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Effect of Beta Blockers and Renin–Angiotensin System Inhibitors on Survival in Patients With Acute Myocardial Infarction Undergoing Percutaneous Coronary Intervention

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Abstract: Because it remains uncertain whether β -blockers (BBs) and/or renin–angiotensin system inhibitors benefit a broad population of acute myocardial infarction (AMI) patients, we sought to evaluate the effectiveness of these drugs in improving survival for post-AMI patients who underwent a percutaneous coronary intervention (PCI).

From the nationwide data of the South Korea National Health Insurance, 33,390 patients with a diagnosis of AMI who underwent a PCI between 2009 and 2013 and survived at least 30 days were included in this study. We evaluated the risk of all-cause death for patients treated with both BB and angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor antagonist (ARB) ($n=16,280$), only BB ($n=3683$), and only ACEI/ARB ($n=9849$), with the drug-untreated patients ($n=3578$) as the reference.

Over a median follow-up of 2.4 years, although treated patients displayed a trend toward improved survival, there were no significant differences in the adjusted risk of all-cause death when patients were treated with both drugs (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.70–1.06, $P=0.154$), BB (HR 0.88, 95% CI 0.68–1.14, $P=0.325$), or ACEI/ARB (HR 0.84, 95% CI 0.68–1.04, $P=0.111$). No additional benefit was found for the combination therapy compared with either isolated BB (HR 0.98, 95% CI 0.80–1.21,

$P=0.856$) or ACEI/ARB (HR 1.03, 95% CI 0.89–1.19, $P=0.727$) therapy.

Treatment with BB and/or ACEI/ARB has limited effect on survival in unselected nonfatal AMI patients who undergo PCI.

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Abbreviations: ACEI = angiotensin-converting enzyme inhibitors, AMI = acute myocardial infarction, ARB = angiotensin II receptor antagonist, ATC = Anatomical Therapeutic Chemical, BB = β -blocker, CI = confidence interval, HIRA = Health Insurance Review and Assessment Service, HR = hazard ratio, ICD-10 = International Classification of Diseases, 10th Revision, NHI = National Health Insurance, PCI = percutaneous coronary intervention.

INTRODUCTION

Due to their anti-ischemic and anti-arrhythmic effects, β -blockers (BBs) reduce mortality in patients with acute myocardial infarction (AMI) and heart failure.^{1–3} In addition, early clinical trials have found that angiotensin-converting enzyme inhibitors (ACEIs) prevented ischemic events and mortality in patients with AMI.^{4,5} Thus, secondary prevention protocols including these agents are regarded to be standard therapy following an AMI, along with aspirin and statins. Reflecting the results of the Valsartan in Acute Myocardial Infarction (VALIANT) trial, which showed equivalent outcomes between captopril and valsartan in post-AMI patients,⁶ the current guidelines advocate the long-term use of a BB and an ACEI/angiotensin II receptor antagonist (ARB) in patients who recover from an AMI regardless of their individual cardiovascular risk profiles.^{7–9} Although there is no doubt that these medications offer the most benefit to AMI patients complicated with left ventricular dysfunction or heart failure, there is still uncertainty about prescribing these agents to a real population of unselected AMI patients. Several previous studies have documented less benefit with these agents in patients with lower-risk myocardial infarctions.^{5,10} Moreover, most of these studies were conducted before the modern era of reperfusion with percutaneous coronary intervention (PCI), and the routine implementation of this more effective treatment raises further questions about the relevance of current BB- and ACEI/ARB-related secondary prevention recommendations in all post-AMI patients.¹¹ Therefore, we sought to evaluate the effectiveness of BB and/or ACEI/ARB treatment in improving survival using the nationwide data from the National Health Insurance (NHI) in South Korea by including all consecutive AMI patients who underwent a PCI.

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METHODS

Data Sources and Study Population

This study was supported by the National Strategic Coordinating Center of Clinical Research and the Health Insurance Review and Assessment Service (HIRA) and was approved by the Institutional Review Board of Asan Medical Center, Seoul, South Korea. All South Koreans are beneficiaries of the NHI system of South Korea and all healthcare providers are legally required to join the NHI system on a fee-for-service basis. The HIRA is a quasigovernmental organization that systematically evaluates the medical expenses reported from healthcare providers to minimize the risk of redundant and unnecessary medical services. Consequently, all NHI claims are reviewed by the HIRA and are systematically classified and recorded in an independent computerized database. The individual diagnoses are coded according to the *International Classification of Diseases, 10th Revision* (ICD-10). All prescribed medications were exclusively recorded with high accuracy and were basically classified according to the international Anatomical Therapeutic Chemical (ATC) classification system of the WHO Collaborating Center for Drug Statistics Methodology.¹² Specific information about the drugs and procedures were identified by self-developed codes from the HIRA.

From the HIRA database, we identified patients aged 18 years and older who had undergone a PCI (M6551, M6552, M6561-4, M6571, and M6572) for the diagnosis of an AMI (ICD-10 codes I21.X–I23.X) from June 2009 to July 2013. Patients who had a previous record of any type of coronary artery disease (ICD-10 codes I20.X–25.X) were excluded to ensure that we only enrolled patients with their first episode of AMI. Patients who died during hospitalization or within 30 days after the index procedure were excluded to reduce patient-related confounding factors by creating a more homogeneous population. We also excluded patients with incomplete data on any of the relevant covariates included in the final regression model.

Study Variables

Individual comorbid conditions were identified using the ICD-10 codes, including diabetes with/without chronic complications, hyperlipidemia, hypertension, congestive heart failure, cardiac arrhythmia, valvular heart disease, peripheral vascular disorder, cerebrovascular disease, chronic pulmonary disease, moderate or severe liver disease, renal disease, any malignancy, and rheumatic disease. To measure the patients' comprehensive life expectancy, the Charlson comorbidity index was calculated and used in the analysis.¹³

The hospital discharge medications considered for our present analysis were antiplatelet agents (ATC code: B01AC), statins (ATC codes: C10AA, C10BA, and C10BX), ACEIs (ATC codes: C09AA, C09BA, and C09BB), ARBs (ATC codes: C09CA, C09DA, and C09DB), calcium channel blockers (ATC codes: C08, C09BB, C09DB, and C10BX), diuretics (ATC codes: C03, C07B, C07C, C09BA, and C09DA), and BBs (ATC code: C07). Patients were grouped into exposure categories according to the combination of BB and ACEI/ARB prescribed. The 4 mutually exclusive exposure categories were constructed as “no drugs” (i.e., no BB or ACEI/ARB), “BB only”, “ACEI/ARB only”, and “BB and ACEI/ARB.” The primary outcome of our current analyses was all-cause mortality. Death was identified by all in- and outpatient claims records that indicated death. All claims data until December 2013 were used for our present analysis.

Statistical Analysis

Categorical variables are summarized as frequencies with percentages, and continuous variables as mean values with standard deviation. Between-group comparisons were performed using the Pearson χ^2 test for categorical variables, and one-way ANOVA for numerical variables. To investigate the associations of BB and/or ACEI/ARB treatment with mortality after AMI, relative risks of death were estimated using Cox proportional hazards regression models, with “no drugs” group as the reference. Clinically relevant variables listed in Table 1 were selected as potential risk-adjusting variables. Variables with a P value ≤ 0.1 in univariate analyses were included in a multivariable Cox regression model. The final models for each end point were determined by backward stepwise elimination procedures in which the least significant variable was discarded 1 by 1 from the full model. All reported P values are 2-sided and a probability value of $P < 0.05$ was considered significant. Data management and statistical analyses were conducted using SAS Version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

A total of 44,627 patients who underwent PCI with a diagnosis of AMI between July 2009 and June 2013 were identified. The main analysis cohort comprised 33,390 patients who met the eligibility criteria; 16,280 patients were treated with both BB and ACEI/ARB, whereas 3683 received only BB, 9849 received only ACEI/ARB, and 3578 took neither of these types of medications (Figure 1). The baseline characteristics of the study patients are presented in Table 2. The mean age of the cohort was 62 years and it comprised 24,847 men (74.4%). Overall, diabetes was observed in 10,014 patients (30.0%) and 1183 (3.5%) suffered from malignancy. The number of patients who underwent PCI for AMI gradually increased over time during the study period, from 6743 in 2009 to 2010 to 9674 in 2012 to 2013 (a 43% increase). Most of the study population was treated with aspirin (94.2%) and statins (94.0%). Carvedilol (73.7%) was the predominantly prescribed BB, followed by nebivolol (9.3%) and bisoprolol (7.8%), while among ACEI/ARBs, valsartan (23.1%), candesartan (21.8%), and losartan (17.5%) were used in a similar frequency (Supplemental Table 1, <http://links.lww.com/MD/A740>). The patient characteristics according to the prespecified study categories are displayed in Table 1. Patients in the “no drugs” category tended to be older and had a higher prevalence of renal disease and malignancy. Patients in the “BB and ACEI/ARB” category were more likely to have hypertension and hyperlipidemia. The Charlson comorbidity index score was highest in the “no drugs” group and lowest in the “BB only” group and this trend was relatively consistent throughout the study period (Table 3). The proportion of patients treated with BB or ACEI/ARB during the study period is shown in Figure 2. Overall, the proportion of AMI patients treated with either BB or ACEI/ARB gradually decreased over time, whereas those treated with BB showed a considerable decrease of 17% from 2009–2010 to 2012–2013. Specifically, the proportion of patients treated with ACEI/ARB alone substantially increased, whereas the ratios of those treated with BB alone were relatively steady throughout the 4-year period. Notably, a 17.6% decrease in patients treated with both BB and ACEI/ARB occurred between 2009–2010 and 2012–2013 with a gradual increase in the patient proportion that took neither of these medications.

TABLE 1. Patient Characteristics According to the Exposure Category

	No Drug (n = 3578)	BB Only (n = 3683)	ACEI/ARB Only (n = 9849)	BB and ACEI/ARB (n = 16,280)	p Value
Age, yr	63.0 ± 13.2	61.9 ± 12.8	62.6 ± 12.8	61.7 ± 12.5	<0.001
Sex, male	2675 (74.8)	2775 (75.4)	7285 (74.0)	12,112 (74.4)	0.400
Comorbid conditions					
Diabetes without complications	663 (18.5)	662 (17.8)	2018 (20.5)	3338 (20.5)	<0.001
Diabetes with chronic complications	354 (9.9)	291 (7.9)	985 (10.0)	1703 (10.5)	<0.001
Hyperlipidemia	694 (19.4)	680 (18.5)	2076 (21.1)	3562 (21.9)	<0.001
Hypertension	1066 (29.8)	1121 (30.4)	4119 (41.8)	7296 (44.8)	<0.001
Congestive heart failure	132 (3.7)	78 (2.1)	364 (3.7)	561 (3.5)	<0.001
Cardiac arrhythmia	116 (3.2)	102 (2.8)	273 (2.8)	431 (2.7)	0.280
Valvular disease	11 (0.3)	6 (0.2)	34 (0.4)	57 (0.4)	0.320
Peripheral vascular disorder	310 (9.5)	337 (9.2)	1003 (10.2)	1623 (10.0)	0.030
Cerebrovascular disease	359 (10.0)	296 (8.0)	1030 (10.5)	1557 (9.6)	<0.001
Chronic pulmonary disease	635 (17.8)	562 (15.3)	1753 (17.8)	2549 (15.7)	<0.001
Moderate or severe liver disease	13 (0.4)	12 (0.3)	26 (0.3)	49 (0.3)	0.800
Renal disease	182 (5.1)	61 (1.7)	149 (1.5)	273 (1.7)	<0.001
Malignancy	166 (4.6)	135 (3.7)	366 (3.7)	516 (3.2)	<0.001
Rheumatic disease	82 (2.3)	74 (2.0)	205 (2.1)	354 (2.2)	0.810
Charlson comorbidity index	1.38 ± 1.97	1.13 ± 1.65	1.27 ± 1.69	1.23 ± 1.67	<0.001
Medication at discharge					
Aspirin	2881 (80.5)	3507 (95.2)	9340 (94.8)	15,728 (96.6)	<0.001
ADP receptor antagonists	2667 (74.5)	3246 (88.1)	8746 (88.8)	14,609 (92.9)	<0.001
Statins	3286 (91.8)	3473 (94.3)	9288 (94.3)	15,336 (94.2)	<0.001
Calcium channel blockers	707 (19.8)	654 (17.8)	2280 (23.2)	3859 (23.7)	<0.001
Diuretics	706 (19.7)	916 (24.9)	3185 (32.3)	5591 (34.3)	<0.001

Data are the mean ± SD or numbers (percentage).

ACEI = angiotensin-converting enzyme inhibitor, ADP = adenosine diphosphate, ARB = angiotensin II receptor antagonist, BB = β-blocker.

The median length of follow-up was 2.4 years (interquartile range, 1.4–3.4 years). During the follow-up period, there were 1080 deaths (3.2%), of which 164 (4.6%), 109 (3.0%), 293 (3.0%), and 514 (3.2%) occurred in “no drugs”, “BB only”, “ACEI/ARB only,” and “BB and ACEI/ARB” group, respectively. Overall, compared with the reference group of “no drugs,” the unadjusted risk of all-cause death was significantly lower when AMI patients were treated with either BB (hazard ratio [HR] 0.59, 95% confidence interval [CI] 0.46–0.75, *P* < 0.001) or ACEI/ARB (HR 0.64, 95% CI 0.53–0.78, *P* < 0.001) after PCI (Figure 3). However, after adjustment for possible clinical confounders, the difference failed to reach statistical significance, although there was a trend toward improved survival in those populations (BB only: adjusted HR 0.88, 95% CI 0.68–1.14, *P* = 0.325; ACEI/ARB only: adjusted HR 0.84, 95% CI 0.68–1.04, *P* = 0.111). Although patients treated with both drugs showed a similar survival trend (adjusted HR 0.86, 95% CI 0.70–1.06,

P = 0.154), no additional benefit was found versus those treated with each drug alone (Table 4).

DISCUSSION

In our present analysis of South Korean NHI data that included 33,390 unselected nonfatal AMI individuals who underwent PCI and survived at least 30 days, we found that treatment with BB or ACEI/ARB was associated with a non-significant reduction in the risk of all-cause mortality (12%–16%) during a median follow-up of 2.4 years and that treatment with the 2 drugs together had no further survival benefit over treatment with either alone.

The clinical benefit of BB or ACEI/ARB in patients after AMI may be partly mediated by a reduction in the risk of recurrent ischemic events, improvement in hemodynamics, and reduction in congestive heart failure.^{14,15} By virtue of these benefits, several randomized controlled trials have shown a

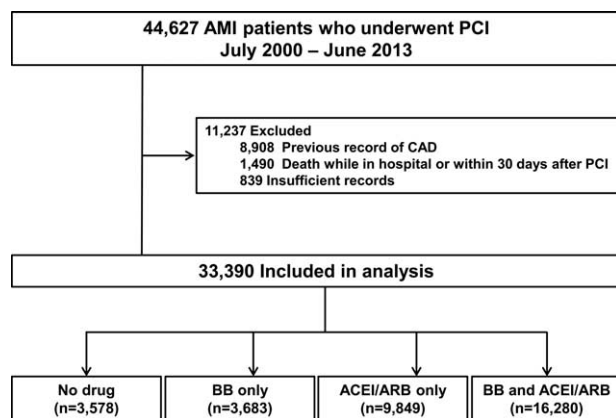


FIGURE 1. Overview of the study population, ACEI = angiotensin-converting enzyme inhibitor; AMI = acute myocardial infarction; ARB = angiotensin II receptor antagonist; BB = β -blocker; CAD = coronary artery disease; PCI = percutaneous coronary intervention.

TABLE 2. Baseline Characteristics of the Study Population

Characteristics	n = 33,390
Age, yr	62.1 \pm 12.7
Sex, male	24,847 (74.4)
Enrolled subjects	
July 2009 to June 2010	6743 (20.2)
July 2010 to June 2011	8286 (24.8)
July 2011 to June 2012	8687 (26.0)
July 2012 to June 2013	9674 (29.0)
Comorbid conditions	
Diabetes without complications	6681 (20.0)
Diabetes with chronic complications	3333 (10.0)
Hyperlipidemia	7012 (21.0)
Hypertension	13,602 (40.7)
Congestive heart failure	1135 (3.4)
Cardiac arrhythmia	922 (2.8)
Valvular heart disease	108 (0.3)
Peripheral vascular disorder	3273 (9.8)
Cerebrovascular disease	3242 (9.7)
Chronic pulmonary disease	5499 (16.5)
Moderate or severe liver disease	100 (0.3)
Renal disease	665 (2.0)
Malignancy	1183 (3.5)
Rheumatic disease	715 (2.1)
Charlson comorbidity index	1.25 \pm 1.71
Medication at discharge	
Aspirin	31,456 (94.2)
ADP receptor antagonists	29,268 (87.7)
Statins	31,383 (94.0)
Calcium channel blockers	7500 (22.5)
Diuretics	10,398 (31.1)
BBs	19,963 (59.8)
ACEI or ARBs	26,129 (78.3)

Data are the mean \pm SD or numbers (percentage).

ACEI = angiotensin-converting enzyme inhibitor, ADP = adenosine diphosphate, ARB = angiotensin II receptor antagonist, BB = β -blocker.

survival benefit of these drugs for secondary prevention, with some studies emphasizing that these 2 drugs have an additive effect.^{1,16–19} The results of these studies have long been reflected in the clinical guidelines, which recommend routine use of BB and ACEI/ARB in all AMI patients unless contraindicated.^{7–9,20} However, concerns have been raised about these recommendations because most of the data to support the use of these drugs predate the era of reperfusion therapy and modern secondary prevention, making them low-quality evidence from the current perspective. Moreover, it is controversial whether this medical prevention improves clinical outcomes in relatively low-risk patient groups (e.g., small AMI, normal left ventricular function, single-vessel disease) and several studies suggested that there might be different drug responses in different patient subgroups after AMI (e.g., sex, cardiac rhythm, type of AMI).^{21,22} Thus, considering the potential adverse events attributed to therapy with BB or ACEI/ARB, treatment of the unselected AMI population with these agents might be inappropriate in the modern PCI era. Our current study, based on reliable nationwide data that included all AMI patients who underwent PCI from 2009 to 2013, may provide an important “real world” insight into this debatable issue.

In our present analysis, the unadjusted incidence of all-cause death was significantly lower in patients who were treated with either BB or ACEI/ARB than in those who were not. This finding may be partly explained by the characteristics of the patients allocated to the control group because they were older and had a more severe medical condition, as reflected by a higher Charlson comorbidity index. However, after adjusting for possible confounding variables, the statistical differences in the risk of death among all study groups disappeared. Nonetheless, we observed a trend for a reduction in mortality risk in BB- and/or ACEI/ARB-treated patients compared with untreated ones. There may be several possible explanations for our present study findings. First, the beneficial effects of BB or ACEI/ARB may have been offset by a more effective reperfusion therapy. In patients with AMI, PCI can reduce the size of the infarction or the residual myocardium in jeopardy and thus modify the underlying substrate responsible for the patient’s future risk of cardiac events.^{23–25} A recent meta-analysis conducted by Bangalore et al²⁶ that focused on BB therapy reported this important issue. After analyzing 60 trials including 102,003 patients, they found that treatment of AMI patients with BB reduced mortality in the prereperfusion era but not in the reperfusion era. Because many trials eligible for the reperfusion era in this meta-analysis included those from the fibrinolytic era, we can speculate that a more effective reperfusion method such as PCI may further reduce the benefit of BB in the setting of AMI. On the basis of this theory, the impact of reperfusion therapy on the effect of ACEI/ARB therapy may be extrapolated by considering how ACEIs/ARBs benefit post-AMI patients.^{4,5} Second, other drugs that protect against cardiovascular events and mortality in contemporary practice may have played a role. These drugs, particularly adenosine diphosphate receptor antagonists and statins, were not systematically used in early BB and ACEI/ARB trials and, furthermore, fewer study patients received aspirin compared with the current practice.^{1,16–19} Although these drugs exploit somewhat different mechanisms to prevent events after AMI, wide use of antiplatelet agents and statins in our study may have attenuated the survival benefit of BB and ACEI/ARB. Finally, our current findings may be attributable to a mixed population of different cardiovascular risk factors. Evidence indicates that both BB and ACEI/ARB may be of less benefit in certain patient subgroups

TABLE 3. Charlson Comorbidity Index Score According to the Patient Group and Study Period

Category	July 2009 to June 2010		July 2010 to June 2011		July 2011 to June 2012		July 2012 to June 2013		p Value
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	
No drug	568	1.500 ± 2.106	753	1.371 ± 1.977	987	1.287 ± 1.809	1270	1.400 ± 2.017	0.7907
BB only	713	1.041 ± 1.543	977	1.087 ± 1.623	912	1.067 ± 1.578	1081	1.278 ± 1.782	0.0042
ACEI/ARB only	1585	1.233 ± 1.609	2105	1.245 ± 1.690	2700	1.255 ± 1.632	3459	1.311 ± 1.773	0.8377
BB and ACEI/ARB	3877	1.216 ± 1.685	4451	1.201 ± 1.653	4088	1.230 ± 1.663	3864	1.267 ± 1.696	0.1699
P value		0.003		0.0076		0.0029		0.9168	
Total	6743	1.225 ± 1.695	8286	1.215 ± 1.692	8687	1.227 ± 1.663	9674	1.301 ± 1.778	

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor antagonist, BB = β-blocker, SD = standard deviation.

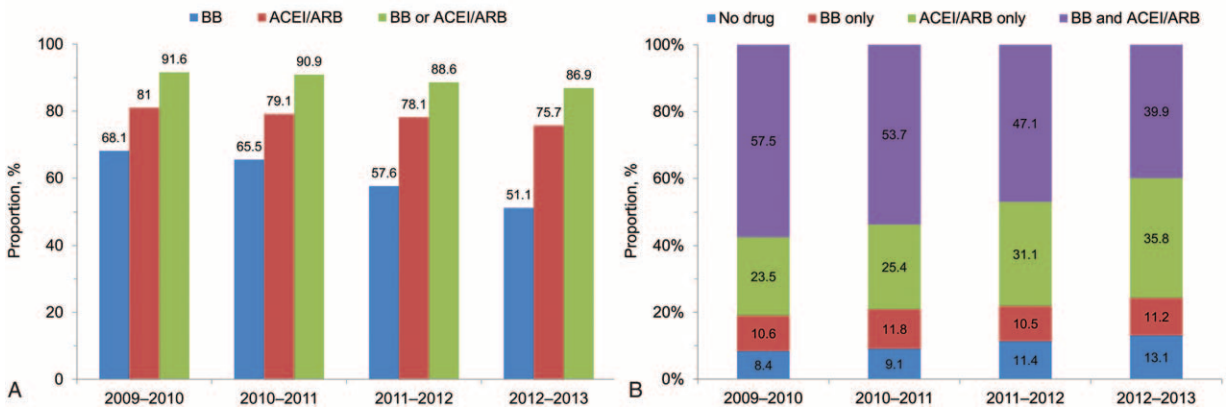


FIGURE 2. Drug use trends. A, Trends in the use of β-blocker or renin-angiotensin system inhibitor according to each study period. B, Trends in the use of β-blocker and/or renin-angiotensin system inhibitor according to the study group. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor antagonist; BB = β-blocker.

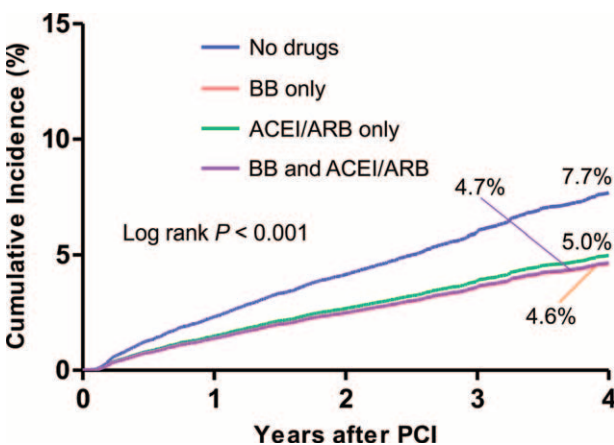


FIGURE 3. Cumulative incidence of death according to each patient category. Log rank $P < 0.001$ for patients in the “no drugs” category versus others. PCI = percutaneous coronary intervention.

with lower cardiac risk.^{10,11,18,27–30} In a clinical situation, most AMI patients may be classified as a low-risk population according to the Trandolapril Cardiac Evaluation study.¹⁵ That Danish study consecutively screened all patients with enzyme-confirmed AMI, with the investigators estimating that their higher risk patients—selected by echocardiography—represent 25% of the AMI population. Moreover, because our present cohort only included patients who survived at least 30 days after the index procedure, more patients with preserved left ventricular function and a relatively lower cardiac risk profile may have been selected. Thus, it is likely that the greater benefits of BB or ACEI/ARB observed in the more selective trials are diluted because many patients who would not benefit from these medications were included in our study. Conversely, a patient subset that would greatly benefit from these medical therapies may exist in our study population, an aspect that needs to be clarified in the future.

It is important to note that BBs have not been systematically investigated in contemporary AMI trials using PCI.³⁰ Also, opinions still differ on whether ACEIs/ARBs should be given to all post-AMI patients or to selected at-risk patients only.^{8,9,31} Accordingly, the adherence to these guideline-based

TABLE 4. Crude and Adjusted Hazard Ratios for All-Cause Mortality

	Crude		Multivariable Adjusted	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
YN vs. NN	0.59 (0.46–0.75)	<0.001	0.88 (0.68–1.14)	0.325
NY vs. NN	0.64 (0.53–0.78)	<0.001	0.84 (0.68–1.04)	0.111
YY vs. NN	0.60 (0.50–0.71)	<0.001	0.86 (0.70–1.06)	0.154
YN vs. NY	0.92 (0.74–1.15)	0.482	1.05 (0.84–1.31)	0.689
YY vs. YN	1.01 (0.82–1.24)	0.930	0.98 (0.80–1.21)	0.856
YY vs. NY	0.93 (0.81–1.08)	0.342	1.03 (0.89–1.19)	0.727

CI = confidence interval, NN = no drug, NY = renin-angiotensin system inhibitor only, YN = β -blocker only, YY = both β -blocker and renin-angiotensin system inhibitor.

medications differs substantially among cardiovascular societies.^{32,33} In South Korea, based on our nationwide data, BBs (59.8%) and ACEIs/ARBs (78.3%) were used far less often during the study period than other evidence-based medicines such as aspirin, adenosine diphosphate receptor antagonists, and statins. Particularly, as the number of PCIs for AMI increased, BB treatment decreased substantially over time, with only half of the patients treated in the 2012 to 2013 period receiving PCI. This approach contrasts with the American Heart Association guidelines, which recommend oral BBs as a class I indication for all patients with AMI for at least 3 years.⁷ Although this trend was less dominant for ACEIs/ARBs, the lack of evidence to support routine use of BB and ACEI/ARB in AMI patients who underwent PCI may have contributed to this discrepancy. Further investigation is needed to resolve this issue.

Our present study had limitations inherent to its nonrandomized, observational design. First, similar to previous studies using an administrative database, we did not have full information on the medication dose and frequency, limiting the interpretation of our results concerning the effective guideline-recommended dose. Second, we had no clinical data regarding the cardiac test findings or vital signs of each individual, such as the ventricular ejection fraction, type of AMI, Killip class, or the extent of coronary artery disease. Thus, although we adjusted for a wide range of patient characteristics, we could not rule out the possible influence of unmeasured confounding factors or selection bias. However, patients who died during hospitalization or within 30 days after the index procedure were excluded by our study design, which may have reduced possible biases due to differences in baseline characteristics between the groups. Third, because Korean population was exclusively included in our study, it is uncertain whether these findings can be applied to other ethnic groups with different patient characteristics and procedural strategies.^{34,35} Finally, our study population did not include AMI patients who underwent coronary artery bypass graft surgery or medical treatment alone, limiting its applicability to the entire AMI population. However, most patients receive PCI as the primary therapy in the real-world setting and a large sample size and the reflection of current real-world practice, such as high rates of aspirin and statin use, may be the strengths of our study.

CONCLUSION

In unselected AMI patients who underwent PCI and survived at least 30 days, the effects of BBs and/or ACEIs/ARBs

on survival, in conjunction with broad use of antiplatelet agents and statins, are limited. These results should be confirmed by future dedicated large, randomized clinical trials with a long-term follow-up.

REFERENCES

- 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.
- Freemantle N, Cleland J, Young P, et al. beta Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ*. 1999;318:1730–1737.
- Vantrimpont P, Rouleau JL, Wun CC, et al. Additive beneficial effects of beta-blockers to angiotensin-converting enzyme inhibitors in the Survival and Ventricular Enlargement (SAVE) Study. SAVE Investigators. *J Am Coll Cardiol*. 1997;29:229–236.
- Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized, trials. ACE Inhibitor Myocardial Infarction Collaborative Group. *Circulation*. 1998;97:2202–2212.
- Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet*. 2000;355:1575–1581.
- Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349:1893–1906.
- Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACC secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol*. 2011;58:2432–2446.
- Hamm CW, Bassand JP, Agewall S, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32:2999–3054.

9. Steg PG, James SK, Atar D, et al., Task Force on the management of ST-segment elevation. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33:2569–2619.
10. Kernis SJ, Harjai KJ, Stone GW, et al. Does beta-blocker therapy improve clinical outcomes of acute myocardial infarction after successful primary angioplasty? *J Am Coll Cardiol*. 2004;43:1773–1779.
11. Ozasa N, Kimura T, Morimoto T, et al. Lack of effect of oral beta-blocker therapy at discharge on long-term clinical outcomes of ST-segment elevation acute myocardial infarction after primary percutaneous coronary intervention. *Am J Cardiol*. 2010;106:1225–1233.
12. WHO Collaborating Centre for Drug Statistics Methodology: the Anatomical Therapeutic Chemical classification system. Available at: http://www.whocc.no/atc/structure_and_principles. Accessed June 9, 2015.
13. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43:1130–1139.
14. Gheorghiadu M, Goldstein S. Beta-blockers in the post-myocardial infarction patient. *Circulation*. 2002;106:394–398.
15. Kaski JC, Fernandez-Berges D. Secondary prevention after acute myocardial infarction and coronary revascularisation: focus on Angiotensin converting enzyme inhibitors. *Cardiovasc Drugs Ther*. 2008;22:185–191.
16. Hjalmarson A, Elmfeldt D, Herlitz J, et al. Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial. *Lancet*. 1981;2:823–827.
17. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. *N Engl J Med*. 1995;332:80–85.
18. Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med*. 1995;333:1670–1676.
19. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative, Group. *Lancet*. 1986;2:57–66.
20. Jones K, Saxon L, Cunningham W, et al., Guideline Development G. Secondary prevention for patients after a myocardial infarction: summary of updated NICE guidance. *BMJ*. 2013;347:f6544.
21. Gunnell AS, Einarsdottir K, Sanfilippo F, et al. Improved long-term survival in patients on combination therapies following an incident acute myocardial infarction: a longitudinal population-based study. *Heart*. 2013;99:1353–1358.
22. Amann U, Kirchberger I, Heier M, et al. Effect of renin-angiotensin system inhibitors on long-term survival in patients treated with beta blockers and antiplatelet agents after acute myocardial infarction (from the MONICA/KORA Myocardial Infarction Registry). *Am J Cardiol*. 2014;114:329–335.
23. Simoons ML, Serruys PW, van den Brand M, et al. Early thrombolysis in acute myocardial infarction: limitation of infarct size and improved survival. *J Am Coll Cardiol*. 1986;7:717–728.
24. Serruys PW, Simoons ML, Suryapranata H, et al. Preservation of global and regional left ventricular function after early thrombolysis in acute myocardial infarction. *J Am Coll Cardiol*. 1986;7:729–742.
25. A prospective trial of intravenous streptokinase in acute myocardial infarction (I.S.A.M.). Mortality, morbidity, and infarct size at 21 days. The I.S.A.M. Study Group. *N Engl J Med*. 1986;314:1465–1471.
26. Bangalore S, Makani H, Radford M, et al. Clinical outcomes with beta-blockers for myocardial infarction: a meta-analysis of randomized trials. *Am J Med*. 2014;127:939–953.
27. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004;351:2058–2068.
28. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366:1622–1632.
29. Winchester DE, Pepine CJ. Usefulness of Beta blockade in contemporary management of patients with stable coronary heart disease. *Am J Cardiol*. 2014;114:1607–1612.
30. Huang BT, Huang FY, Zuo ZL, et al. Meta-analysis of relation between oral beta-blocker therapy and outcomes in patients with acute myocardial infarction who underwent percutaneous coronary intervention. *Am J Cardiol*. 2015;115:1529–1538.
31. Lymperopoulos A, Sturchler E, Bathgate-Siryk A, et al. Different potencies of angiotensin receptor blockers at suppressing adrenal beta-Arrestin1-dependent post-myocardial infarction hyperaldosteronism. *J Am Coll Cardiol*. 2014;64:2805–2806.
32. Bauer T, Gitt AK, Junger C, et al. Guideline-recommended secondary prevention drug therapy after acute myocardial infarction: predictors and outcomes of nonadherence. *Eur J Cardiovasc Prev Rehabil*. 2010;17:576–581.
33. Kotseva K, Wood D, De Backer G, et al. Use and effects of cardiac rehabilitation in patients with coronary heart disease: results from the EUROASPIRE III survey. *Eur J Prev Cardiol*. 2013;20:817–826.
34. Kook HY, Jeong MH, Oh S, et al. Current trend of acute myocardial infarction in Korea (from the Korea Acute Myocardial Infarction Registry from 2006 to 2013). *Am J Cardiol*. 2014;114:1817–1822.
35. Yeh RW, Sidney S, Chandra M, et al. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362:2155–2165.