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ORIGINAL ARTICLE

Long-term impact of β-blocker in elderly patients without myocardial infarction after percutaneous coronary intervention

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Abstract

Aims Little is known about the long-term outcomes of β-blockers use in patients with coronary artery disease (CAD) without myocardial infarction (MI) and reduced ejection fraction (rEF). However, more attention should be paid to the oral administration of β-blockers in elderly patients who are susceptible to heart failure (HF), sinus node dysfunction, or rate response insufficiency. We aimed to evaluate the long-term impact of β-blockers in elderly patients with CAD without MI or systolic HF who have undergone percutaneous coronary intervention.

Methods and results A total of 1018 consecutive elderly patients with CAD (mean age, 72 ± 7 years; 77% men) who underwent their first intervention between 2010 and 2018 were included in this study. According to the presence or absence of the use of β-blockers, 514 patients (50.5%) were allocated to the β-blocker group, and 504 (49.5%) to the non-β-blocker group. We evaluated the incidence of 4-point major adverse cardiovascular events (4P-MACE), including cardiovascular death, non-fatal MI, non-fatal stroke, admission for HF, target vessel revascularization (TVR), and all-cause death. We focused on the association between chronotropic incompetence of β-blockers and incidence of a new HF and analysed the results using an exercise electrocardiogram regularly performed in the outpatient department after percutaneous coronary intervention. During a median follow-up duration of 5.1 years, 83 patients (8.3%) developed 4P-MACE, including cardiovascular death in 17, non-fatal MI in 13, non-fatal stroke in 25, and admission for HF in 39 patients. Additionally, 124 patients (12.2%) had a TVR and 104 (10.2%) died of other causes. Kaplan–Meier analysis showed that the cumulative incidence rate of 4P-MACE in the β-blocker group was significantly higher than that in the non-β-blocker group (15.4% vs. 10.0%, log-rank test, $P = 0.015$). Above all, the cumulative incidence rate of admission for HF in the β-blocker group was significantly higher (8.8% vs. 3.2%, log-rank test, $P < 0.001$). The β-blocker group had significantly lower resting heart rate, stress heart rate, and stress-rest Δ heart rate on exercise electrocardiogram. Multivariate Cox hazard analysis revealed that EF, β-blocker use, stress-rest Δ heart rate, and CKD were strong independent predictors of admission for HF.

Conclusions Long-term β-blocker use was significantly associated with an increased risk of adverse cardiovascular events in elderly patients with CAD without MI or systolic HF. In particular, the chronotropic incompetence action of β-blockers could increase the risk of admission for HF in elderly patients with CAD without MI and systolic HF, and the present findings warrant further investigation.

Keywords β-Blockers; Heart failure; Coronary artery disease; Percutaneous coronary intervention; Long term

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Introduction

β-Blockers play an important and multifaceted role and are often used for management of ischaemic heart disease, heart failure (HF), hypertension, tachycardia, and arrhythmia in the field of cardiology. Above all, there are many reports on the long-term outcomes of β-blockers for management of myocardial infarction (MI), and it has been reported that β-blocker treatment greatly contributes to the reduction of mortality and cardiovascular events.[1–3] In particular, guidelines have proposed the use of β-blockers in patients with ST-segment elevation MI as follows: early intravenous β-blockers should be considered due to reduction of malignant ventricular arrhythmia and extent of microvascular obstruction in the acute phase, and routine oral treatment with β-blockers should be indicated in patients with reduced ejection fraction (rEF) unless contraindicated in the chronic phase.[4,5]

However, whether β-blockers affect outcomes in patients with coronary artery disease (CAD) without prior MI after percutaneous coronary intervention (PCI) remains uncertain. Although there are some reports on the association between β-blocker use and short-term or mid-term cardiovascular events in patients with CAD without prior MI,[6–10] little is known about the long-term outcomes of β-blocker use in these patients. Long-term β-blocker use is associated with concerns regarding side effects. Major cardiac side effects caused by β-blockers include precipitation or worsening of congestive HF, significant negative chronotropy, symptomatic bradycardia, and withdrawal syndrome.[11,12] In particular, more attention should be paid to elderly patients who are susceptible to HF, sinus node dysfunction, and rate response insufficiency.[13,14] Thus, we aimed to evaluate the long-term impact of β-blockers in elderly patients with CAD without prior MI or systolic HF after PCI.

Methods

Study population

This single-centre, observational, retrospective cohort study was conducted at our institution. We enrolled 1298 consecutive elderly patients with CAD (aged 60 years and older according to the United Nations) without prior MI (ST-elevation MI and non-ST-elevation MI) who underwent their first intervention for de novo coronary artery lesions between January 2010 and February 2018. The exclusion criteria comprised the following patients: (i) with rEF (EF $<$ 40%), (ii) undergoing haemodialysis, (iii) with prior HF or atrial fibrillation/flutter, and (iv) previously implanted with a permanent pacemaker.

We diagnosed the patients based on clinical scenarios such as a classical history of anginal symptoms and new onset of HF or left ventricular dysfunction, which were suspected to be CAD, and CAD was detected at screening even if it was asymptomatic. In addition, we confirmed the presence or absence of oral administration of all drugs on admission, and then we verified that of β-blockers at discharge after the first catheter intervention.

This study was approved by the ethics committee of our institution and all participants provided written informed consent. The study protocol has been priorly approved by the ethics committee of our institution. The investigation conforms with the principles outlined in the 'Declaration of Helsinki'.[15]

Data collection and definitions

Data on patient characteristics were collected from the institutional database. Blood samples were collected in the morning, the day before the intervention, after an overnight fast, and all blood tests were performed at the same laboratory.

Patients with a blood pressure $>$ 140/90 mmHg or those receiving antihypertensive drugs were regarded as hypertensive.[16] Dyslipidaemia was defined as either a triglyceride (TG) level $\geq$ 150 mg/dL, low-density lipoprotein cholesterol (LDL-C) level $\geq$ 140 mg/dL, high-density lipoprotein cholesterol (HDL-C) level $<$ 40 mg/dL, or the administration of lipid-lowering therapy.[17] Diabetes mellitus was defined as either a haemoglobin A1c level of $\geq$6.5% or the administration of oral hypoglycaemic drugs or insulin injections.[18] Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate of $<$60 mL/min/1.73 m^2, as calculated by the Modification of the Diet in Renal Disease equation, which was modified with a Japanese coefficient using the baseline serum creatinine level.[19] Patients were classified as anaemic based on haemoglobin levels using the World Health Organization definition ($<$12.0 g/dL in women and $<$13.0 g/dL in men).[20] A positive family history of cardiovascular disease was defined as the presence of any first degree relative with premature cardiovascular disease (age $<$55 years for men and $<$65 years for women).[21] We analysed the type of coronary artery lesion (A, B1, B2, or C) according to the classification proposed by the American Heart Association (AHA)/American College of Cardiology (ACC).[22]

In addition, we regularly performed exercise electrocardiography corresponds to 6 metabolic equivalents (METs),[23] as a simplified evaluation of exercise tolerance in the outpatient setting after PCI.

Study endpoint

The endpoints of this study were 4-point major adverse cardiovascular events (4P-MACE), defined as a composite of cardiovascular death, non-fatal MI, non-fatal stroke, admission

for HF, target vessel revascularization (TVR), and all-cause death. Cardiovascular death was defined as death resulting from acute MI, sudden cardiac death, HF, stroke, cardiovascular procedures, cardiovascular haemorrhage, and other cardiovascular causes. MI was composed of ST-segment elevation MI (ST elevation, abnormal biomarkers) and non-ST elevation MI (no ST elevation, abnormal biomarkers). Stroke was defined as ischaemic stroke, symptomatic intracerebral haemorrhage, symptomatic subarachnoid haemorrhage, and not otherwise specified according to the classification proposed by the Neurologic Academic Research Consortium, because we considered it important in clinical practice to clearly distinguish between clinically meaningful and incidental findings. With regard to admission for HF, a patient was required to have an unscheduled hospital admission for a primary diagnosis of HF with a length of stay that either exceeded 24 h or crossed a calendar day, and typical signs, symptoms, and diagnostic testing results with the diagnosis of HF. Any HF hospitalization was defined as the first onset of HF in each patient. TVR was defined as any repeated percutaneous intervention or surgical bypass of any segment of the target vessel, including the target lesion.[24–26]

Clinical follow-up data were collected from the patients' medical records or by contacting the patients or their families if they had not been followed up at our institution after the intervention. Information about the circumstances and date of death was obtained from the families of patients who died at home, and details of events associated with the cause of death were supplied by the staff of other hospitals or clinics to which the patient had been admitted. Blinded investigators collected all data.

Statistical analysis

Categorical data were presented as numbers and percentages and compared using the χ^2 test. Continuous variables were expressed as mean ± standard deviation or as median and interquartile range and compared using one-way analysis of variance or the Kruskal–Wallis test. The Kolmogorov–Smirnov test examined whether scores were likely to follow a certain distribution in all patients. If $P < 0.05$, we did not believe that the variable follows a normal distribution. Kaplan–Meier analysis for the cumulative incidence of 4P-MACE, TVR, and all-cause death was used to compare the two groups based on the presence or absence of β-blockers, and differences between groups were assessed using the log-rank test. Multivariate Cox analysis was performed using stepwise selection with entry/stay criteria of 0.20/0.20. Regarding 4P-MACE, β-blocker use, age, sex, brain natriuretic peptide (BNP) levels, LDL-C levels, EF, CKD, and anaemia were included in the list of candidate covariates. Furthermore, we evaluated the associations between β-blocker use and 4P-MACE after adjustment for age, sex, BNP levels, LDL-C levels, EF, CKD, anaemia, hypertension, and smoking, either the candidate covariates shown in the multivariate Cox hazard analysis or the factors with significant differences between the two groups.

All probabilities were expressed as two-tailed values, with statistical significance set at $P < 0.05$. All confidence intervals (CIs) were computed at 95% level. All data were analysed using JMP Version 14.2 for Macintosh (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Overall, we studied 1018 consecutive elderly patients with CAD without MI after PCI. We excluded 169 patients with rEF (EF < 40%), 93 undergoing haemodialysis, 123 with prior HF or atrial fibrillation/flutter, and 15 previously implanted with a permanent pacemaker. A total of 514 patients (50.5%) were allocated to the β-blocker group, and 504 (49.5%) were allocated to the non-β-blocker group (*Figure 1*). In addition, the breakdown of β-blockers was 58% for bisoprolol, 34% for carvedilol, and 8% for other β-blockers.

Baseline clinical characteristics are summarized in *Table 1*. The mean age was 72 ± 7 years, and 77% of the patients were men. The prevalence of hypertension, dyslipidaemia, diabetes mellitus, anaemia, and CKD was 75%, 76%, 41%, 34%, and 23%, respectively. The β-blocker group had significantly higher BNP levels, TG levels, and proportion of hypertension and CKD, as well as lower heart rate, HDL-C levels, EF, and proportion of smoking (all $P < 0.05$).

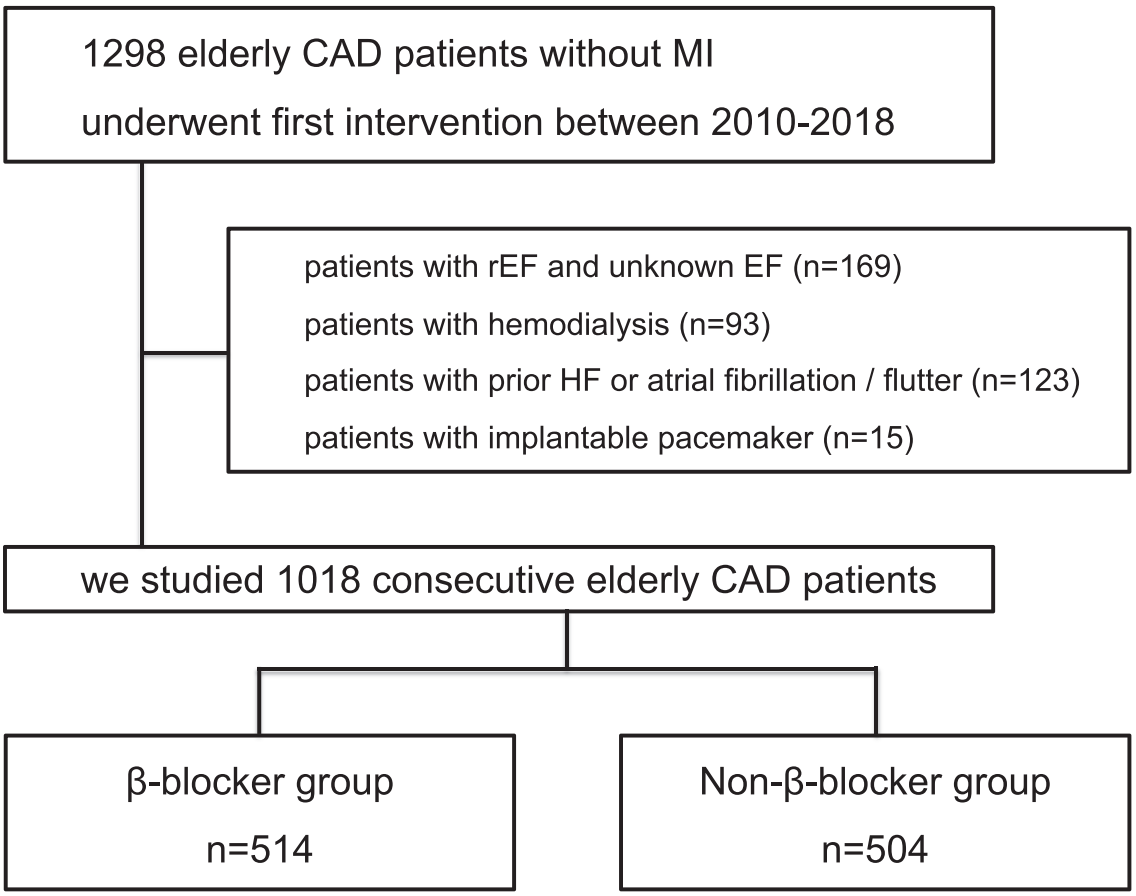
With regard to baseline lesion and procedural characteristics, we investigated lesion site, classification, length, and reference diameter; and stent type, length, and diameter. There was no significant difference between the two groups in either lesion or procedural characteristics (*Table 2*).

Clinical outcome

The median follow-up duration was 5.1 years (interquartile range, 3.1–7.2 years), and the prognostic data were fully documented during the entire follow-up period. During the follow-up, 83 patients (8.3%) developed 4P-MACE, including cardiovascular death in 17, non-fatal MI in 13, non-fatal stroke in 25, and admission for HF in 39. In addition, 124 patients (12.2%) had a TVR, and 104 (10.2%) died of other causes.

Kaplan–Meier analysis showed that the cumulative incidence rate of 4P-MACE in the β-blocker group was significantly higher than that in the non-β-blocker group (15.4% vs. 10.0%, log-rank test, $P = 0.015$) [*Figure 2(A)*]. However, the analysis showed that there was no significant difference between the two groups for TVR (15.1% vs. 14.3%, log-rank

Figure 1 Study flow chart. Among 1298 elderly CAD patients without MI, we excluded the following persons: patients with rEF (EF < 40%), patients undergoing haemodialysis, patients with prior HF or atrial fibrillation, and patients previously implanted permanent pacemaker. We studied 1018 patients with CAD. The patients were divided into two groups based on the presence or absence of β-blockers. A total of 514 patients (50.5%) were allocated to the β-blocker group, and 504 patients (49.5%) were allocated to the non-β-blocker group. CAD, coronary artery disease; EF, ejection fraction; HF, heart failure; MI, myocardial infarction; rEF, reduced ejection fraction.



test, *P* = 0.628) [*Figure 2(B)*] and all-cause death (11.4% vs. 17.8%, log-rank test, *P* = 0.257) [*Figure 2(C)*]. In addition, with regard to the breakdown of 4P-MACE, the cumulative incidence rate of admission for HF in the β-blocker group was significantly higher than in the non-β-blocker group (8.8% vs. 3.2%, log-rank test, *P* < 0.001) [*Figure 3(A)*], but the Kaplan–Meier curves for cardiovascular death (*P* = 0.607), non-fatal MI (*P* = 0.944), and non-fatal stroke (*P* = 0.877) between the two groups were not significantly different. Even if it was limited to patients with EF ≥ 50% [so-called preserved EF (pEF)] except for the patients with EF 40–49% (mildly reduced EF), Kaplan–Meier analysis showed that the cumulative incidence rate of admission for HF in the β-blocker group was significantly higher than that in the non-β-blocker group (6.9% vs. 3.0%, log-rank test, *P* = 0.013) [*Figure 3(B)*].

Table 3 shows results of multivariable Cox hazard analysis revealing that age (1 year increase) [hazard ratio (HR), 1.05; 95% CI, 1.02–1.09; *P* = 0.001], EF (1% increase) (HR, 0.97; 95% CI, 0.95–0.99; *P* = 0.008), CKD (HR, 1.84; 95% CI, 1.15–2.92; *P* = 0.012), and β-blocker use (HR, 1.65; 95% CI, 1.05–2.64; *P* = 0.029) were strong independent predictors of 4P-MACE. Furthermore, after adjustment for various confounders including with significant difference between the two groups, the β-blocker group was significantly associated with an increased risk of 4P-MACE compared with the non-β-blocker group (*Table 4*).

Discussion

The major findings of this study are as follows: (i) the β-blocker group was significantly associated with a higher incidence of 4P-MACE compared with the non-β-blocker group in elderly patients with CAD without MI in the long term, and (ii) even after adjustments for important covariates, long-term oral administration of β-blockers was strongly associated with an increased incidence of 4P-MACE.

Table 1 Patients' baseline clinical characteristics

	Overall $n = 1018$	β-Blocker group $n = 514$	Non-β-blocker group $n = 504$	*P* value
Clinical characteristics				
Age, years	72 ± 7	72 ± 8	72 ± 7	0.532
Male sex, *n* (%)	780 (77)	388 (75)	392 (78)	0.388
BMI, kg/m^2	24.0 ± 3.2	24.1 ± 3.3	23.9 ± 3.2	0.228
SBP, mmHg	144 ± 24	144 ± 24	145 ± 24	0.527
DBP, mmHg	76 ± 14	76 ± 15	77 ± 13	0.643
HR, /min	66 ± 10	63 ± 10	68 ± 11	<0.001
TC level, mg/dL	167 ± 36	166 ± 35	168 ± 37	0.238
TG level, mg/dL	126 ± 66	132 ± 74	120 ± 57	0.002
HDL-C level, mg/dL	46 ± 13	44 ± 12	48 ± 14	<0.001
LDL-C level, mg/dL	97 ± 31	96 ± 28	97 ± 33	0.329
Haemoglobin, g/dL	13.3 ± 1.6	13.2 ± 1.6	13.2 ± 1.7	0.575
Fasting blood glucose, mg/dL	105 ± 28	106 ± 30	103 ± 26	0.126
HbA1c level, %	6.2 ± 0.8	6.3 ± 0.9	6.2 ± 0.8	0.287
Hs-CRP level, g/dL	0.08 (0.03, 0.21)	0.08 (0.04, 0.21)	0.07 (0.03, 0.21)	0.581
BNP level, pg/mL	38.5 (21.1, 78.3)	48.4 (16.7, 97.2)	31.9 (16.2, 59.8)	<0.001
Ejection fraction, %	65.0 ± 8.4	64.2 ± 9.0	65.8 ± 7.8	0.003
Comorbidity				
Hypertension, *n* (%)	762 (75)	402 (78)	360 (71)	0.013
Dyslipidaemia, *n* (%)	772 (76)	396 (77)	376 (75)	0.363
Diabetes mellitus, *n* (%)	422 (41)	215 (42)	207 (41)	0.806
Chronic kidney disease, *n* (%)	239 (23)	137 (27)	102 (20)	0.016
Anaemia, *n* (%)	323 (34)	150 (31)	173 (37)	0.075
Smoking, *n* (%)	640 (63)	308 (60)	332 (66)	0.049
Family history, *n* (%)	275 (27)	140 (27)	135 (27)	0.871
Medication				
Statin, *n* (%)	897 (88)	456 (89)	441 (88)	0.549
Aspirin, *n* (%)	1005 (99)	506 (99)	498 (99)	0.808
CCB, *n* (%)	462 (45)	228 (44)	234 (46)	0.507
ACE-i/ARB, *n* (%)	501 (49)	268 (52)	233 (46)	0.059
OHA, *n* (%)	285 (28)	140 (27)	145 (29)	0.586
Insulin, *n* (%)	77 (8)	37 (7)	40 (8)	0.656

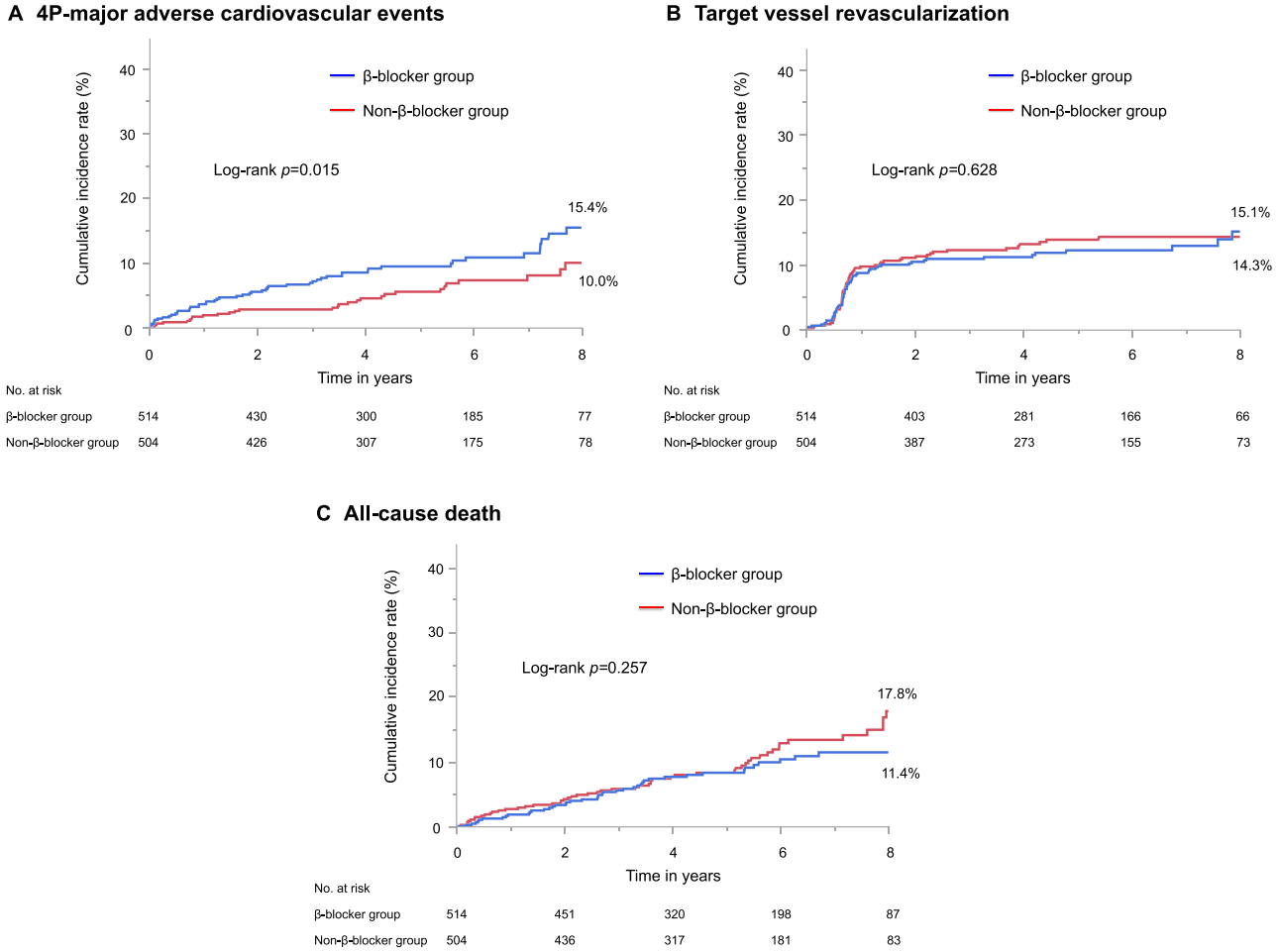
ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CCB, calcium channel blocker; DBP, diastolic blood pressure; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; Hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; OHA, oral hypoglycaemic agent; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Table 2 Patients' baseline lesion and procedural characteristics

	Overall $N = 1018$	β-Blocker group $N = 514$	Non-β-blocker group $N = 504$	*P* value
Lesion characteristics				
Lesion site				
Right coronary artery, *n* (%)	272 (27)	130 (25)	142 (29)	0.307
Left main coronary trunk, *n* (%)	46 (5)	28 (5)	18 (4)	0.146
Left anterior descending artery, *n* (%)	503 (50)	245 (48)	258 (51)	0.273
Left circumflex coronary artery, *n* (%)	187 (18)	105 (21)	82 (16)	0.084
Lesion classification				
Type A, *n* (%)	42 (4)	24 (5)	18 (4)	0.378
Type B1, *n* (%)	219 (22)	110 (21)	109 (22)	0.930
Type B2, *n* (%)	347 (34)	170 (33)	177 (35)	0.491
Type C, *n* (%)	410 (40)	210 (41)	200 (40)	0.703
CTO lesion, *n* (%)	82 (8)	49 (10)	33 (7)	0.079
Lesion length, mm	17.9 ± 13.3	17.7 ± 13.2	18.0 ± 13.4	0.652
Lesion reference diameter, mm	2.87 ± 0.44	2.87 ± 0.43	2.86 ± 0.45	0.804
Procedural characteristics				
Use of BMS, *n* (%)	88 (9)	40 (8)	48 (10)	0.336
Use of 1st DES, *n* (%)	16 (2)	6 (1)	10 (2)	0.298
Use of 2nd DES, *n* (%)	724 (72)	373 (74)	351 (70)	0.232
Use of 3rd DES, *n* (%)	153 (15)	76 (15)	77 (15)	0.856
Stent length, mm	22.7 ± 8.2	22.7 ± 8.1	22.7 ± 8.3	0.982
Stent diameter, mm	2.90 ± 0.40	2.88 ± 0.40	2.91 ± 0.41	0.335

BMS, bare-metal stent; CTO, chronic total occlusion; DES, drug-eluting stent.

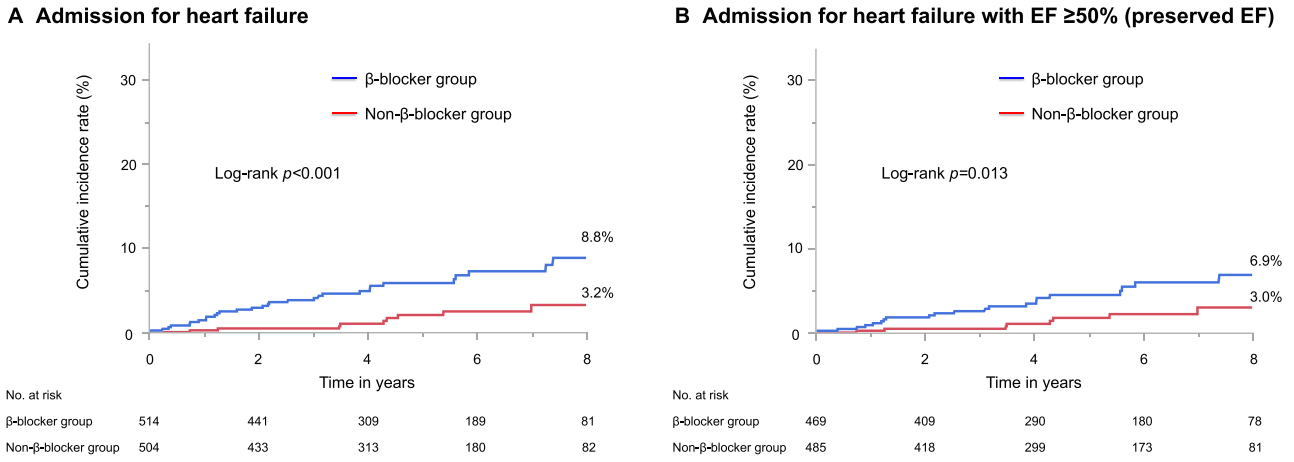
Figure 2 Kaplan–Meier curves for 4P-MACE, TVR, and all-cause death between β-blocker group and non-β-blocker group. (A) The cumulative incidence of 4-point major adverse cardiovascular events. (B) The cumulative incidence of target vessel revascularization. (C) The cumulative incidence of all-cause death. 4P-MACE, 4-point major adverse cardiovascular events; TVR, target vessel revascularization.



β-Blockers are able to improve cardiac function due to various actions, including antihypertensive action, anti-ischaemic action, reduction in renin release, angiotensin II and aldosterone production, improvement of left ventricular structure and function, and anti-arrhythmic effect.[27–30] Based on this hypothesis, it has been speculated that the prognostic benefits of β-blockers would extend to the population of patients with CAD, even without a history of MI or HF with rEF. However, this study showed that not only was there no significant difference between the two groups for cardiovascular death and hospitalization for MI but also the cumulative incidence rate of admission for HF in the β-blocker group was significantly higher than in the non-β-blocker group. In short, we did not observe the benefits of β-blocker use in elderly patients with CAD without MI but rather an increased incidence of admission for HF. A previous study reported a significant association between β-blocker use and admission for HF, but no clear cause could be investigated.[10] Although the mechanism of this association and the potential for harm remain unclear, we inferred some possible causes.

First, HF in the elderly is superimposed on comorbidities that are often the primary determinant of life prognosis, such as CAD, arrhythmia, valvular heart disease, hypertension, diabetes mellitus, CKD, chronic obstructive pulmonary disease (COPD), and anaemia.[31] In particular, β-blockers could lead to masking of hypoglycaemic symptoms or worsening glycaemic control in patients with diabetes mellitus and may be associated with deterioration of respiratory condition in patients with COPD.[32,33] However, there was no significant difference between the two groups with or without use of β-blockers for major comorbidities, as shown in *Table 1*. In addition, similar results were obtained regarding the incidence of symptomatic bradycardia or ventricular arrhythmia, and the prevalence of valvular heart disease or COPD, which were insignificant overall.

Figure 3 Kaplan–Meier curves for admission for heart failure between β-blocker group and non-β-blocker group. (A) The cumulative incidence of admission for heart failure. (B) The cumulative incidence of admission for heart failure limited to EF ≥ 50% (preserved EF). EF, ejection fraction.



Second, elderly patients are more likely to be affected by lifestyle factors that directly contribute to HF, such as insufficient salt and water restriction, obesity, poor medication compliance, stress, or depression.[31] In particular, they may forget their doses of β-blockers and develop withdrawal syndrome, which results in a hyperadrenergic state due to increased sympathetic activity and reflection of adrenergic receptor up-regulation.[34] As far as the medical records revealed, most of the elderly patients with CAD who were hospitalized for HF in this study were able to manage oral administration of medications well by themselves or with assistance from their families. In addition, the onset of HF was often triggered by an infectious disease, rather than account of excessive salt intake.

Third, we considered the involvement of chronotropic incompetence caused by β-blockers. The heart rate slowing effects of β-blockers are generally important in improving prognosis, and patients with HF with greater heart rate reductions gain additional prognostic benefits.[35,36] In contrast, it has been reported that chronotropic incompetence on exercise tests is independently predictive of all-cause mortality and cardiovascular events in the elderly population or patients with CAD without prior HF.[37,38] Thus, such patients in this study were expected to be susceptible to heart rate response insufficiency due to β-blocker use, accompanied by alterations in the autonomic system such as vagal attenuation and sympathetic exacerbation caused by aging. We analysed resting heart rate, stress heart rate, and stress-rest Δ heart rate on exercise stress of 6 METs in the outpatient department after PCI. The β-blocker group had a significantly lower resting heart rate (63 ± 10/min vs. 68 ± 11/min, $P < 0.001$), stress heart rate (85 ± 12/min vs. 92 ± 16/min, $P < 0.001$), and stress-rest Δ heart rate (22 ± 8/min vs. 24 ± 9/min, $P = 0.017$) than the non-β-blocker group. Furthermore, multivariate Cox hazard analysis revealed that EF, stress-rest Δ heart rate, CKD, and β-blocker use were strongly independent predictors of admission for HF (*Table 5*). As mentioned above, we considered that the chronotropic incompetence action of β-blockers could increase the risk of admission for HF in elderly CAD patients without prior HF. Thus, we need to pay

Table 3 Univariate and multivariate Cox hazards analysis of 4-point major adverse cardiovascular events

	Univariate		Multivariable	
Covariate	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, 1 year increase	1.07 (1.03–1.10)	<0.001	1.05 (1.02–1.09)	0.001
CKD	2.36 (1.50–3.68)	<0.001	1.84 (1.15–2.92)	0.012
BNP, 100 pg/mL increase	1.29 (1.14–1.42)	<0.001		
EF, 1% increase	0.96 (0.94–0.99)	0.002	0.97 (0.95–0.99)	0.008
Anaemia	1.85 (1.58–2.93)	0.010		
β-Blocker use	1.75 (1.11–2.77)	0.016	1.65 (1.05–2.64)	0.029
Male	1.47 (0.85–2.72)	0.172		
LDL-C, 10 mg/dL increase	1.05 (0.98–1.10)	0.178		

BNP, brain natriuretic peptide; CI, confidence interval; CKD, chronic kidney disease; EF, ejection fraction; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.

Table 4 Risk for 4-point major adverse cardiovascular events according to the β-blocker use

	Hazard ratio (95% confidence interval)	*P* value
β-blocker group vs. non-β-blocker group		
Crude	1.75 (1.11–2.77)	0.019
Model 1	1.78 (1.13–2.80)	0.014
Model 2	1.98 (1.16–3.38)	0.012
Model 3	1.96 (1.15–3.36)	0.014

BNP, brain natriuretic peptide; CKD, chronic kidney disease; EF, ejection fraction; HT, hypertension; LDL-C, low-density lipoprotein-cholesterol.
β-Blocker group ($n = 514$). Non-β-blocker group ($n = 504$). Model 1 for age and sex. Model 2 for age, sex, BNP levels, LDL-C levels, EF, CKD, and anaemia. Model 3 for age, sex, BNP levels, LDL-C levels, EF, CKD, anaemia, HT, and smoking.

Table 5 Univariate and multivariate Cox hazards analysis of admission for heart failure

	Univariate		Multivariable	
Covariate	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, 1 year increase	1.10 (1.05–1.15)	<0.001		
EF, 1% increase	0.92 (0.89–0.95)	<0.001	0.93 (0.89–0.97)	<0.001
BNP, 100 pg/mL increase	1.38 (1.20–1.54)	<0.001		
β-Blocker use	3.31 (1.64–7.41)	<0.001	2.71 (1.06–8.32)	0.038
CKD	2.99 (1.56–5.61)	0.001	2.76 (1.14–6.40)	0.026
Stress-rest Δ heart rate, 5/min increase	0.75 (0.56–0.98)	0.037	0.74 (0.55–0.96)	0.025
Anaemia	1.72 (0.88–3.28)	0.110		

BNP, brain natriuretic peptide; CI, confidence interval; CKD, chronic kidney disease; EF, ejection fraction; HR, hazard ratio.

close attention to inadvertent β-blocker administration in elderly patients with CAD without MI, after catheterization.

This study had several limitations that require consideration. First, as this was a single-centre, retrospective, observational study, unknown confounding factors might have affected the outcomes regardless of analytical adjustments, and the relatively small number of enrolled patients limited the statistical power of the study. Second, this study was only analysed for people over the age of 60 from the PCI database of our institution. Thus, these outcomes cannot be applied to younger patients. Third, the current study included only Japanese patients. Thus, the dosage of β-blockers may differ from that in other countries. Fourth, we evaluated exercise tolerance using exercise electrocardiography; however, cardiopulmonary exercise testing, which precisely defines maximum exercise capacity through measurement of peak oxygen uptake, would have been capable of obtaining more information. Fifth, frequency of complications of CAD and hypertension was high, and the definition of hypertension included patients taking antihypertensive drugs. Thus, it was difficult to exactly determine whether or not the drugs was taken only for angina symptoms. Actually, for patients with or without effort angina, there was significant difference in the β-blockers use, but not the prevalence of hypertension.

In conclusion, long-term β-blocker use was significantly associated with an increased risk of adverse cardiovascular events in elderly patients with CAD without MI and systolic HF, after PCI. In particular, we discussed that the chronotropic incompetence action of β-blockers could lead to an increased risk of admission for HF, with a review of the literature. Thus, close attention should be paid to inadvertent β-blocker administration in elderly patients with CAD without MI and systolic HF, after catheterization, and the present findings warrant further investigation.

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Conflict of interest

None declared.

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