results as medium-dose group was associated with a lowest risk of mortality. Notably, the survival rate in >50% dose group rapidly decreased after 1 year, which was also similar to our results. Another registry compared 6-month and 2-year risks of major adverse cardiac events between patients with ACS with low-dose (≤25% of an equivalent dose of 200 mg metoprolol) and high-dose (≥50% of an equivalent dose of 200 mg metoprolol) β-blockers, and found no significant differences.[21] However, one critical limitation of these studies was that they categorized groups based on β-blocker dose at a single time point, mostly at discharge. Our data showed that the dose of β-blockers was actively adjusted during the follow-up as only 55% of the patients remained consistently within their dose category (Online Figure 3). However, the high-dose group showed a highest maintenance rate during the follow-up (80%). Our results suggest that the pursuit of the non-titrated full dose β-blockers may not be an ideal strategy for therapy in patients with ACS, and that the carefully titrated maximal tolerable dose would be adequate to obtain the best outcomes.

Another important characteristic of β-blockers is their vasodilating property. Conventional β-blockers elevate central blood pressure and cause metabolic derangement, whereas vasodilating β-blockers do not have these adverse effects. This property may explain the inferiority of atenolol to other classes of antihypertensive drugs in preventing cardiovascular events in many randomized trials.[22] Previously, we reported for the first time that vasodilating β-blocker therapy was associated with lower risk of cardiac death in patients with MI using 1-year follow-up data from the Korea Acute Myocardial Infarction Registry.[4] Our current study verified this finding using another multicenter registry−−the Grand-DES registry. Furthermore, the current study provides expanding evidence for the 3-year follow up and for patients with ACS other than those with MI.

There are some limitations to the current study. First, despite multivariable and inverse probability weighting adjustment, unmeasured confounding variables may exist due to inheriting the limitations of registry data. Second, there might be some limitations in pooling 5 different multicenter registries constituting the Grand-DES registry as each registry handled a different DES. However, because all registries were designed to have similar structure and were hosted by Seoul National University Hospital, the confounding effect would be minimal. Third, the data regarding the contraindication for patients not receiving β-blockers, the reasons for discontinuation of β-blockers during the follow-up, and the indication of β-blockers as anti-anginal therapy were not available in the current database. Fourth, as we compared the clinical outcomes in the groups categorized by dose and type of β-blockers, there is a possibility that our findings could be affected by the result of chance because of the multiple testing. Also, we acknowledge that there could be a risk of overfitting in the hazard regression model due to relatively few outcome events. Last, for the current study, we excluded patients whose prescription records of β-blockers are not available and those with non-continuous use of β-blockers during the follow-up period, which may act as a potential bias to the study results.

In conclusion, β-blocker therapy was associated with better clinical outcomes in patients with ACS, especially with medium-dose and vasodilating β-blockers. Further randomized clinical trials would be warranted to confirm our findings regarding optimal dose and type of β-blockers in ACS.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.09.044.

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