Doctor of Medicine

Prognostic effect of beta-adrenergic receptor blockades in patients with coronary artery disease undergoing contemporary percutaneous coronary intervention: A nationwide cohort study

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ABSTRACT

Background: Beta-adrenergic receptor blockers are used in patients with coronary artery disease (CAD) to reduce the deleterious effects of excessive adrenergic activation on the heart. However, there is limited evidence regarding the benefit of beta-blockers in the context of contemporary management following percutaneous coronary intervention (PCI).

Methods: The nationwide South Korea National Health Insurance database was used to identify 79,021 patients with a diagnosis of either acute myocardial infarction (AMI; n = 30,404) or angina pectoris (n = 48,617) who underwent PCI between 2011 and 2015, and survived to be discharged from hospital. The risk of all-cause mortality in patients treated with a beta-blocker was compared with those who did not receive beta-blocker therapy using a propensity-score matching analysis.

Results: Beta-blockers were used in a higher proportion of patients with AMI (83.4%) than those with angina pectoris (62.7%). Over a median follow-up of 2.1 years (interquartile range, 1.2–3.2 years), the risk of death was comparable between the two groups in the overall population (hazard ratio [HR]: 0.98; 95% confidence interval [CI]: 0.90–1.06; p = 0.58). However, the mortality risk was significantly lower in patients treated with a beta-blocker in the AMI group (HR: 0.74; 95% CI: 0.63–0.86; p < 0.001). In the angina group, the mortality risk was comparable regardless of beta-blocker use (HR: 1.04; 95% CI: 0.94–1.15; p = 0.44). The survival benefit associated with beta-blocker therapy was most significant in the first year after the AMI event.

Conclusions: In unselected CAD patients who underwent contemporary post-PCI management, beta-blocker treatment was associated with a significant reduction in mortality in patients with AMI but not in those with angina.

Keywords: Angina pectoris, Beta-blocker, Coronary artery disease, Myocardial infarction

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INTRODUCTION

Beta-adrenergic receptors are the primary mediators of adrenergic activation in the heart and work to augment heart rate, contractility, and blood pressure.[1, 2] Excessive catecholamine stimulation therefore increases myocardial oxygen demand and predisposes to the development of ischemia or atrial and ventricular arrhythmias. Chronic adrenergic stimulation, which leads to receptor desensitization and down-regulation, eventually results in a decline in the inotropic reserve of the heart and induces myocardial apoptosis and fibrosis. Because activation of the adrenergic system occurs in a variety of coronary artery disease (CAD) settings, beta-adrenergic receptor blockers have been evaluated and used in this patient group to determine the clinical benefits of reducing the deleterious effects of adrenergic activation on the heart.[3]

Early clinical trials demonstrated that beta-blocker use reduces mortality in patients with acute myocardial infarction (AMI) or heart failure, and these agents therefore form the basis of current guidelines, which advocate the long-term use of a beta-blocker in patients recovering from an AMI regardless of their cardiovascular risk profile.[4-6] However, these recommendations are considered to be out-of-date in contemporary practice where additional therapies (i.e., percutaneous coronary intervention [PCI] and statins) with proven survival benefits are commonly used as part of AMI management. Moreover, clinical trials have not adequately studied whether beta-blockers reduce the risk of major cardiovascular events, including mortality, in patients with CAD who had not experienced a previous or recent myocardial infarction.[3, 7, 8] Therefore, real-world beta-blocker use in patients with CAD has been shown to vary considerably between countries and communities.[9] To address this knowledge gap and to evaluate real-world practice regarding the use of beta-blockers in South Korea, nationwide cohort data from the National Health Insurance (NHI) database

have been evaluated, focusing on two representative CAD populations (AMI and angina pectoris) undergoing PCI.

METHODS

Data Sources

The National Health Insurance (NHI) service of South Korea is a compulsory social insurance service that provides affordable health coverage for all citizens. All healthcare providers are obligated to join the NHI system on a fee-for-service basis.[10] The Health Insurance Review & Assessment (HIRA) service of South Korea is a quasi-governmental organization that systematically evaluates the medical expenses reported from healthcare providers to minimize the risk of redundant and unnecessary medical services. As a result, all NHI claims are reviewed by the HIRA and are systematically classified and recorded in an independent computerized database. Individual diagnoses in the HIRA database are coded according to the International Classification of Diseases, 10th Revision (ICD-10). Specific information about the drugs, medical devices, and procedures were identified by self-developed codes from the HIRA. The study protocol was approved by the local institutional review board of the Ulsan University Hospital, Ulsan, Korea.

Study Population

The HIRA claims database was used to identify patients aged ≥18 years of age who had undergone PCI (M6551, M6552, M6561–4, M6571, and M6572) for the treatment of a CAD (ICD-10 codes I20.X-I25.X) between July 2011 and June 2015. Patients with at least 6 months of eligibility prior to the index day were selected. Patients were excluded if the HIRA database indicated a previous history of CAD (ICD-10 codes I20.X–25.X) within 6

months of the index day to ensure that the study included only patients with a first diagnosis of CAD. Patients who died during hospitalization after the index procedure were excluded to reduce patient-related confounding factors and to create a more homogeneous beta-blocker-tolerant study population. Patients with incomplete data on any of the relevant covariates required for the final regression model were also excluded. Patients were categorized into two representative groups: AMI or angina pectoris, and the impact of beta-blocker use on patient outcomes was evaluated. AMI was defined using hospital discharge information from the HIRA databases (ICD-10 codes I21.X–I22.X).

Study Variables

Individual comorbid conditions were identified using the ICD-10 codes, such as diabetes with or without chronic complications, hyperlipidemia, hypertension, congestive heart failure, arrhythmia, valvular heart disease, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, moderate-to-severe liver disease, renal disease, cancer, and rheumatologic disease. Patients were also considered to have diabetes mellitus, hypertension, and hyperlipidemia if anti-diabetic, anti-hypertensive, and anti-hyperlipidemic drugs were identified from the medication codes in the HIRA database within 6 months of the index day.[18] The Charlson comorbidity index was calculated from these data to measure the patients' comprehensive life expectancy.

Cardiovascular medication was characterized as antiplatelet agents, statins, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and beta-blockers. Patients were grouped into mutually exclusive exposure categories according to the use of beta-blockers (i.e., beta-blocker group or no beta-blocker group) at the time of hospital discharge. Specific subtypes of beta-blockers and stents used during PCI (drug-eluting stent: J5083XXX; bare-metal stent: J5231XXX) were identified for each patient. Non-stent

coronary balloon angioplasty was assigned if device codes were not accompanied by a code indicating a drug-eluting stent or a bare-metal stent.

Clinical Outcomes

The primary endpoint of this study was all-cause mortality. Any subsequent coronary revascularization was evaluated as a secondary endpoint. Death was identified by all in- and outpatient claims records that indicated death. Coronary revascularization was identified using the procedure codes of PCI (M6551, M6552, M6561-4, M6571, and M6572) and coronary artery bypass surgery (O1641, O1642, O1647, OA641, OA642, and OA647) in the HIRA database. In patients with multiple revascularization events, the first event was included in the analysis. All claims data until June 2016 were used.

Statistical Analysis

The beta-blocker vs. no beta-blocker groups were compared within each patient category of AMI and angina. Continuous variables are presented as mean ± standard deviation, while categorical variables are shown as n (%). Continuous variables were compared using Student's t-test or the Wilcoxon rank-sum test, while categorical variables were compared using the $\chi 2$ statistics or Fisher's exact test, as appropriate. Cumulative event rates and probability curves were generated using the Kaplan–Meier method. Propensity-score matching analysis was performed to control for potential confounders and to minimize any selection bias. Propensity scores were estimated nonparametrically by fitting a logistic regression model using the variables outlined in **Table 1** (e.g., age, gender, comorbidities, type and number of stents, and Charlson comorbidity score). Matching was performed using a 1:1 matching protocol with a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score. Standardized differences were estimated for all the baseline covariates before and after matching, and values of < 5% for a given covariate indicate a

relatively small imbalance (**Figure 1**). Paired t-test or the McNemar test was used to assess the covariate balance between the two matched groups. Cox proportional hazards regression model with robust standard errors that accounts for the clustering of the pairs was used to compare the risks of outcomes in the matched cohort. The P-values were two-sided and those <0.05 were considered significant. Data analyses were performed using R software version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population and Characteristics

In the study period, a total of 191,926 patients aged ≥18 years were diagnosed with CAD and underwent PCI. Of these, 79,021 patients met the eligibility criteria; 55,853 of which (70.7%) were treated with a beta-blocker. A total of 30,404 patients had been diagnosed with AMI, and 48,617 patients were diagnosed with angina as the first event of CAD (**Figure 2**). The overall baseline patient characteristics are presented in **Table 1**. The mean age of the cohort was 64.1 years and 70.1% were male. Overall, diabetes was observed in 26,074 patients (33.0%), and 2,010 (2.5%) suffered from malignancy. When compared with patients with AMI, those with angina were generally older and had a higher frequency of cardiovascular risk factors. The number of patients who underwent PCI for angina gradually increased over time, from 10,986 in 2011–2012 to 13,081 in 2014–2015, representing a 19% increase. However, the number decreased in patients with AMI during the study period. The majority of the study population were treated with drug-eluting stents (93.4%); the average number of stents used was 1.4 ± 0.6. After PCI, secondary preventive drugs were used routinely, including aspirin (99.4%), P2Y12 receptor inhibitors (98.7%), and statins (88.7%).

Beta-blocker Use

Beta-blockers were used in a higher proportion of patients with AMI (83.4%) than those with angina (62.7%). Carvedilol (41.6%) and bisoprolol (33.8%) were the most commonly prescribed beta-blockers, followed by nebivolol (6.1%) and atenolol (1.9%); these proportions were similar in both the AMI and angina groups (**Table 2**). **Table 3** shows the patient characteristics according beta-blocker use in each of the diagnosis categories. Overall, patients who received no beta-blocker tended to be older and had a higher prevalence of cerebrovascular disease and malignancy. However, differences in patients characteristics between the beta-blocker versus no beta-blocker groups were also present according to the diagnostic category, i.e., patients who received a beta-blocker for angina were more likely to be female and have a history of heart failure or renal disease, whereas those who received beta-blockers following an AMI were less likely to be female or have diabetes, heart failure, or renal disease. The Charlson comorbidity index score was higher in patients receiving no beta-blockers in both the AMI and angina groups. The proportion of patients treated with beta-blockers during the study period is shown in **Figure 3**. Beta-blocker use was consistently high after AMI (>80%), although the proportion gradually decreased over time. However, the use of beta-blockers in the angina group was relatively stable (approximately 60%) throughout the 4 year study period.

Clinical Outcomes

The median length of follow-up was 2.1 years (interquartile range, 1.2–3.2 years). The primary outcome of death occurred in 2,604 (4.7%) patients in the beta-blocker group and 1,154 patients (5.0%) in the no beta-blocker group (**Figure 4**). Repeat revascularization was performed in 7,876 patients. Overall, the mortality rate was significantly lower in patients treated with a beta-blocker compared with those without (2 year event rate: 4.2% vs. 4.7%; log-rank p = 0.005). After propensity-score matching to assemble a cohort of patients with

clinical equipoise for beta-blocker and no beta-blocker therapy at baseline, there were 16,893 matched pairs of patients in the angina cohort and 4,963 pairs in the AMI cohort. Baseline characteristics in the propensity-score matched cohort are shown in **Table 4**, and the event rates and risks for clinical outcomes of the matched cohort are shown in **Figure 5** and **Table 5**. A differential prognosis was found between the two populations in that there was no difference in the risk of death between the beta-blocker and no beta-blocker groups in patients with angina (hazard ratio [HR]: 1.04; 95% confidence interval [CI]: 0.94–1.15; p = 0.44), whereas the mortality risk was significantly lower with beta-blocker treatment in patients with AMI (HR: 0.74; 95% CI: 0.63–0.86; p < 0.001). A similar trend was observed for the composite outcome of death and repeat coronary revascularization. The survival benefit associated with beta-blocker use was most significant within 1 year of the AMI event, as indicated by the landmark analysis (**Figure 5B**). The treatment effect for the primary outcome in prespecified subgroups of the overall and matched AMI cohort is shown in **Figure 6**. The risk of mortality between beta-blocker and no beta-blocker treatment across the subgroups was generally consistent with the overall results of AMI, with the exception of those stratified by the presence or absence of congestive heart failure and renal disease. Beta-blocker treatment was associated with a neutral risk of the primary outcome in patients with congestive heart failure or renal disease, resulting in a significant interaction between those variables and the relative treatment effect of beta-blockers.

Table 1. Baseline characteristics of the study population

Characteristics	Overall n=79,021	Angina pectoris n=48,617	AMI n=30,404
Age, years	64.1 ± 12.1	65.0 ± 11.5	62.8 ± 12.9
Male	55,366 (70.1)	32,450 (66.7)	22,916 (75.4)
Enrolled subjects			
July 2011 to June 2012	18,712 (23.7)	10,986 (22.6)	7,726 (25.4)
July 2012 to June 2013	19,373 (24.5)	11,713 (24.1)	7,660 (25.2)
July 2013 to June 2014	20,417 (25.8)	12,837 (26.4)	7,580 (24.9)
July 2014 to June 2015	20,519 (26.0)	13,081 (26.9)	7,438 (24.5)
Comorbid conditions			
Diabetes	26,074 (33.0)	18,268 (37.6)	7,806 (25.7)
Diabetes with chronic complications	209 (0.3)	148 (0.3)	61 (0.2)
Hyperlipidemia	30,039 (38.0)	22,368 (46.0)	7,671 (25.2)
Hypertension	44,148 (55.9)	30,833 (63.4)	13,315 (43.8)
Congestive heart failure	4,413 (5.6)	3,497 (7.2)	916 (3.0)
Cardiac arrhythmia	5,009 (6.3)	4,090 (8.4)	919 (3.0)
Valvular heart disease	297 (0.4)	245 (0.5)	52 (0.2)
Peripheral vascular disorder	8,069 (10.2)	5,711 (11.7)	2,358 (7.8)
Cerebrovascular disease	9,212 (11.7)	6,936 (14.3)	2,276 (7.5)
Chronic pulmonary disease	11,910 (15.1)	8,129 (16.7)	3,781 (12.4)
Moderate-to-severe liver disease	40 (0.1)	26 (0.1)	14 (0.05)
Renal disease	3,336 (4.2)	2,599 (5.3)	737 (2.4)
Malignancy	2,010 (2.5)	1,393 (2.9)	617 (2.0)

Rheumatic disease	146 (0.2)	100 (0.2)	46 (0.2)
Charlson comorbidity index	1.23 ± 1.36	1.42 ± 1.41	0.94 ± 1.21
Type of treatment for PCI			
Drug-eluting stent	73,837 (93.4)	45,350 (93.3)	28,487 (93.7)
Bare-metal stent	981 (1.2)	541 (1.1)	440 (1.4)
Plain balloon angioplasty	4,203 (5.3)	2,726 (5.6)	1,477 (4.9)
Number of stents per person	1.39 ± 0.64	1.41 ± 0.66	1.36 ± 0.60
Medication at discharge			
Aspirin	75,181 (95.1)	46,030 (94.7)	29,151 (95.9)
ADP receptor antagonists	78,100 (98.9)	47,867 (98.5)	30,233 (99.4)
Statins	70,078 (88.7)	42,201 (86.8)	27,877 (91.7)
ACEI or ARBs	53,768 (68.0)	30,495 (62.7)	23,273 (76.5)

Data are shown as the mean ± SD or n (%).

ADP, adenosine diphosphate; ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin II receptor antagonist; PCI, percutaneous coronary intervention.

Table 2. Type of beta-blocker used

Drugs	Overall n=55,853	Angina pectoris n=30,492	AMI n=25,361
Carvedilol	23,380	12,462	10,918
Bisoprolol	18,877	9,994	8,883
Nebivolol	3,388	2,062	1,326
Atenolol	1,046	816	230
Propranolol	847	603	244
Metoprolol	675	485	190
Labetalol	231	189	42
Bevantolol	229	159	70
Celiprolol	123	98	25
Amosulalol	88	67	21
Betaxolol	85	66	19
Sotalol	15	13	2
Arotinolol	13	12	1
Others	6,856	3,466	3,390

AMI, acute myocardial infarction

Table 3. Characteristics of the study patients according to beta-blocker use

Characteristics	Angina pectoris n=48,617			AMI n=30,404		
	No beta-blocker n=18,125	Beta-blocker n=30,492	P-value	No beta-blocker n=5,043	Beta-blocker n=25,361	P-value
Enrolled number			0.004			<0.001
July 2011 to June 2012	4,111 (22.7)	6,875 (22.5)		1,190 (23.6)	6,536 (25.8)	
July 2012 to June 2013	4,366 (24.1)	7,347 (24.1)		1,131 (22.4)	6,529 (25.7)	
July 2013 to June 2014	4,636 (25.6)	8,201 (26.9)		1,290 (25.6)	6,290 (24.8)	
July 2014 to June 2015	5,012 (27.7)	8,069 (26.5)		1,432 (28.4)	6,006 (23.7)	
Baseline characteristics						
Age, years	65.3±11.0	64.8±11.7	0.001	64.5±13.1	62.4±12.9	<0.001
Male	12,221 (67.4)	20,229 (66.3)	0.014	3,719 (73.7)	19,197 (75.7)	0.004
Diabetes	6,836 (37.7)	11,432 (37.5)	0.628	1,372 (27.2)	6,434 (25.4)	0.007
Diabetes with chronic complications	57 (0.3)	91 (0.3)	0.799	12 (0.2)	49 (0.2)	0.492
Hyperlipidemia	8,854 (48.8)	13,514 (44.3)	<0.001	1,306 (25.9)	6,365 (25.1)	0.234

Hypertension	11,562 (63.8)	19,271 (63.2)	0.192	2,270 (45.0)	11,045 (43.6)	0.058
Congestive heart failure	1,162 (6.4)	2,335 (7.7)	<0.001	180 (3.6)	736 (2.9)	0.013
Cardiac arrhythmia	1,571 (8.7)	2,519 (8.3)	0.120	173 (3.4)	746 (2.9)	0.065
Valvular heart disease	99 (0.5)	146 (0.5)	0.321	15 (0.3)	37 (0.1)	0.024
Peripheral vascular disease	2,173 (12.0)	3,538 (11.6)	0.205	392 (7.8)	1,966 (7.8)	0.954
Cerebrovascular disease	2,688 (14.8)	4,248 (13.9)	0.006	466 (9.2)	1,810 (7.1)	<0.001
Chronic pulmonary disease	3,096 (17.1)	5,033 (16.5)	0.102	721 (14.3)	3,060 (12.1)	<0.001
Moderate-to-severe liver disease	5 (0.03)	21 (0.1)	0.067	4 (0.1)	10 (0.04)	0.270
Renal disease	879 (4.8)	1,720 (5.6)	<0.001	145 (2.9)	592 (2.3)	0.024
Malignancy	567 (3.1)	826 (2.7)	0.008	124 (2.5)	493 (1.9)	0.021
Rheumatologic disease	40 (0.2)	60 (0.2)	0.605	9 (0.2)	37 (0.1)	0.553
Charlson comorbidity index	1.43 ± 1.39	1.41 ± 1.43	0.004	1.03 ± 1.28	0.92 ± 1.20	<0.001
Type of treatment for PCI			0.035			<0.001
Drug-eluting stent	16,858 (93.0)	28,492 (93.4)		4,618 (91.6)	23,869 (94.1)	
Bare-metal stent	191 (1.1)	350 (1.1)		64 (1.3)	376 (1.5)	
Plain balloon angioplasty	1,076 (5.9)	1,650 (5.4)		361 (7.2)	1,116 (4.4)	

Number of stents per person	1.37 ± 0.64	1.43 ± 0.68	<0.001	1.36 ± 0.60	1.36 ± 0.60	0.558
Medication at discharge						
Aspirin	16,740 (92.4)	29,290 (96.1)	<0.001	4,676 (92.7)	24,475 (96.5)	<0.001
ADP receptor antagonists	17,616 (97.2)	30,251 (99.2)	<0.001	4,964 (98.4)	25,269 (99.6)	<0.001
Statins	14,806 (81.7)	27,395 (89.8)	<0.001	4,405 (87.3)	23,472 (92.6)	<0.001
ACEI or ARBs	8,585 (47.4)	21,910 (71.9)	<0.001	2,936 (58.2)	20,337 (80.2)	<0.001

Data are shown as the mean ± SD or n (%).

ADP, adenosine diphosphate; ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin II receptor antagonist; PCI, percutaneous coronary intervention.

Table 4. Characteristics of propensity-score matched patients according to the beta-blocker use

Characteristics	Angina pectoris n=33,786			AMI n=9,926		
	No beta-blocker n=16,893	Beta-blocker n=16,893	P-value	No beta-blocker n=4,963	Beta-blocker n=4,963	P-value
Baseline characteristics						
Age, years	65.2±11.1	65.0±11.5	0.30	64.4±13.0	64.0±13.1	0.89
Male	11,355 (67.2)	11,265 (66.7)	0.22	3,662 (73.8)	3,665 (73.8)	0.48
Diabetes	6,281 (37.2)	6,218 (36.8)	0.22	1,347 (27.1)	1,389 (28.0)	0.15
Diabetes with chronic complications	52 (0.3)	55 (0.3)	0.70	11 (0.2)	13 (0.3)	0.54
Hyperlipidemia	8,058 (47.7)	7,905 (46.8)	0.19	1,280 (25.8)	1,283 (25.9)	0.82
Hypertension	10,689 (63.3)	10,745 (63.6)	0.66	2,231 (45.0)	2,217 (44.7)	0.42
Congestive heart failure	1,098 (6.5)	1,180 (7.0)	0.61	174 (3.5)	162 (3.3)	0.78
Arrhythmia	1,444 (8.5)	1,429 (8.5)	0.85	170 (3.4)	178 (3.6)	0.87
Valvular disease	91 (0.5)	80 (0.5)	0.12	13 (0.3)	15 (0.3)	0.99

Peripheral vascular disease	1,973 (11.7)	1,949 (11.5)	0.82	385 (7.8)	409 (8.2)	0.32
Cerebrovascular disease	2,422 (14.3)	2,392 (14.2)	0.79	446 (0.9)	457 (9.2)	0.83
Chronic pulmonary disease	2,863 (16.9)	2,793 (16.5)	0.44	701 (14.1)	699 (14.1)	0.79
Moderate-to-severe liver disease	5 (0.03)	6 (0.04)	0.51	3 (0.1)	3 (0.1)	0.68
Renal disease	825 (4.9)	872 (5.2)	0.88	142 (2.9)	134 (2.7)	0.51
Cancer	512 (3.0)	499 (3.0)	0.41	119 (2.4)	102 (2.1)	0.59
Rheumatologic disease	36 (0.2)	39 (0.2)	0.10	9 (0.2)	5 (0.1)	0.79
Charlson comorbidity index	1.41 ± 1.38	1.40 ± 1.41	0.99	1.02 ± 1.27	1.03 ± 1.27	0.48
Type of treatment for PCI						
Drug-eluting stent	15,758 (93.3)	15,799 (93.5)	0.29	4,579 (92.3)	4,573 (92.1)	0.97
Bare-metal stent	179 (1.1)	163 (1.0)	0.36	63 (1.3)	58 (1.2)	0.044
Number of stent per person	1.38 ± 0.65	1.41 ± 0.66	0.636	1.36 ± 0.60	1.36 ± 0.60	0.504
Medication at discharge						
Antiplatelet agents	16,820 (99.6)	16,818 (99.6)	0.43	4,957 (99.9)	4,949 (99.7)	0.34
Statin	14,706 (87.1)	14,605 (86.5)	0.59	4,397 (88.6)	4,406 (88.8)	0.69

ACEI/ARB	8,580 (50.8)	8,712 (51.6)	0.74	2,936 (59.2)	2,985 (60.1)	0.14

Data are expressed as n (%) and mean ± SD.

ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; PCI; percutaneous coronary intervention

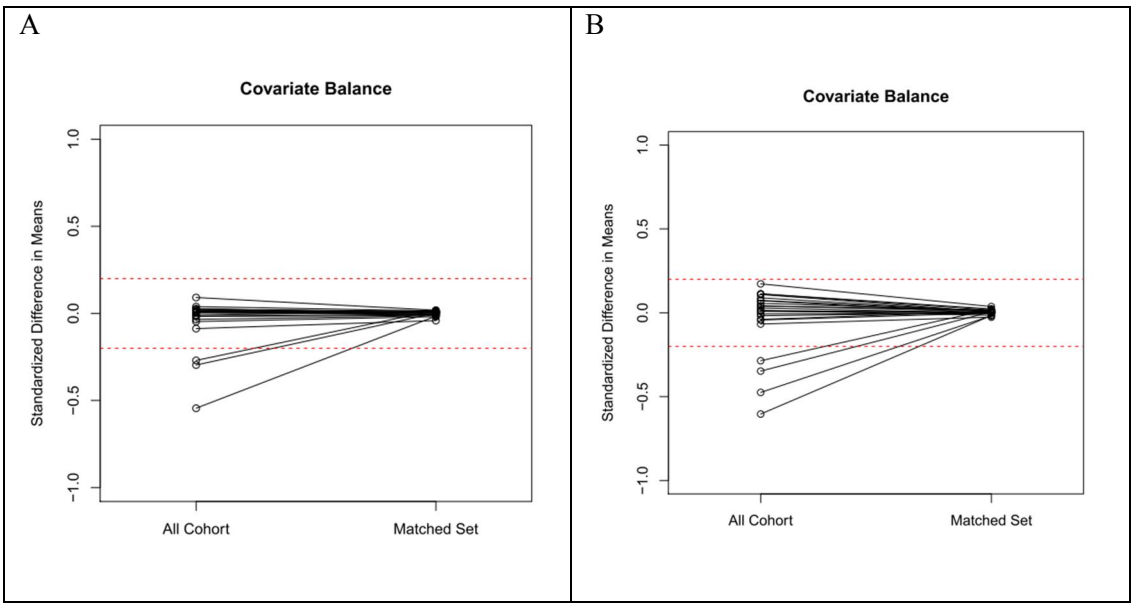
Table 5. Clinical outcomes in propensity-score matched patients according to beta-blocker use

Outcomes	Angina pectoris (16,893 pairs)		AMI (4,963 pairs)	
	HR (95% CI)	P-value	HR (95% CI)	P-value
All-cause of death	1.040 (0.942–1.148)	0.436	0.735 (0.626–0.864)	<0.001
Death or coronary revascularization	1.019 (0.961–1.081)	0.522	0.801 (0.729–0.880)	<0.001

Hazard ratios are for patients who received beta-blocker vs. no beta-blocker therapy

AMI, acute myocardial infarction; CI, confidence interval; HR, hazard ratio

Figure 1. Covariate balance before and after matching for each comparison.



All values were <0.05.

A; Angina pectoris population, B; Acute myocardial infarction population

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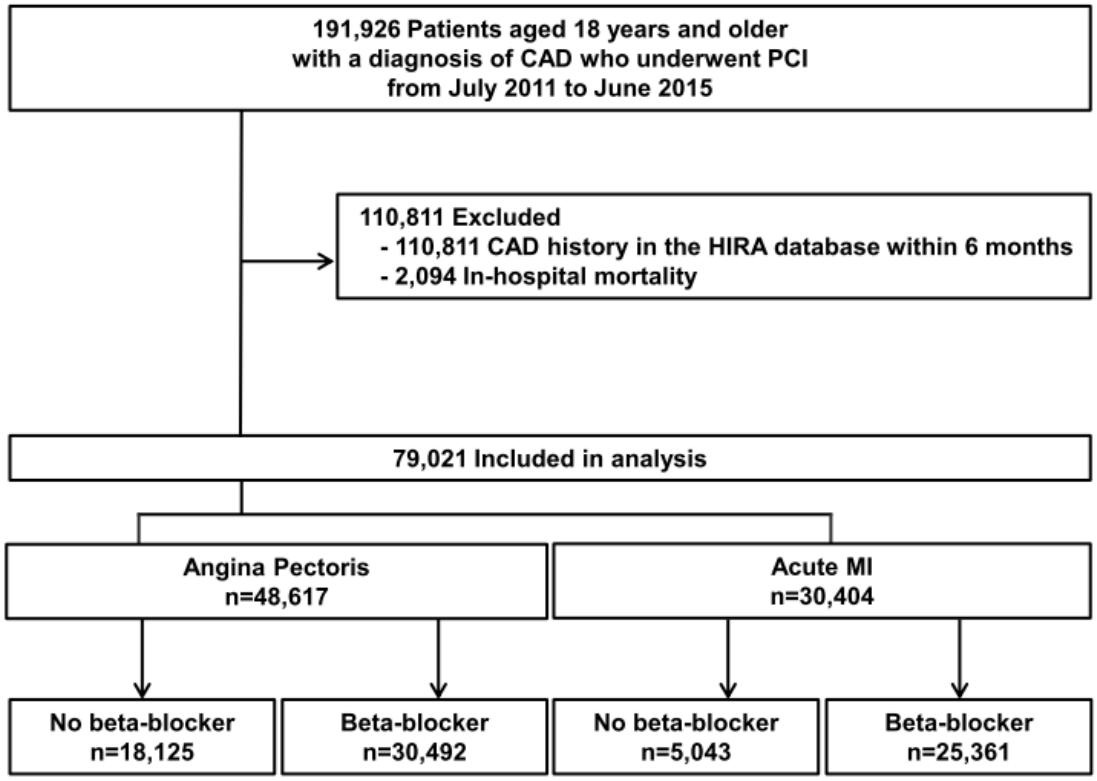
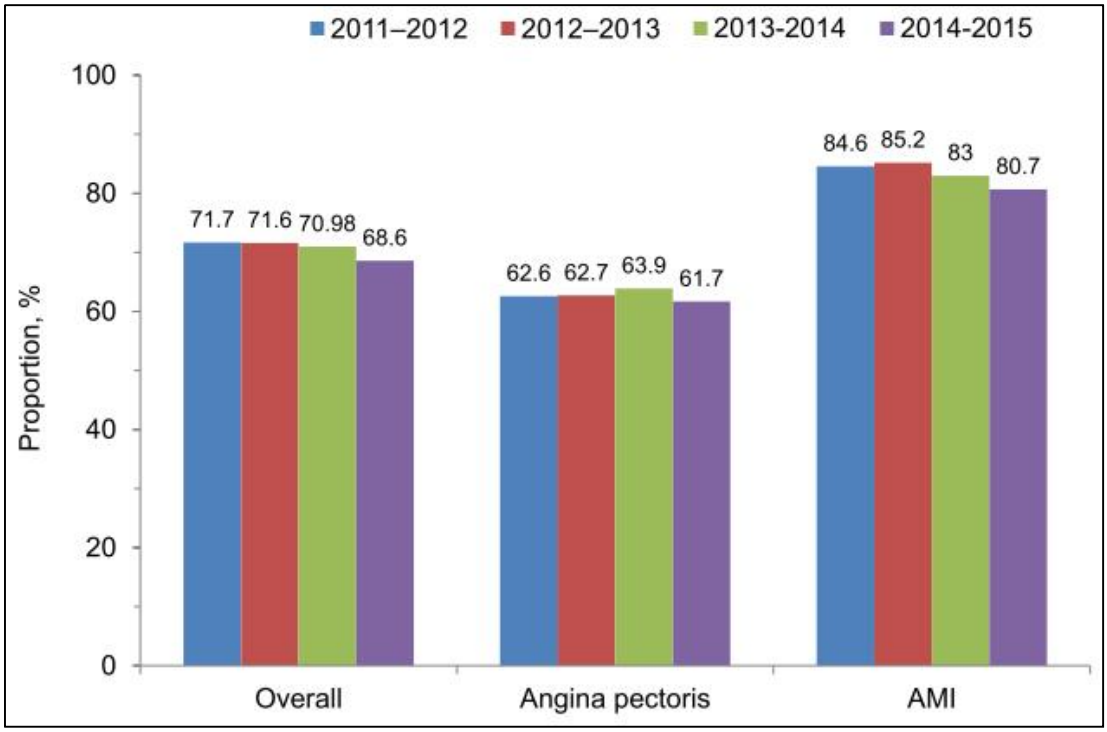
Figure 2. Overview of the study population



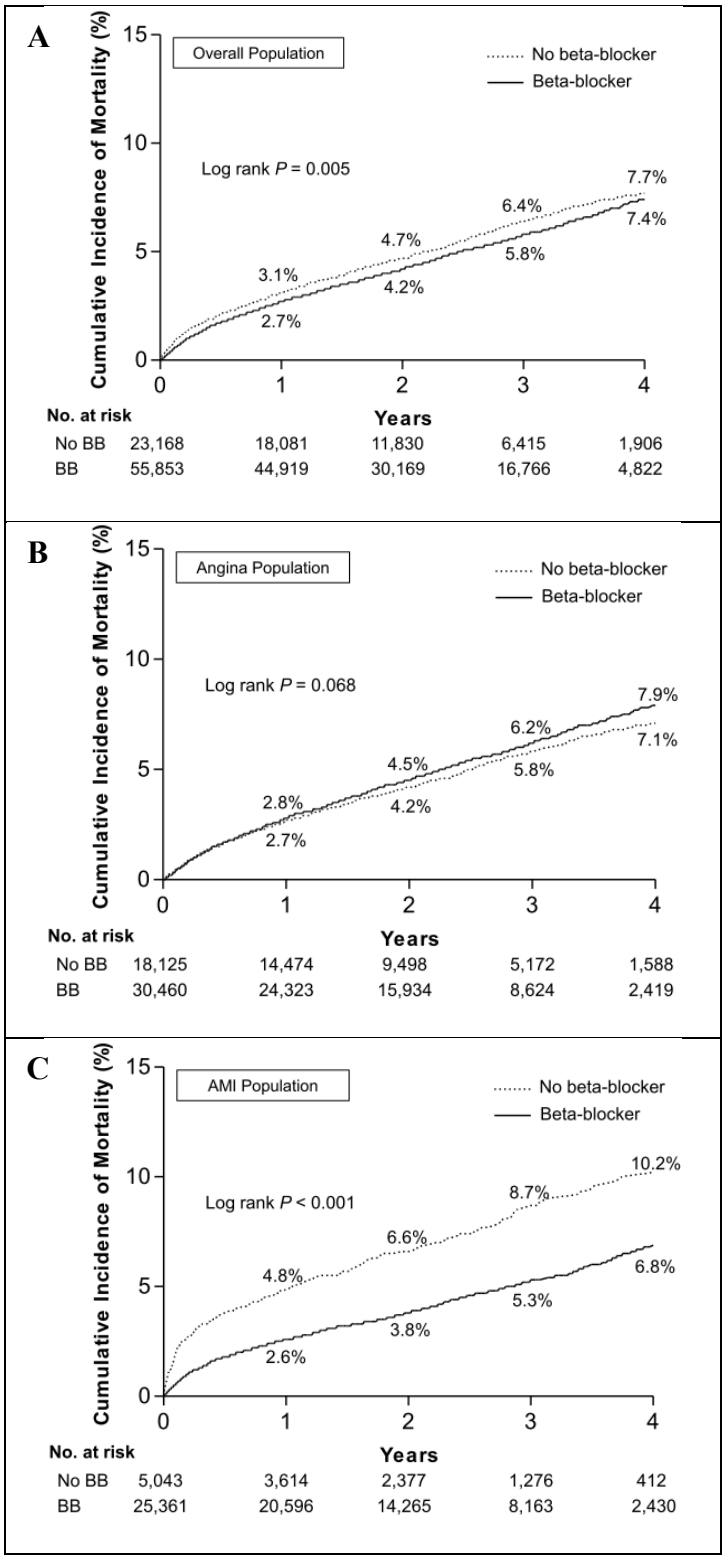
CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention

Figure 3. Trends in beta-blocker use



AMI, acute myocardial infarction

Figure 4. Kaplan-Meier cumulative event curves for mortality in the unmatched cohort

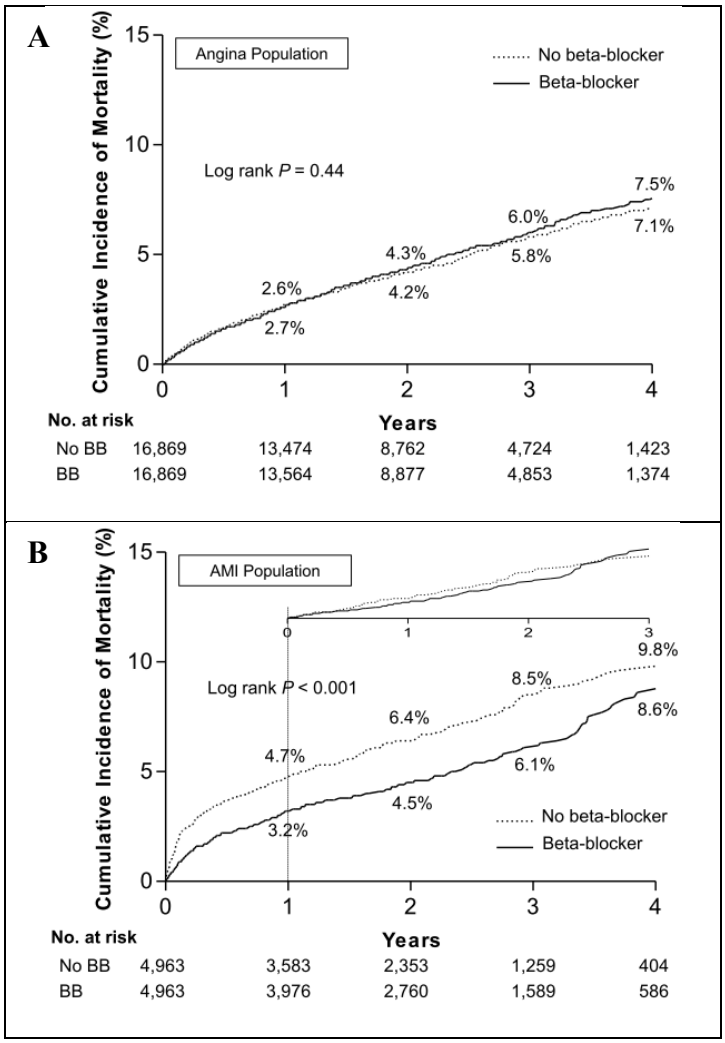


The cumulative incidence rates for all-cause death between the beta-blocker and no beta-blocker therapy groups in the overall population (A), patients with angina pectoris (B), and patients with AMI (C).

The numbers in each figure represent the cumulative incidence rates at each time point.

AMI, acute myocardial infarction; BB, beta-blocker

Figure 5. Kaplan-Meier cumulative event curves for mortality in the matched cohort

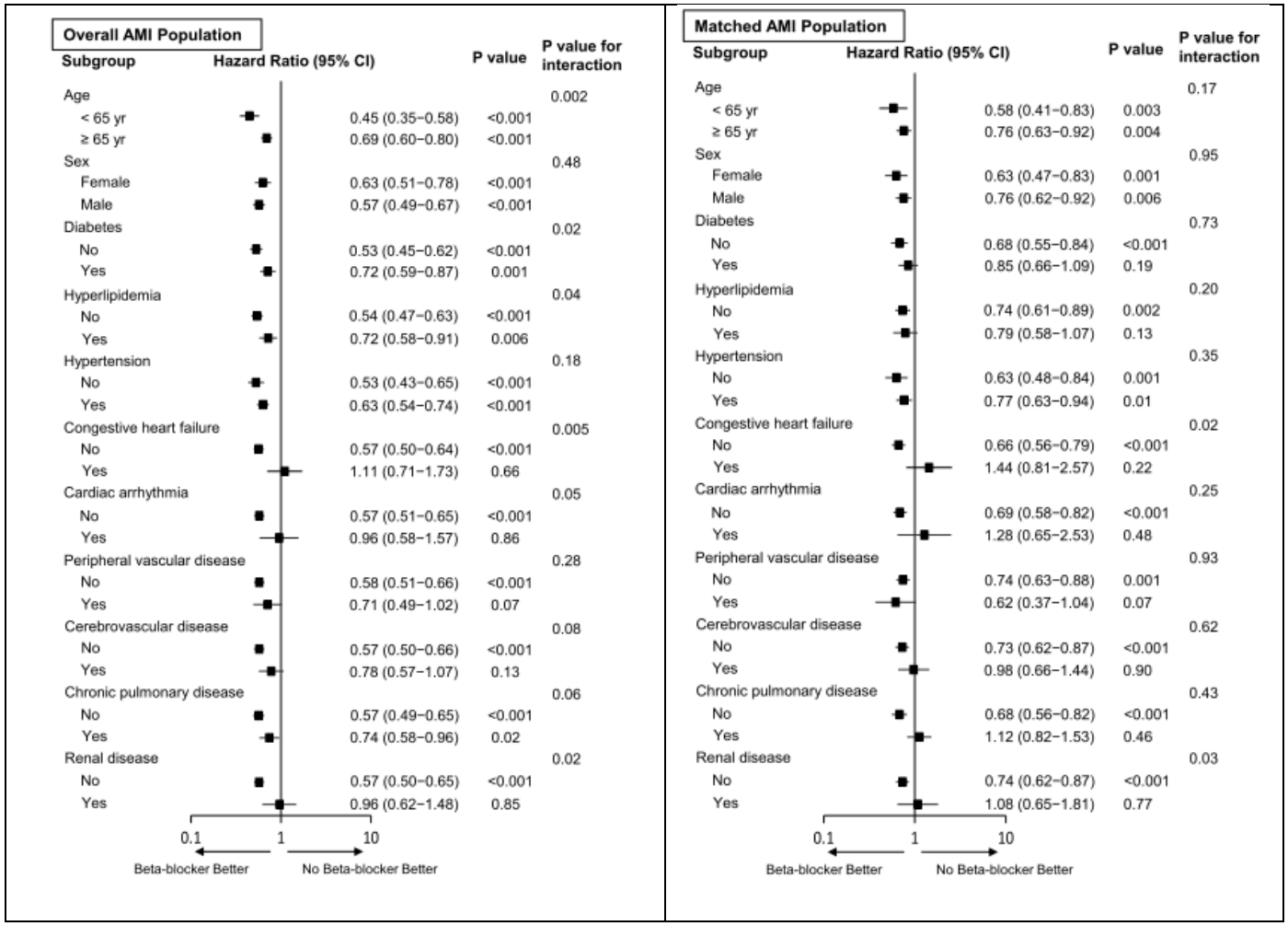


The cumulative incidence rates for all-cause death between the beta-blocker and no beta-blocker therapy groups in patients with angina pectoris (A) and those with AMI (B).

The numbers in each figure represent the cumulative incidence rates at each time point.

AMI, acute myocardial infarction; BB, beta-blocker

Figure 6. Subgroup analysis for the primary outcome in the AMI cohort



Hazard ratios are for the beta-blocker group compared with the no beta-blocker group. The P-value for interaction represents the likelihood of interaction between the subgroups and the treatment.

AMI, acute myocardial infarction; CI, confidence interval

DISCUSSION

This nationwide cohort study included data from 79,021 patients with angina or AMI who underwent PCI and received contemporary medical treatment in Korea. The main findings are as follows: (1) beta-blockers were prescribed in a high percentage of patients after AMI from 2011–2015 in real-world clinical practice; (2) treatment with beta-blockers was associated with a significant reduction in mortality in patients with AMI but not in those with angina; (3) the survival benefit associated with beta-blocker use was most significant within 1 year of the AMI event.

Available evidence strongly supports the use of beta-blockers to reduce mortality or cardiovascular events in patients with recent myocardial infarction with reduced ejection fraction. In a population of patients with left ventricular dysfunction post-myocardial infarction, the CAPRICORN (Carvedilol Post-Infarct Survival Control in LV dysfunction) study demonstrated that over a mean period of 1.3 years, carvedilol reduced the risk of mortality by 23% compared with placebo.[4] Together with the proven survival benefit of beta-blockers in patients with heart failure with reduced ejection fraction,[11-16] there is no doubt that considering beta-blockers for these selected AMI patients is appropriate. However, there is continued debate about the broader use of beta-blockers in unselected patients after AMI.[17-20] A considerable number of studies have shown a consistent mortality benefit associated with beta-blocker use in these patients, with study periods extending from several months to up to 3 years.[5] However, these trials were primarily conducted in the 1980s and 1990s, before the widespread use of PCI and other proven medical therapies, raising the question of whether the demonstrated benefits would still be observed in the context of contemporary clinical management. Moreover, no placebo-controlled trials have been conducted to evaluate the effect of intermediate- to long-term use of beta-blockers on major clinical outcomes in patients with CAD without prior myocardial infarction. The lack of

study data is a challenge that is faced in real-world practice. Therefore, the current study, based on reliable nationwide data that included all CAD patients who underwent PCI from 2011–2015, was designed to provide valuable insight and evidence to inform daily clinical practice.

The essential finding of our study is that in the AMI setting, beta-blocker use was associated with an approximately 29% and 12% reduction in mortality at 2 and 4 years, respectively. This result should be considered in light of the fact that the majority of the study population received modern PCI using drug-eluting stents and secondary preventive drugs, including antiplatelet agents and statins. These modern interventional advances and preventive drugs have resulted in a decline in the mortality rate of patients with AMI compared with early periods, and this was presumed to be the reason why the survival benefit associated with beta-blocker use that was observed in historical trials was not reproduced in recent observational studies and meta-analyses. However, because the mechanism by which reperfusion therapy, platelet inhibitors, or statins improves clinical outcomes differs from that of beta-blockers, it is reasonable to assume that the benefits of beta-blocker therapy will be preserved in patients receiving contemporary post-myocardial infarction management. One important observation in our analysis is that the survival benefit associated with beta-blocker use was most significant within 1 year of an AMI event. This implies that patients who survived during hospitalization after PCI for AMI remain at risk of major cardiac events due to vulnerable myocardium and coronary vessels for a certain period, during which beta-blockers can be of benefit. By contrast, this early benefit of beta-blocker treatment was not present in the angina population, and these data support the current guidelines that recommend the use of beta-blockers as a first-line treatment for the control of ischemic symptoms.

The results reported here support the need for contemporary randomized trials that examine the usefulness and appropriate duration of beta-blockers in a broad AMI population. The

lack of evidence to support the routine use of beta-blockers in AMI patients who have undergone PCI has resulted in contradictory recommendations among the guidelines. The American Heart Association guidelines recommend oral beta-blockers as a class I indication for all patients with AMI for at least 3 years,[6] whereas the European guidelines provide no recommendations for beta-blockers during and after an AMI episode in patients with normal or mildly depressed left ventricular function.[7, 8] As a result, the use of beta-blockers differs substantially among cardiovascular societies, from less than half of eligible patients to >80%.[21-26] Although a high proportion of AMI patients in the current study received beta-blockers, it is interesting to note that the prescription rate rose sharply due to the government's adequacy evaluation project for ischemic heart disease.[27] The REDUCE-SWEDEHEART (Evaluation of Decreased Usage of Betablockers After Myocardial Infarction in the SWEDHEART Registry) and DANBLOCK (Danish Trial of Beta Blocker Treatment After Myocardial Infarction Without Reduced Ejection Fraction) trials are in progress and will provide further guidance on these issues.[28,29]

This study has several limitations. First, the retrospective and observational design is associated with inherent bias. Second, similar to previous studies using an administrative database, clinical data regarding the cardiac test findings or vital signs of each individual (such as the ventricular ejection fraction, type of AMI [e.g., ST segment elevation or non-ST segment elevation myocardial infarction], Killip class, or the extent of CAD) were not available, further limiting the adjustment of meaningful clinical factors. This limitation also hindered the evaluation of the effectiveness or safety of beta-blockers in subgroups of interest. In the same context, it would be difficult to interpret the finding that beta-blocker treatment was associated with a neutral risk of mortality in patients with congestive heart failure, as a history of heart failure does not necessarily mean that the patient had depressed left ventricular systolic function. Third, drug use was determined only by the discharge medication, and full information on the dose and frequency was unavailable, limiting the

interpretation of our results concerning the effective guideline-recommended dose or duration. Finally, as this study only included a Korean population, it is uncertain whether these findings can be applied to other ethnic groups with different patient characteristics and procedural approaches.

CONCLUSION

In this population of unselected CAD patients who underwent contemporary post-PCI management, beta-blocker treatment was associated with a significant reduction in mortality in patients with AMI but not in those with angina. These results support the current guidelines, which recommend beta-blockers as first-line therapy to improve prognosis after AMI and to improve ischemic symptoms in patients with stable CAD. The findings should be confirmed by randomized clinical trials with an appropriate duration of follow-up.

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국문 요약

배경: 베타-아드레날린 수용체 차단제는 심장에 대한 과도한 아드레날린 활성에 따른 유해한 영향을 감소시키기 위하여 관상 동맥 질환 환자에서 사용되어 왔다. 그러나, 관상동맥 중재술 및 이후의 현대적인 약물치료의 배경하에서 베타차단제의 임상 효과에 대한 증거는 부족하다.

방법: 우리나라의 건강보험심사평가원 자료를 바탕으로 2011년부터 2015년까지 심근경색 (30,404명) 또는 협심증 (48,617명)을 최초 진단받아 경피적 관상동맥 중재시술을 받은 환자를 대상으로 하였다. 성향 점수 매칭 분석을 사용하여 베타차단제 치료를 받은 환자와 받지 않은 환자에서 사망률을 비교하였다.

결과: 베타 차단제는 협심증 환자 (62.7%)보다 심근경색 환자 (83.4%)에서 더 높은 비율로 사용되었다. 2.1년의 추적 관찰 기간 동안, 전체 환자에서의 사망률은 베타 차단제 사용군에서 사용하지 않은 군에 비해 유의하게 낮았다 (2년 사망률: 베타 차단제 사용군 4.2%, 베타 차단제 비사용군 4.7%; p=0.005). 성향 점수 매칭 분석에서 진단에 따른 예후 차이를 보였는데, 심근경색 코호트에서 베타 차단제 치료군에서 사망의 위험이 유의하게 낮았으며 (위험비: 0.74; 95 % 신뢰 구간 : 0.63-0.86; p <0.001), 협심증 코호트에서는 차이를 보이지 않았다 (위험비: 1.04; 95 % 신뢰구간: 0.94-1.15; p=0.44). 베타 차단제와 관련된 생존 증가 효과는 심근경색 사건 후 1년 이내에 가장 컸다.

결론: 관상동맥 중재술 및 현대적인 시술 후 약물치료를 받은 선택되지 않은 관상동맥질환 환자에서 베타 차단제 치료는 심근경색 환자에서 사망률의 유의한 감소와 관련이 있었지만 협심증 환자에서는 그렇지 않았다.

중심단어: 협심증, 베타차단제, 관상동맥질환, 심근경색