Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.8932-21
Intern Med 61: 2711-2719, 2022
http://internmed.jp

【 ORIGINAL ARTICLE 】

A Propensity Score Matched Analysis of Statin Effects on Major Adverse Cardiac Events after Percutaneous Coronary Intervention in Patients Over 75 Years Old

Takeo Horikoshi[1], Takamitsu Nakamura[1], Toru Yoshizaki[1], Jun Nakamura[2], Yosuke Watanabe[1], Manabu Uematsu[1], Aritaka Makino[3], Yukio Saito[4], Jun-ei Obata[1], Takao Sawanobori[4], Hajime Takano[5], Ken Umetani[3], Akinori Watanabe[2], Tetsuya Asakawa[6], Akira Sato[1] and Kiyotaka Kugiyama[1]

Abstract:

Objective In an extremely aging society, it is beneficial to reconsider the value of medical treatment for extremely elderly patients. We therefore focused on the efficacy of statin therapy in extremely elderly patients. This study investigated the efficacy of statins for secondary prevention in patients over 75 years old.

Methods This prospective multicenter registry included 1,676 consecutive extremely elderly patients with coronary artery disease who underwent successful percutaneous coronary intervention (PCI). The patients were followed up clinically for up to three years or until the occurrence of major adverse cardiac events (MACEs), defined as a composite of all-cause death and non-fatal myocardial infarction. Using propensity score methodology to eliminate selection bias, in a 1:1 matching ratio, we selected 466 pairs of patients for the analysis.

Results During the median follow-up period of 25 months, MACEs occurred in 176 patients. The Kaplan-Meier analysis showed that statin treatment correlated with a lower probability of initial MACE occurrences within 30 days compared with no statin treatment (log-rank test, $p<0.001$). According to a landmark analysis at day 30, statin treatment still showed consistent effectiveness for reducing MACE occurrence during the follow up period ($p=0.04$). A multivariable Cox hazard analysis showed that statin therapy significantly reduced MACE occurrence (hazard ratio 0.55 [0.40-0.75], $p<0.001$). In the stratification analysis, statin therapy was especially beneficial in patients without symptomatic heart failure.

Conclusion Statins were effective in preventing MACEs in extremely elderly patients after PCI.

Key words: aging, cardiovascular diseases, mortality, percutaneous coronary intervention, statin

(Intern Med 61: 2711-2719, 2022)
(DOI: 10.2169/internalmedicine.8932-21)

Introduction

In this century, Japan has faced many problems due to its extremely aging population, where the proportion of people ≥65 years old in the total population is the highest worldwide (1). However, many elderly individuals are still robust and active. Therefore, the Japan Gerontological Society and the Japan Geriatrics Society reconsidered the definition of extremely elderly and redefined it as individuals over 75 years old (2).

Cardiovascular disease is the leading cause of death

[1]Department of Internal Medicine II, Faculty of Medicine, University of Yamanashi, Japan, [2]Department of Cardiology, Fujieda Municipal General Hospital, Japan, [3]Department of Internal Medicine, Yamanashi Prefectural Central Hospital, Japan, [4]Department of Cardiology, Kofu Municipal Hospital, Japan, [5]Department of Cardiology, Kofu Jonan Hospital, Japan and [6]Department of Cardiology, Yamanashi Kosei Hospital, Japan

Received: November 1, 2021; Accepted: January 16, 2022; Advance Publication by J-STAGE: February 26, 2022
Correspondence to Dr. Takeo Horikoshi, thorikoshi@yamanashi.ac.jp

among the elderly (3). Therefore, establishing prevention and treatment strategies to reduce cardiovascular disease is an important clinical issue, even for extremely elderly patients. It has been shown that statin therapy for the secondary prevention of cardiovascular events was effective in decreasing the overall mortality and cardiac and cerebrovascular event rates in the general population (4-7). However, previous high-quality studies excluded extremely elderly patients (8). Therefore, discussing the use of statin for secondary prevention among patients over 75 years old may be valuable, especially in high-risk groups with coronary artery disease (CAD).

In the context of an extremely aging society, it is important to examine the efficacy of statin therapy for secondary prevention in extremely elderly patients according to the new definition. Therefore, the present study investigated the effectiveness of statin therapy for secondary prevention in elderly patients who enrolled in a multicenter cohort registry.

Materials and Methods

Study patients

This study was performed using some of the FUJISUN registry data. The FUJISUN registry is a prospective, single-arm, multicenter, cohort registry conducted at six Japanese sites. This registry was planned to investigate the prognostic factors after successful percutaneous coronary intervention (PCI). A total of 7,173 patients who underwent PCI for CAD at any of the participating hospitals between May 2008 and December 2018 were enrolled in the registry. Written informed consent was obtained from all the patients prior to enrollment in the registry. The ethics committees at each site approved the study protocol, and the study conformed to the principles outlined in the 1975 Declaration of Helsinki.

In this present study, data from patients over 75 years old were abstracted from the registry data. The study initially included 2,585 consecutive extremely elderly patients. The exclusion criteria were as follows: 1) unsuccessful PCI, 2) hemodialysis, or 3) a history of PCI or coronary artery bypass graft (CABG). Patients were followed up clinically for up to three years or until an event occurred.

Study protocol

This study was registered at the URL 'https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000050862' (unique identifier: UMIN000044531). This study analyzed the time to the first major adverse cardiac event (MACE), which was evaluated prospectively for up to three years from the index date. The index date was defined as the date of PCI when patients were initially enrolled in the registry. MACEs were defined as a combination of all-cause death and non-fatal myocardial infarction (MI). If the first hospitalization for MI culminated in death from progressive pump failure or sudden cardiac death during the follow-up period, the event was counted as a death. Non-fatal MI was diagnosed by typical ischemic chest pain with either a creatine kinase-MB level ≥2-fold the upper limit of normal or a troponin T level >0.1 ng/mL, or characteristic ischemic changes on the electrocardiogram at the event and the patient being discharged from the hospital alive.

The baseline clinical characteristics of the patients included in this study are summarized in Table 1. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg during hospitalization, or receiving treatment for high blood pressure before admission. Diabetes mellitus was defined as casual glucose ≥200 mg/dL, fasting plasma glucose ≥126 mg/dL, hemoglobin A1c ≥6.5% (National Glycohemoglobin Standardization Program), or receiving treatment with anti-diabetic drugs before admission. Stroke was defined as a history of symptomatic brain dysfunction from a vascular cause. Peripheral artery disease was defined as an ankle-brachial index <0.9 or a history of peripheral artery revascularization.

Blood samples were collected from a peripheral vein in the early morning, a few days before discharge from the hospital. Drug prescriptions were obtained at discharge after index PCI. Medications were prescribed at the discretion of the physician in charge of the patient. Patients received standard medical treatment after admission (6), which continued throughout the follow-up period. The optimal lifestyle changes and diets were instructed before discharge and were recommended to be continued throughout the follow-up period. All data related to comorbidities, PCI procedures, and outcomes were obtained at each center. Clinical follow-up information was obtained through clinical visits, telephone surveys, validated questionnaires, and referring physicians. All endpoint data were checked strictly for accuracy, consistency, and completeness of follow-up by the investigators. The investigators (T.H. and T.N.) verified all data, performed the statistical analyses, and ensured data file security.

Laboratory measurements

The plasma levels of brain natriuretic peptide (BNP) were measured using an immunoradiometric assay (Shionogi Pharmaceutical, Osaka, Japan). Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula. On echocardiography performed a few days before discharge, the left ventricular ejection fraction (LVEF) was calculated through the motion-mode method using the Teichholz formula.

Statistical analyses

Data are expressed as either the median, interquartile range (25th and 75th percentiles), or frequency (%). To remove selection bias and balance out observable characteristics between the statin and non-statin groups, patient characteristic differences were adjusted using the propensity score methodology, which was performed using propensity scores

Table 1. Comparisons of Clinical Characteristics between Patients with and without Statin.

	Overall (n=932)	With statin (n=466)	Without statin (n=466)	p value
Follow-up period, month	25 (8, 36)	24 (8, 36)	26 (8, 36)	0.79
Age, years	81 (78, 85)	81 (78, 85)	81 (78, 85)	0.55
Sex, male, no (%)	629 (67.5)	314 (67.4)	315 (67.6)	1.00
BMI, kg/m^2	22.2 (20.2, 24.2)	22.4 (20.3, 24.0)	22.0 (20.0, 24.2)	0.42
Hypertension, no (%)	691 (74.1)	347 (74.5)	344 (73.8)	0.88
Diabetes mellitus, no (%)	335 (35.9)	168 (36.1)	167 (35.8)	1.00
PAD, no (%)	48 (5.2)	23 (4.9)	25 (5.4)	0.88
Stroke, no (%)	104 (11.2)	53 (11.4)	51 (10.9)	0.92
Current smoking, no (%)	134 (14.4)	71 (15.2)	63 (13.5)	0.51
HbA1c, %	5.8 (5.5, 6.3)	5.8 (5.5, 6.3)	5.8 (5.5, 6.3)	0.91
TG, mg/dL	92 (66, 125)	95 (68, 125)	90 (63, 124)	0.22
HDL-C, mg/dL	47 (38, 57)	49 (40, 57)	47 (38, 57)	0.12
LDL-C, mg/dL	102 (82, 120)	101 (80, 122)	102 (83, 118)	0.95
eGFR, mL/min/1.73 m^2	56 (43, 68)	57 (45, 68)	54 (41, 67)	0.01
BNP, pg/mL	134 (53, 427)	112 (49, 379)	158 (60, 486)	0.01
LVEF<40%, no (%)	164 (17.6)	79 (17.0)	85 (18.2)	0.67
NYHA HF classification, no (%)				0.21
Class I	515 (55.3)	256 (54.9)	259 (55.6)	
Class II	207 (22.2)	114 (24.5)	93 (20.0)	
Class III	102 (10.9)	50 (10.7)	52 (11.2)	
Class IV	108 (11.6)	46 (9.9)	62 (13.3)	
Medications, no (%)				
Beta-blocker	324 (34.8)	164 (35.2)	160 (34.3)	0.84
CCB	318 (34.1)	164 (35.2)	154 (33.0)	0.53
ACE-I/ARB	506 (54.3)	258 (55.4)	248 (53.2)	0.55
Insulin	37 (4.0)	18 (3.9)	19 (4.1)	1.00
PCI variables				
ACC/AHA lesion classification, no (%)				0.29
Type A	132 (14.2)	57 (12.2)	75 (16.1)	
Type B1	217 (23.3)	117 (25.1)	100 (21.5)	
Type B2	293 (31.4)	147 (31.5)	146 (31.3)	
Type C	290 (31.1)	145 (31.1)	145 (31.1)	
ACS, no (%)	541 (58.0)	270 (57.9)	271 (58.2)	1.00
Rota, no (%)	21 (2.3)	11 (2.4)	10 (2.1)	1.00
Use of DES, no (%)	543 (58.3)	278 (59.7)	265 (56.9)	0.43
Stent diameter, mm	3.0 (2.75, 3.5)	3.0 (2.75, 3.5)	3.0 (2.5, 3.5)	0.01
Stent length, mm	23 (16, 32)	23 (18, 32)	23 (16, 32)	0.18

Data are expressed as the median (25th, 75th percentiles) or the number (%) of patients. BMI: body mass index, PAD: peripheral artery disease, HbA1c: hemoglobin A1c, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate, BNP: brain natriuretic peptide, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, HF: heart failure, CCB: calcium channel blocker, ACE-I: angiotensin converting enzyme inhibitor, ARB: angiotensin II receptor blocker, PCI: percutaneous coronary intervention, ACC: American College of Cardiology, AHA: American Heart Association, ACS: acute coronary syndrome, Rota: rotational atherectomy, DES: drug eluting stent

calculated from a logistic regression model to predict the prescription of statin therapy. In this logistic regression model, covariates were included in every observable factor expressed in Table 1, except for follow-up period, BNP, stent diameter, and stent length. We matched patients using the nearest neighbor method with a 1:1 matching procedure without replacement and a caliper width of 0.05, calculated by 0.2×standard deviation of the logit of the propensity score. Comparisons of patient backgrounds after adjustment are shown in Table 1.

Continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared between the two groups using Pearson's chi-square analysis or Fisher's exact test, as appropriate. The correlation between the clinical variables and the event-free survival was tested using the Kaplan-Meier method, log-rank tests, and Cox proportional hazards regression. A landmark analysis was used to evaluate the relative risk of MACE occurrence in surviving patients after day 30. In the multivariable analysis, backward stepwise Cox regression was selected for variable

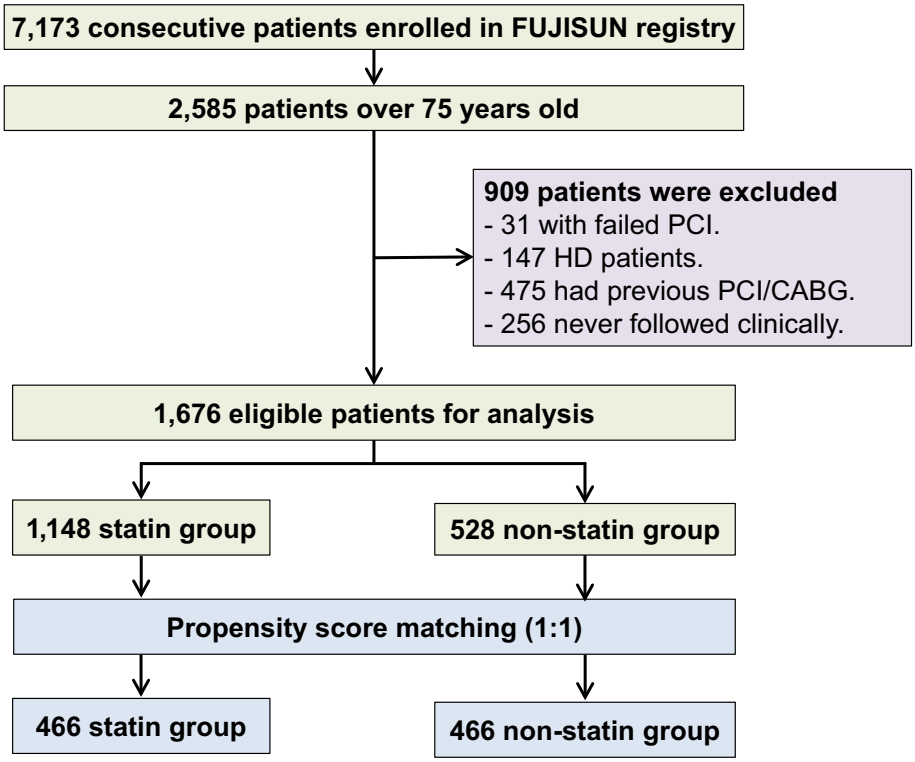

Figure 1. **Flow chart of patient selection.**

selection in the study sample. Statistical significance was defined as $p<0.05$. Analyses were performed using SPSS version 25 (IBM, Armonk, USA).

Results

Study patients (Table 1)

This study initially included 2,585 extremely elderly patients. However, based on the exclusion criteria, 31 patients with failed PCI, 147 who had received hemodialysis, and 475 who had undergone PCI or CABG previously were excluded from this study. After enrollment, 256 patients were never clinically followed. All patients participated in this prospective study assessing the incidence of MACEs after the index date. Finally, the remaining 1,676 patients were analyzed in this study, including 1,148 who received statin therapy, and 528 who did not receive statin therapy.

The baseline patient characteristics before propensity matching was shown in Supplementary material. After propensity score matching, we selected 466 pairs of patients for the analysis (Fig. 1). The median follow-up period was 25 months (interquartile range, 8-36 months). During the follow-up period, 176 MACEs occurred (162 all-cause deaths and 14 non-fatal MIs). Of 162 total deaths, 93 were cardiac deaths, and 69 were non-cardiac deaths. The clinical characteristics of the two matched groups are shown in Table 1. There were no statistically significant differences between the two groups except for in the estimated glomerular filtration rate (eGFR), BNP level, and stent diameter.

The comparison of clinical parameters between patients with and without MACEs (Table 2)

The rate of statin therapy was significantly higher in patients without MACEs than in those with MACEs ($p<0.001$). Furthermore, the age at the index date, high-density lipoprotein cholesterol, eGFR, BNP levels, rate of low LVEF, usage of calcium channel blocker, and rate of acute coronary syndrome (ACS) were significantly different between the patients with and without MACEs. In addition, the New York Heart Association (NYHA) heart failure (HF) classification was significantly higher in the patients with MACEs than in those without, and the American College of Cardiology/American Heart Association (ACC/AHA) lesion classifications were significantly worse in those with MACEs than in those without.

Relationship between MACEs and statin use

Of the 932 study patients, MACEs occurred in 61 of 466 patients (13.1%) in the statin group and 115 of 466 patients (24.7%) in the non-statin group ($p<0.001$) during the follow-up period.

In the univariable Cox proportional hazards risk analysis, statin therapy was significantly associated with a lower incidence of MACEs [hazard ratio (HR) 0.53; 95% confidence interval (CI), (0.39-0.72), $p<0.001$] (Table 3). The age, BNP level, low LVEF, higher NYHA class, worse ACC/AHA lesion type and ACS were significantly correlated with an increased incidence of MACEs. Conversely, the high-density lipoprotein cholesterol level, LDL-C level, eGFR, and calcium channel blocker usage were significantly associated

Table 2. Comparisons of Clinical Characteristics between Patients with and without MACE.

	Overall (n=932)	With MACE (n=176)	Without MACE (n=756)	p value
Age, years	81 (78, 85)	82 (79, 87)	80 (78, 84)	<0.001
Sex, male, no (%)	629 (67.5)	118 (67.0)	511 (67.6)	0.93
BMI, kg/m^2	22.2 (20.2, 24.2)	21.8 (19.9, 24.4)	22.4 (20.3, 24.1)	0.31
Hypertension, no (%)	691 (74.1)	122 (69.3)	569 (75.3)	0.11
Diabetes mellitus, no (%)	335 (35.9)	68 (38.6)	267 (35.3)	0.43
PAD, no (%)	48 (5.2)	13 (7.4)	35 (4.6)	0.13
Stroke, no (%)	104 (11.2)	20 (11.4)	84 (11.1)	0.90
Current smoking, no (%)	134 (14.4)	26 (14.8)	108 (14.3)	0.91
HbA1c, %	5.8 (5.5, 6.3)	5.9 (5.4, 6.3)	5.8 (5.5, 6.3)	0.95
TG, mg/dL	92 (66, 125)	90 (60, 121)	94 (66, 126)	0.13
HDL-C, mg/dL	47 (38, 57)	43 (36, 56)	49 (40, 58)	<0.001
LDL-C, mg/dL	102 (82, 120)	100 (77, 116)	102 (82, 120)	0.10
eGFR, mL/min/1.73 m^2	56 (43, 68)	49 (37, 62)	57 (45, 69)	<0.001
BNP, pg/mL	134 (53, 427)	369 (115, 775)	114 (49, 337)	<0.001
LVEF<40%, no (%)	164 (17.6)	63 (35.8)	101 (13.4)	<0.001
NYHA HF classification, no (%)				<0.001
Class I	515 (55.3)	53 (30.1)	462 (61.1)	
Class II	207 (22.2)	41 (23.3)	166 (22.0)	
Class III	102 (10.9)	30 (17.0)	72 (9.5)	
Class IV	108 (11.6)	52 (29.5)	56 (7.4)	
Medications, no (%)				
Beta-blocker	324 (34.8)	52 (29.5)	272 (36.0)	0.11
CCB	318 (34.1)	43 (24.4)	275 (36.4)	0.003
ACE-I/ARB	506 (54.3)	86 (48.9)	420 (55.6)	0.11
Statin	466 (50.0)	61 (34.7)	405 (53.6)	<0.001
Insulin	37 (4.0)	9 (5.1)	28 (3.7)	0.39
PCI variables				
ACC/AHA lesion classification, no (%)				0.005
Type A	132 (14.2)	16 (9.1)	116 (15.3)	
Type B1	217 (23.3)	31 (17.6)	186 (24.6)	
Type B2	293 (31.4)	58 (33.0)	235 (31.1)	
Type C	290 (31.1)	71 (40.3)	219 (29.0)	
ACS, no (%)	541 (58.0)	119 (67.6)	422 (55.8)	0.005
Rota, no (%)	21 (2.3)	7 (4.0)	14 (1.9)	0.09
Use of DES, no (%)	543 (58.3)	93 (52.8)	450 (59.5)	0.11
Stent diameter, mm	3.0 (2.75, 3.5)	3.0 (2.75, 3.5)	3.0 (2.75, 3.5)	0.71
Stent length, mm	23 (16, 32)	24 (18, 32)	23 (16, 32)	0.71

Data are expressed as the median (25th, 75th percentiles) or the number (%) of patients. MACE: major adverse cardiovascular event, other abbreviations are same as Table 1.

with a decreased incidence of MACEs (Table 3).

The multivariable Cox proportional hazards model adjusted for relevant clinical factors demonstrated that the age, prevalence of hypertension, eGFR, NYHA class, and presence of statin therapy remained significant independent indicators of MACEs (Table 3). The covariates included in this multivariable model were the age, hypertension, diabetes mellitus, peripheral artery disease (PAD), stroke, current smoking, eGFR, NYHA class, statin use, ACS, and use of a drug-eluting stent.

The Kaplan-Meier analysis showed that there was a significantly lower incidence of initial MACEs within 30 days in the statin group than in the non-statin group (log-rank test, p<0.001) (Fig. 2). Furthermore, a landmark analysis at day 30 demonstrated that the statin group still had a consistently lower incidence of MACEs during the follow-up period than the non-statin group (log-rank test, p=0.04) (Fig. 2).

A stratification analysis for MACEs (Fig. 3)

The covariates selected in the stratification analysis were arranged based on the thrombolysis in myocardial infarction risk score for secondary prevention (TRS 2°P) (9). In the stratification analysis, statin therapy showed significant effectiveness in reducing the incidence of MACEs. First, the patients with non-symptomatic HF gained a significant benefit from statin therapy compared with the symptomatic HF patients. Second, the patients without a history of stroke,

Table 3. Cox Proportional Hazards Regression Analysis for Occurrence of MACE.

	Univariable		Multivariable	
	HR (95% CI)	p value	HR (95% CI)	p value
Age, per 5 years	1.46 (1.26, 1.68)	<0.001	1.24 (1.07, 1.44)	0.004
Male gender	0.99 (0.72, 1.06)	0.96		
BMI, per SD	1.06 (0.90, 1.26)	0.49		
Hypertension	0.74 (0.53, 1.01)	0.06	0.74 (0.53, 1.02)	0.07
Diabetes mellitus	1.10 (0.81, 1.49)	0.54	not selected	
PAD	1.54 (0.88, 2.72)	0.13	not selected	
Stroke	0.99 (0.63, 1.59)	0.98	not selected	
Current smoking	1.01 (0.67, 1.53)	0.96	not selected	
HbA1c, per SD	1.01 (0.87, 1.18)	0.86		
TG, per SD	0.95 (0.78, 1.15)	0.59		
HDL-C, per SD	0.73 (0.62, 0.86)	<0.001		
LDL-C, per SD	0.83 (0.71, 0.98)	0.02		
BNP, per SD	1.56 (1.41, 1.72)	<0.001		
eGFR, per SD	0.62 (0.53, 0.73)	<0.001	0.80 (0.67, 0.94)	0.007
LVEF<40%	3.16 (2.32, 4.30)	<0.001		
NYHA HF classification				
Class I	1.00 (Ref.)	-	1.00 (Ref.)	-
Class II	2.17 (1.45, 3.27)	<0.001	2.02 (1.34, 3.06)	0.001
Class III	3.30 (2.11, 5.17)	<0.001	2.79 (1.76, 4.40)	<0.001
Class IV	6.43 (4.39, 9.44)	<0.001	5.24 (3.51, 7.83)	<0.001
Medications				
Beta-blocker	0.79 (0.57, 1.10)	0.16		
CCB	0.57 (0.40, 0.80)	0.001		
ACE-I/ARB	0.76 (0.56, 1.02)	0.06		
Statin	0.53 (0.39, 0.72)	<0.001	0.55 (0.40, 0.75)	<0.001
Insulin	1.38 (0.71, 2.71)	0.34		
PCI variables				
ACC/AHA lesion classification				
Type A	1.00 (Ref.)	-		
Type B1	1.21 (0.66, 2.21)	0.54		
Type B2	1.73 (0.99, 3.02)	0.05		
Type C	2.39 (1.39, 4.12)	0.002		
ACS	1.59 (1.16, 2.18)	0.004	not selected	
Rota	1.66 (0.78, 3.54)	0.19		
Use of DES	0.91 (0.68, 1.23)	0.54	not selected	
Stent Diameter	1.04 (0.88, 1.23)	0.64		
Stent length	1.00 (0.99, 1.01)	0.85		

Data are expressed as the odds ratio (95% confidence interval). HR: hazard ratio, CI: confidence interval, SD: standard deviation, Ref.: reference, other abbreviations are same as Tables 1 and 2.

PAD, or tobacco use may have benefited more from statin therapy than other patients. In addition, the statin therapy had a significant benefit in patients regardless of hypertension, diabetes mellitus, or renal dysfunction. There were no statistically confounding effects between statin treatment and clinical factors included in this stratification analysis.

Discussion

This study demonstrated the efficacy of statin therapy for the secondary prevention of cardiovascular events in extremely elderly patients after PCI. In particular, statin therapy had significant benefits in patients without symptomatic HF, a history of stroke, PAD, or a current smoking status. Furthermore, the statin therapy had a significant benefit in patients regardless of hypertension, diabetes mellitus, or renal dysfunction.

To date, the efficacy of statin therapy for secondary prevention has been validated in various papers (10, 11). However, extremely elderly patients were excluded from the study protocol in these papers, and a detailed investigation is still warranted (8). Furthermore, several studies have examined the effectiveness of statins in the elderly, but the available information is still limited. A sub-group analysis of the PROSPER revealed the efficacy of statin therapy for secondary prevention in elderly patients over 70 years old (12). Although the subjects of this study were elderly, their ages actually ranged from 70-82 years old, deeming many of

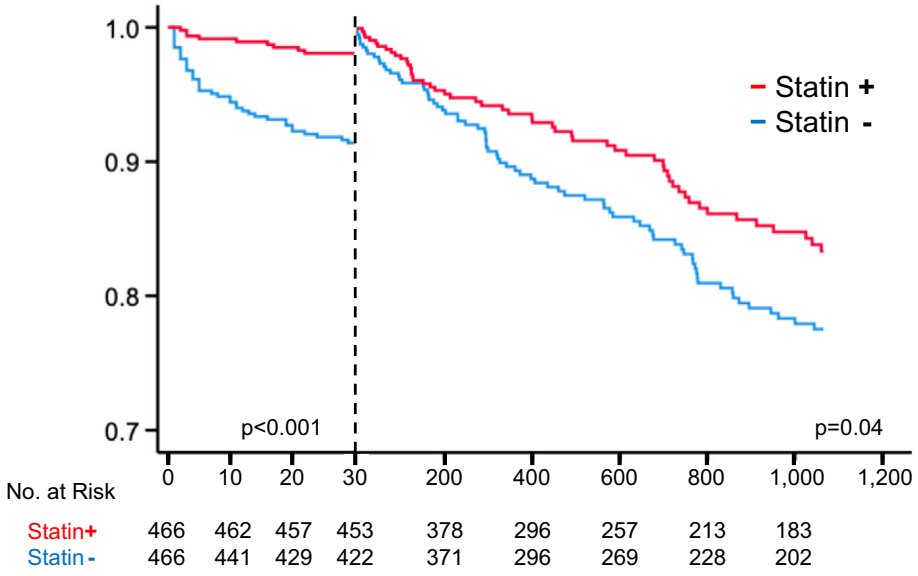

Figure 2. **Kaplan-Meier curve evaluating the occurrence of MACEs in elderly patients with and without statin treatment. The red line indicates the group with statin treatment. The blue line indicates the group without statin treatment. The dotted line indicates day 30 after the first PCI procedure. The left-side Kaplan-Meier curve demonstrates the initial survival rate from the index date to 30 days, which was analyzed before propensity matching. The right-side Kaplan-Meier curve is the landmark analysis at day 30 after treatment demonstrating the survival rate analyzed after propensity matching.**

Subgroup	Statin	Non Statin	HR 95%CI	p value for interaction
	patient number (%)			
HTN				
YES	334 (75.2)	328 (73.9)	0.59 (0.41-0.85)	0.29
NO	110 (24.8)	116 (26.1)	0.41 (0.23-0.73)	
DM				
YES	157 (35.4)	157 (35.4)	0.59 (0.36-0.97)	0.54
NO	287 (64.6)	287 (64.6)	0.49 (0.33-0.73)	
Stroke				
YES	52 (11.7)	51 (11.5)	0.70 (0.28-1.70)	0.56
NO	392 (88.3)	393 (88.5)	0.51 (0.37-0.71)	
PAD				
YES	32 (7.2)	26 (5.9)	1.13 (0.38-3.38)	0.19
NO	412 (92.8)	418 (94.1)	0.50 (0.38-0.69)	
Smoke				
YES	57 (12.8)	64 (14.4)	0.56 (0.25-1.22)	0.90
NO	387 (87.2)	380 (85.6)	0.52 (0.37-0.73)	
eGFR				
≤60	255 (57.4)	264 (59.5)	0.40 (0.22-0.75)	0.23
>60	189 (42.6)	180 (40.5)	0.62 (0.43-0.88)	
NYHA				
I	182 (41.0)	180 (40.5)	0.41 (0.28-0.60)	0.08
II-IV	262 (59.0)	264 (59.5)	0.76 (0.44-1.32)	

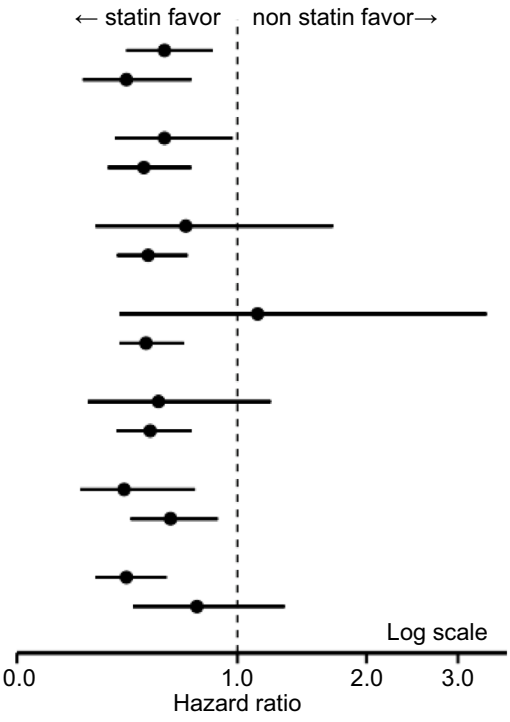

Figure 3. **Results of a stratification analysis. The black dot indicates the hazard ratio. The black line indicates 95% confidence intervals. The horizontal axis was described by the logarithmic scale. The dotted line indicates the hazard ratio of 1.0. HR: hazard ratio, CI: confidence interval, HTN: hypertension, DM: diabetes mellitus, PAD: peripheral artery disease, NYHA: New York Heart Association**

them younger than the novel definition of elderly (12). Furthermore, another study reported that statin therapy for secondary prevention had no efficacy in patients with acute myocardial infarction over 80 years old (13). This paradoxical result might be explained by the fact that many older individuals have multiple comorbidities and that the impact of the risk factors for atherosclerosis is attenuated with age (14).

Since the period when such evidence was accumulated, the Japanese population has been undergoing extreme aging, and the number of robust elderly people has been increasing. For this reason, it is important to re-examine statin effectiveness in elderly patients based on recent data.

The associations of some traditional risk factors with cardiovascular disease are attenuated in elderly patients (14). As expected, LDL-C was inversely associated with the occurrence of MACEs in this study. However, some recent studies have revealed that there is an inverse relationship between LDL-C levels and cardiovascular events in elderly patients. To explain this contradiction, the association between low LDL-C levels and critical illness, including malignant cancer or infection, is often pointed out (15). The fact that statin therapy was effective in patients without a low body mass index (BMI) in the stratification analysis (data not shown) was consistent with a previous study reporting its effectiveness among frail patients (16).

As is often pointed out, statins exert pleiotropic effects via several physiological mechanisms (17, 18). These pleiotropic effects have various beneficial effects on the vascular, immune, central nervous, and musculoskeletal systems (17).

The patients' backgrounds, comorbidities, frailty, and biological heterogeneity vary, which may be linked to differences in drug efficacy. For this reason, the decision to treat statins should be individualized (19). Although the effects of risk factors are attenuated with age, it is beneficial to use statins even in elderly patients if they are tolerated. Furthermore, aggressive statin administration may be more effective in the patient groups where its usefulness was suggested based on the stratification analysis. The present findings may prove useful for selecting the optimal statin treatment for each patient.

Study Limitations

Several limitations associated with the present study warrant mention. First, this study was not a randomized trial, and the possibility of selection bias should be considered. To minimize selection bias, we adopted the propensity score methodology and multivariable regression model. Although the possibility of selection bias and potential confounders cannot be ruled out even after adjusting, statin therapy has consistently proven effective on MACE occurrence. Second, drug prescription data were obtained at discharge after the index PCI procedure. Thus, whether or not statins had been initiated before the index PCI is unknown. Unfortunately, information on the statin type and dosage was not available. However, this was a real-world prospective cohort study. Thus, our results may suggest that patients who are eligible for statin treatment should be managed aggressively. Furthermore, approximately 10% patients were never followed clinically, which may have influenced the study results. In addition, the number of patients included in this study was small. Therefore, it is necessary to avoid over-interpretation regarding the efficacy of statin therapy, although the effectiveness of statin therapy was consistent with previous studies. Larger randomized clinical studies are needed for better subgroup analyses. Finally, this cohort study did not accumulate patient comorbidities related to malignant cancer. Although our findings might have been influenced by the fatal outcome, this cohort focused on anti-atherosclerotic treatment for secondary prevention after PCI.

Conclusion

In conclusion, this study indicated that statin therapy was effective in reducing MACEs in extremely elderly patients. Furthermore, in the stratification analysis, statin use particularly improved the outcomes in patients without symptomatic HF, a history of stroke, PAD, or current tobacco use. Further studies will be needed to investigate approaches to reduce the high cardiac and atherosclerotic risks in elderly patients.

Author's disclosure of potential Conflicts of Interest (COI).
Kiyotaka Kugiyama: Scholarchip donations, Takeda, Daiichi Sankyo, Astellas, Boehringer Ingelheim, MSD, Boston Scientific Japan, Abbott, Medtronic, Biotronik Japan and St. Jude Medical.

Financial Support
This work was supported by the JSPS KAKENHI grant numbers B2-19390209 and B-22390158.

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