Higher Hemoglobin A1c After Discharge Is an Independent Predictor of Adverse Outcomes in Patients With Acute Coronary Syndrome

– Findings From the PACIFIC Registry –

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Background: Optimal medical therapy (OMT) and the management of coronary risk factors are necessary for secondary prevention of major adverse cardiac and cerebrovascular events (MACCE) in post-acute coronary syndrome (ACS) patients. However, the effect of post-discharge patient adherence has not been investigated in Japanese patients.

Methods and Results: The Prevention of Atherothrombotic Incidents Following Ischemic Coronary Attack (PACIFIC) registry was a multicenter, prospective observational study of 3,597 patients with ACS. Death or MACCE occurred in 229 patients between hospitalization and up to 1 year after discharge. Among 2,587 patients, the association between OMT adherence and risk factor control at 1 year and MACCE occurring between 1 and 2 years after discharge was assessed. OMT was defined as the use of antiplatelet agents, angiotensin-converting enzyme inhibitors, β -blockers, and statins. Risk factor targets were: low-density lipoprotein-cholesterol <100 mg/dl, HbA1c $<7.0\%$, non-smoking status, blood pressure $<130/80$ mmHg, and $18.5 \leq$ body mass index ≤ 24.9 kg/m². The incidence of MACCE was 1.8% and associated with female sex ($P=0.020$), age ≥ 75 years ($P=0.004$), HbA1c $\geq 7.0\%$ ($P=0.004$), LV ejection fraction $<35\%$ ($P<0.001$), estimated glomerular filtration rate <60 ml/min ($P=0.008$), and history of cerebral infarction ($P=0.003$). In multivariate analysis, lower post-discharge HbA1c was strongly associated with a lower risk of MACCE after ACS ($P=0.004$).

Conclusions: Hyperglycemia after discharge is a crucial target for the prevention of MACCE in post-ACS patients. (*Circ J* 2016; **80**: 1607–1614)

Key Words: Acute coronary syndrome; HbA1c; Major adverse cardiac and cerebrovascular events; Secondary prevention

Received November 10, 2015; revised manuscript received April 14, 2016; accepted April 18, 2016; released online May 19, 2016 Time for primary review: 23 days

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This paper was presented at the 79th Annual Scientific Meeting of the Japanese Circulation Society, Late Breaking Cohort Studies, April 24–26, 2015, Osaka, Japan.

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ISSN-1346-9843 doi:10.1253/circj.CJ-15-1126

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Table 1. Previous Studies of Predictors of Adverse Cardiovascular Events in Post-ACS Patients

Year	Study name	Country	Type of ACS	n	Follow-up period	Outcome	Predictors of outcome
2002 ⁷	JCIS	Japan	AMI underwent PCI	2,221	1 year	Mortality	High age, low LVEF, renal failure, DM, multivessel disease
2004 ⁸	PRAIS UK	UK	NSTEMI	653	2.4 years (mean)	Mortality	High age, male sex, low SBP, high HR, history of HF, ECG change (ST depression or BBB), history of stroke
2005 ⁹	Single center	Japan	AMI	415	4.0 years (mean)	Mortality	High age, history of cerebrovascular disease, renal failure (serum creatinine ≥ 2.0 mg/dl), no PCI, Killip class ≥ 2 , ventricular tachycardia/fibrillation
2007 ¹⁰	Multicenter	New Zealand	ACS	1,057	4 years	Mortality	High age, history of IHD, CHF, high HR, high serum creatinine, high TNI, no in-hospital PCI, no in-hospital CABG, history of smoking, no dyslipidemia
2011 ¹¹	CRUSADE	USA	NSTEMI, Age ≥ 65	43,239	453 days (median)	Mortality	High age, male sex, high serum creatinine, low SBP, HF on presentation, high HR, low weight, no hyperlipidemia, low hematocrit, high troponin, history of stroke, DM, history of PAD, no family history of CAD, history of MI, current/recent smoking, no history of PCI, black/white race, no transient ST elevation, hypertension
2012 ¹²	Multicenter	USA	AMI	2,542	3–24 months	Mortality	High age, male sex, NSTEMI, low eGFR, history of HF, history of stroke, heart failure in hospital, cardiogenic shock in hospital
2013 ¹³	OACIS	Japan	AMI	7,870	3.9 years (median)	Recurrent MI	High age, DM, history of MI

ACS, acute coronary syndrome; AMI, acute myocardial infarction; BBB, bundle branch block; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment elevation MI; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TNI, troponin I.

Optimal medical therapy (OMT) and the management of coronary risk factors are crucial for the secondary prevention of major adverse cardiac and cerebrovascular events (MACCE) in patients after acute coronary syndrome (ACS).

Risk assessment based on evidence of short-term outcomes in post-ACS patients has been established,^{1–3} and previous studies have reported an improvement in short-term outcomes in post-ACS patients with risk management.^{4–6} However, data on long-term outcomes and predictors are relatively limited.

Previous studies have identified prognostic risk factors for long-term outcomes in post-ACS patients among the clinical variables at the time of hospitalization.^{7–13} Older age, male sex, cardiac shock, multivessel disease, a history of heart failure/cerebrovascular disease/coronary artery disease (CAD), low left ventricular ejection fraction (LVEF), renal dysfunction, hypertension, or diabetes mellitus (DM) have been reported as major prognostic factors for subsequent adverse outcomes in post-ACS patients (Table 1). In ACS patients, strict management of these factors is needed for secondary prevention. Indeed, OMT and the management of coronary risk factors are recommended in the Japanese Circulation Society (JCS) guidelines for the secondary prevention of MACCE in post-ACS patients.¹⁴ However, because the effect of patient adherence after discharge on subsequent long-term clinical outcomes has not been investigated in Japanese patients, the present study used the data from the Prevention of Atherothrombotic Incidents Following Ischemic Coronary Attack (PACIFIC) registry to evaluate long-term adherence to OMT and management of coronary risk factors, and investigate the prognostic risk

factors for MACCE after discharge in post-ACS patients.

Methods

Patient Population

The PACIFIC registry was a multicenter, prospective observational study of Japanese ACS patients. A total of 3,597 ACS patients aged ≥ 20 years were enrolled from 96 hospitals between May 2008 and May 2009 and followed for 2 years. Details of the protocol and results of the main study have been published.^{15,16}

In the present study, the analyzed population was patients who received medical therapy for 1 year after discharge from hospital. Therefore, patients who died or had MACCE during hospitalization ($n=119$) or within 1 year of discharge ($n=110$), patients lost to follow-up within 1 year after discharge ($n=727$), and patients with missing data ($n=54$) were excluded. Required data included use of antiplatelet agents, angiotensin-converting enzyme inhibitors (ACEI), β -blockers, and statins, smoking status, body mass index (BMI), blood pressure (BP), low-density lipoprotein-cholesterol (LDL-C), and HbA1c data at 1 year after discharge. Finally, 2,587 patients were included in this study (Figure 1).

Endpoint

The primary endpoint was defined as the occurrence of MACCE, a composite of fatal myocardial infarction (MI), fatal stroke, other cardiovascular death, non-fatal MI, and non-fatal stroke.^{15,16} Time to MACCE was calculated from the date at 1 year after discharge to the date of occurrence of MACCE or censoring.

Figure 1. Schematic of the selection of studied patients from the PACIFIC registry. MACCE, major adverse cardiac and cerebrovascular events.

OMT and Candidate Prognostic Risk Factors for MACCE

A total of 24 variables were considered for the development of a risk model for the occurrence of MACCE (Tables 2,3). According to the JCS guidelines,¹⁴ OMT is defined as the use of antiplatelet agents, ACEIs, β -blockers, and statins. Management goals for coronary risk factors are defined as LDL-cholesterol <100 mg/dl, HbA1c <7.0%, maintenance of non-smoking status, BP <130/80 mmHg, and $18.5 \leq \text{BMI} \leq 24.9 \text{ kg/m}^2$. The data of OMT adherence and coronary risk factor management at 1 year after discharge were evaluated for each patient and considered as long-term adherence and management. Other variables included age ≥ 75 years, sex, hypertension, dyslipidemia, DM, type of ACS (MI or unstable angina), LVEF <35%, estimated glomerular filtration rate (eGFR) <60 ml/min, fasting glucose $\geq 126 \text{ mg/dl}$, triglycerides $\geq 150 \text{ mg/dl}$, high-density lipoprotein-cholesterol <40 mg/dl, and a history of MI, atrial fibrillation, cerebral infarction, or peripheral artery disease as candidate prognostic risk factors.

Statistical Analysis

Baseline characteristics are presented as percentages for categorical variables and median and range for continuous variables.

The incidence of MACCE between 1 and 2 years after discharge was estimated using the Kaplan-Meier method, and a log-rank test was used for statistical comparisons. To identify predictors for the occurrence of MACCE during 1- and 2-year follow-up, Cox regression analysis was performed to determine hazard ratios (HRs) with 95% confidence intervals (CIs) and P values. The prognostic value of OMT and management of coronary risk factors at 1 year after discharge were also determined in a multivariate Cox regression analysis. Use of antiplatelet agents was excluded in this model because these were taken by almost all patients during follow-up (99.6% at discharge, 98.1% at 1 year, 97.8% at 2 years). Variables related to long-term adherence to OMT and management of coronary risk factors were forced into the model. Regarding other candidate factors, variables that were significant in the univariate analysis were also included in the multivariate analysis. Receiver-operating characteristic (ROC) analysis was per-

Table 2. Baseline Characteristics of the Study Patients

	n=2,587
Age (years)	67 (30–95)
Male (%)	78.4
Concomitant diseases (%)	
Diabetes mellitus	34.4
Hypertension	73.3
Dyslipidemia	68.5
CKD (eGFR <60 ml/min)	30.8
Dialysis	1.9
Previous history (%)	
Myocardial infarction	10.5
Atrial fibrillation	4.0
Cerebral infarction	6.7
Peripheral artery disease	3.7
Type of ACS (%)	
Myocardial infarction	67.9
Unstable angina	32.1
LVEF (%) [UCG/LVG]	56 (10–89) [1,302/728]

Data given as % or median (range). CKD, chronic kidney disease; LVG, left ventriculography; UCG, ultrasound echocardiography. Other abbreviations as in Table 1.

formed to assess the optimal cut-off level of the identified predictor. All analyses were performed using JMP 11 (SAS Institute Inc, Cary, NC, USA). P-values <0.05 were considered statistically significant.

Ethics

This study was approved by the Ethics Committee of Hokkaido University Hospital, and complied with the Declaration of Helsinki. The protocol of the PACIFIC registry was approved by the ethics committees of each participating institution. All subjects provided written informed consent and all data were anonymized.

Table 3. Prevalence of Patients Under Optimal Medical Therapy and Management of Coronary Risk Factors

	Admission (n=2,587)	At discharge (n=2,587)	After discharge	
			1 year (n=2,587)	2 years (n=2,544)
OMT (%)				
Antiplatelet agents	27.5	99.6	98.1	97.8
ACEIs/ARBs	31.2	78.5	75.5	73.9
ACEIs	6.0	31.6	24.1	23.1
ARBs	26.5	49.6	53.8	53.3
β-blockers	12.2	49.4	50.2	50.2
Statins	21.1	78.6	80.4	80.6
Management of risk factors (%)				
LDL-C <100 mg/dl	61.6	NA	70.1	69.6
HbA1c (NGSP) <7.0%	77.8	NA	82.0	80.8
Non-smoking status	59.2	NA	85.1	87.4
BP <130/80 mmHg	35.4	NA	46.0	46.3
18.5≤BMI≤24.9 kg/m²	60.3	NA	61.1	62.4

Data given as %. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BMI, body mass index; BP, blood pressure; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein-cholesterol; NA, not available; NGSP, National glycohemoglobin standardization program; OMT, optimal medical therapy.

Table 4. Predictors of MACCE by Univariate and Multivariate Cox Regression Analyses

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
OMT (1 year after discharge)						
Antiplatelet agents	0.26	0.10–1.10	0.065			
ACEIs	0.86	0.41–1.66	0.670	0.83	0.13–3.25	0.814
β -blockers	1.33	0.75–2.41	0.328	2.27	0.71–8.61	0.171
Statins	0.57	0.31–1.10	0.093	0.29	0.09–1.06	0.060
Management of risk factors (1 year after discharge)						
LDL-C <100 mg/dl	1.07	0.51–2.45	0.861	1.17	0.35–4.68	0.803
HbA1c (NGSP) <7.0%	0.57	0.39–0.87	0.004	0.43	0.24–0.76	0.004
Non-smoking status	0.99	0.47–2.42	0.979	2.14	0.40–39.7	0.424
BP <130/80 mmHg	0.84	0.45–1.54	0.584	0.73	0.21–2.27	0.587
18.5≤BMI≤24.9 kg/m ²	0.94	0.50–1.84	0.854	2.22	0.68–8.72	0.190
Other risk factors						
Female	2.09	1.13–3.74	0.020	1.50	0.39–4.83	0.522
Age ≥75 years	2.40	1.34–4.27	0.004	0.57	0.08–2.32	0.464
LVEF <35%	5.50	2.20–12.00	<0.001	2.05	0.30–8.45	0.413
eGFR <60 ml/min	2.19	1.23–3.89	0.008	0.79	0.20–2.60	0.705
Fasting glucose ≥126 mg/dl	1.37	0.68–2.67	0.368			
Triglycerides ≥150 mg/dl	1.23	0.60–2.40	0.564			
HDL-C <40 mg/dl	1.06	0.45–2.24	0.888			
MI	0.93	0.51–1.74	0.789			
History of MI	1.47	0.60–3.08	0.370			
History of AF	2.09	0.63–5.16	0.203			
History of cerebral infarction	3.45	1.57–6.82	0.003	3.74	0.79–13.2	0.089
History of PAD	1.39	0.23–4.52	0.666			
Hypertension	1.80	0.89–4.14	0.109			
Dyslipidemia	0.61	0.34–1.11	0.102			
Diabetes mellitus	1.32	0.73–2.35	0.354			

AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; HDL-C, high-density lipoprotein-cholesterol; MACCE, major adverse cardiac and cerebrovascular events; PAD, peripheral artery disease. Other abbreviations as in Tables 1,3.

Role of the Sponsor and the Authors

The PACIFIC study was designed by the authors in collaboration with the sponsor (Sanofi, Tokyo, Japan). The sponsor made the PACIFIC database available to the PACIFIC steering committee, and the authors conducted this subanalysis using the data. The draft manuscript was fully reviewed and revised by the authors. The authors and sponsor made the final decision on submission of the article.

Results

Baseline Characteristics

The baseline characteristics of the patients ($n=3,597$) in the overall study have been published previously.¹⁶ The characteristics of the 2,587 patients included in the present study are shown in **Table 2**. The incidence of MACCE among these patients between 1 and 2 years after discharge was 1.8% (47/2,587 patients): 2 patients (4.3%) had a fatal MI, 1 (2.1%) had a fatal stroke, 7 (14.9%) had other cardiovascular deaths, 15 (31.9%) had a non-fatal MI, and 22 (46.8%) had a non-fatal stroke.

Assessment of Adherence to OMT and the Management of Risk Factors

Almost all patients (97.8–99.6%) were treated with antiplatelet agents at some time, including at discharge, or 1 or 2 years after discharge (**Table 3**). The use of statins was as high as 78.6–80.6% over the 2 years. The use of ACEIs or angiotensin-receptor blockers and β -blockers at discharge, 1 year and 2 years was approximately 75% and 50%, respectively, and these rates were stable up to 2 years after discharge.

The percentage of patients with LDL-C <100 mg/dl was 70.1% at 1 year after discharge, and did not change at 2 years (69.6%). The percentage with HbA1c $<7.0\%$ was 82.0% at 1 year and remained the same at 2 years (80.8%). The proportion of patients with BP $<130/80$ mmHg was as low as 46.0% at 1 year and 46.3% at 2 years. Almost 60% of patients had $18.5 \leq \text{BMI} \leq 24.9$ kg/m² at both 1 and 2 years. In contrast, the percentage of patients who did not smoke increased from 59.2% at the time of admission to 85.1% at 1 year after discharge and 87.4% at 2 years.

Independent Predictors Associated With MACCE Between 1 and 2 Years

In the univariate analysis (**Table 4**), MACCE was associated with female sex (HR 2.09, 95% CI 1.13–3.74, $P=0.020$), age ≥ 75 years (HR 2.40, 95% CI 1.34–4.27, $P=0.004$), HbA1c $\geq 7.0\%$ (HR 3.04, 95% CI 1.32–6.68, $P=0.004$), LVEF $<35\%$ (HR 5.50, 95% CI 2.20–12.00, $P<0.001$), eGFR <60 ml/min (HR 2.19, 95% CI 1.23–3.89, $P=0.008$), and a history of cerebral infarction (HR 3.45, 95% CI 1.57–6.82, $P=0.003$). In the multivariate analysis incorporating the risk factors that were significant in the univariate analysis, HbA1c $<7.0\%$ at 1-year follow-up was significantly associated with a lower risk of MACCE between 1 and 2 years after discharge (HR 0.43, 95% CI 0.24–0.76, $P=0.004$). According to the ROC analysis, the optimal cut-off level of HbA1c was determined to be 6.4% (area under curve 0.65) (**Figure 2**).

We further conducted subgroup analysis stratified by the presence of DM. HbA1c $\geq 6.4\%$ was found to be an independent predictor of MACCE ($P=0.012$) in the subgroup of DM patients, but not in patients without DM (**Table 5**). LVEF $<35\%$ ($P=0.004$) and a history of cerebral infarction ($P=0.002$) were associated with MACCE in patients without DM.

Figure 2. Determination of optimal HbA1c cut-off value for the occurrence of MACCE by receiver-operating characteristic curve. AUC, area under the curve; MACCE, major adverse cardiac and cerebrovascular events.

Discussion

This is the first report to evaluate the long-term prognosis of adherence to OMT and medical management of coronary risk factors after discharge, based on JCS guidelines, in Japanese post-ACS patients. The unique feature of this study was that it assessed long-term adherence to OMT as well as management of coronary risk factors as predictors of long-term MACCE. The PACIFIC registry contained all the data that enabled us to identify the risk factors for MACCE during long-term follow-up.

The most important finding of the present study was that a lower HbA1c level was independently associated with a lower risk of MACCE in post-ACS patients, and that the optimal cut-off level of HbA1c for secondary prevention of MACCE was 6.4%. These results are consistent with previous studies showing a correlation between intensive glycemic control and favorable cardiovascular outcomes.^{17–19} Similar findings were also reported by the PROactive study, in which pioglitazone treatment was associated with a significantly lower rate of fatal and non-fatal MI and ACS in DM patients with greater decline in median HbA1c.²⁰ These findings also support recommendations for the optimal HbA1c level for secondary prevention to be $<7.0\%$ in the Japanese guidelines,¹⁴ and also in the American Heart Association and American College of Cardiology Foundation guidelines.²¹ The European Society of Cardiology guidelines recommend a target HbA1c level $<7.0\%$ for primary prevention of cardiovascular disease (class I, level of evidence A).²²

In contrast, several recent studies have reported that intensive glycemic control may increase adverse events.^{23,24} Currie et al reported that type 2 DM patients with lower levels of controlled HbA1c had increased all-cause deaths and cardiac events compared with DM patients with median HbA1c 7.5%.²³ In the ACCORD study, intensive glycemic control (goal HbA1c $<6.0\%$ and median HbA1c at 1 year 6.4%) was associated with higher mortality rates compared with standard

Table 5. Predictors of MACCE by Univariate and Multivariate Analyses in Patients With and Without Diabetes Mellitus

Variable	Diabetes mellitus (n=890)				No diabetes mellitus (n=1,697)			
	Univariate	Multivariate			Univariate	Multivariate		
	P-value	HR	95% CI	P-value	P-value	HR	95% CI	P-value
OMT (1 year after discharge)								
Antiplatelet agents	0.577	—	—	—	0.001	—	—	—
ACEIs	0.622	—	—	—	0.397	—	—	—
β -blockers	0.073	—	—	—	0.863	—	—	—
Statins	0.961	—	—	—	0.019	0.55	0.21–1.52	0.234
Management of risk factor (1 year after discharge)								
LDL-C <100 mg/dl	0.562	—	—	—	0.785	—	—	—
HbA1c (NGSP) <7.0%	0.053	—	—	—	0.219	—	—	—
HbA1c (NGSP) <6.4%	0.016	0.19	0.03–0.72	0.012	0.417	—	—	—
Non-smoking status	0.548	—	—	—	0.591	—	—	—
BP <130/80 mmHg	0.287	—	—	—	0.765	—	—	—
18.5≤BMI≤24.9 kg/m ²	0.673	—	—	—	0.886	—	—	—
Other risk factors								
Female	0.012	1.71	0.51–5.30	0.366	0.293	—	—	—
Age ≥75 years	0.004	0.51	0.40–4.79	0.515	0.098	—	—	—
LVEF <35%	0.080	—	—	—	<0.001	5.89	1.91–15.2	0.004
eGFR <60 ml/min	0.081	—	—	—	0.039	0.91	0.34–2.24	0.843
Fasting glucose ≥126 mg/dl	0.893	—	—	—	0.173	—	—	—
Triglycerides ≥150 mg/dl	0.992	—	—	—	0.460	—	—	—
HDL-C <40 mg/dl	0.687	—	—	—	0.623	—	—	—
MI	0.432	—	—	—	0.342	—	—	—
History of MI	0.672	—	—	—	0.399	—	—	—
History of AF	0.759	—	—	—	0.107	—	—	—
History of cerebral infarction	0.230	—	—	—	<0.001	6.04	2.10–15.3	0.002
History of PAD	0.329	—	—	—	0.068	—	—	—
Hypertension	0.835	—	—	—	0.056	—	—	—
Dyslipidemia	0.741	—	—	—	0.044	—	—	—
Insulin	0.127	—	—	—	—	—	—	—
Sulfonylureas	0.264	—	—	—	—	—	—	—
Thiazolidinediones	0.425	—	—	—	—	—	—	—

HR, hazard ratio. Other abbreviations as in Tables 1,3,4.

glycemic control (goal HbA1c 7.0–7.9% and median HbA1c at 1 year 7.5%) in type 2 DM patients with either known CAD or cardiovascular risk factors.²⁴ However, it was also found that intensive glycemic control decreased the incidence of MI, coronary revascularization, and unstable angina in these patients.¹⁹ The reason for these discrepant findings is not clear. A subanalysis of the ACCORD study reported that high average HbA1c was strongly associated with death, and in particular, patients with HbA1c >7.0% despite intensive glucose control therapy had a high mortality risk.²⁵ These results are in accord with our findings. Previous studies also reported that hypoglycemia was associated with an increase in the risk of death²⁶ or CAD.²⁷ However, the incidence of hypoglycemic events was not available in the present study. Further studies are needed to determine the optimal long-term goal for glycemic control as secondary prevention in ACS patients.

The present study included both DM and non-DM patients. In the subgroup of patients with DM, HbA1c ≥6.4% was also an independent predictor of MACCE but not in the subgroup of patients without DM. In non-DM patients, LVEF <35% and a history of cerebral infarction were associated with MACCE. Therefore, glycemic control is considered to be especially

important in post-ACS patients with DM. There was no significant relationship between insulin use and MACCE.

In the univariate analysis, MACCE was associated with female sex, age ≥75 years, HbA1c ≥7.0%, LVEF <35%, eGFR <60 ml/min, and a history of cerebral infarction. These results are consistent with previous studies except for the association with sex.^{7–13} In the present study, non-fatal stroke accounted for 46.8% (22/47) of MACCE events, and female patients had a significantly higher incidence of non-fatal stroke than male patients. A previous study also demonstrated that female sex was a predictor of stroke after MI.²⁸ The reason why female sex was a predictor for MACCE in the present study might be related to the higher incidence of non-fatal stroke after MI in females.

The long-term administration of antiplatelet agents and statins was high, at approximately 100% and 80%, respectively, in agreement with previous studies.^{29,30} In contrast, ACEIs and β -blockers were used in only 25% and 50% of patients, respectively. ACEIs have been shown to reduce deaths and MACCE in patients with MI^{31,32} and are recommended for all CAD patients according to the guidelines.^{14,21} The clinical benefit of ACEI therapy is especially important in patients

with LV dysfunction.³³ However, ACEI efficacy is also reported in patients with preserved LVEF.³⁴ The favorable effects of β -blockers are also well established in ACS patients.³⁵ However, in the present study, β -blockers were used only in half of the post-ACS patients at discharge and thereafter. A higher incidence of coronary artery spasm might be responsible for the lower use of β -blockers. However, according to the guidelines, it is necessary that ACEIs and β -blockers are used more in eligible patients even though their use was not an independent predictor for MACCE in the present analysis.

Study Limitations

There are several potential limitations that should be acknowledged in the present study. First, important clinical variables such as history of heart failure, LVEF at 1-year follow-up, hypoglycemic events, duration of DM, and adverse effects of drugs were not included in the present study. Therefore, we could not study their effect on the outcomes in post-ACS patients in the present study. Second, favorable effects of physical activity and exercise have been well established for secondary prevention in CAD patients.³⁶ However, these factors were not assessed in the present study. Third, the duration of follow-up was 2 years after the onset of ACS. Longer term investigations are definitely needed to generalize the present findings to post-ACS patients. Finally, the number of events was too small to detect the intermediate (eg, ≈ 0.7 of true HR) predictors in the study. Further clarification in a larger study is needed if the prognostic values of intermediate predictors are to be evaluated. However, the beneficial effect of glycemic control is clear even during follow-up of 1 year. Therefore, the effect of hyperglycemia on MACCE should be more significant in the long-term.

In conclusion, maintenance of lower HbA1c after discharge was strongly associated with a lower risk of subsequent MACCE in Japanese post-ACS patients. Of several potential risk factors, hyperglycemia was found to be a crucial treatment target for the long-term secondary prevention of MACCE in post-ACS patients.

Acknowledgments

The authors thank all the enrolled patients, participating cardiologists and other medical professionals who contributed substantially to this cooperative study. The PACIFIC investigators other than authors are listed in the appendix of a previous paper.¹⁶

Disclosures

K.M. has received speakers' bureau/honoraria from MSD, AstraZeneca, Kowa Pharmaceutical, Sanofi, Shionogi, Daiichi-Sankyo, Takeda Pharmaceutical, Pfizer, Astellas Pharma, and Novartis Pharma.

H. Ogawa has received speakers' bureau/honoraria from Actelion Pharmaceuticals Japan, AstraZeneca, Bayer Yakuhin, Nippon Boehringer Ingelheim, Daiichi-Sankyo, Eisai, Kowa Pharmaceutical, Kyowa Hakko Kirin, Mitsubishi Tanabe Pharma, MSD, Otsuka Pharmaceutical, Pfizer, Sanofi, Takeda Pharmaceutical, and Teijin Pharma, and grants from Astellas Pharma, Bayer Yakuhin, Bristol-Myers Squibb, Chugai Pharmaceutical, Daiichi-Sankyo, Dainippon Sumitomo Pharma, Mochida Pharmaceutical, MSD, Novartis Pharma, Otsuka Pharmaceutical, Ono Pharmaceutical, Pfizer, Sanofi, Shionogi, and Takeda Pharmaceutical.

H.Y. has received remuneration for lectures from Daiichi-Sankyo, Sanofi, Takeda Pharmaceutical, MSD, AstraZeneca, Mochida Pharmaceutical, Sanofi, Terumo, Boston Scientific Japan, Abbott Vascular Japan, and Medtronic Japan, and scholarship funds from Takeda Pharmaceutical and Daiichi-Sankyo.

M.M. has received speakers' bureau/honoraria from Otsuka Pharmaceutical, Sanofi, Nippon Boehringer Ingelheim, Daiichi-Sankyo, and Bayer Yakuhin.

M.K. reports no conflict of interest for this work, with personal fees from Takeda Pharmaceutical and Ono Pharmaceutical, and research grants from Mitsubishi Tanabe Pharma and Novartis Pharma outside the submitted

work.

T.K. has received an honorarium and research grants from Sanofi.

Y.I. has received speakers' bureau/honoraria from MSD, AstraZeneca, Sanofi, Daiichi-Sankyo, Takeda Pharmaceutical, Pfizer, Astellas Pharma, and Bayer Yakuhin, research grants from Sanofi, Daiichi-Sankyo, Pfizer, Bayer Yakuhin, and MSD, advisory fees from Terumo, Kaneka, and Nipro, and a royalty from Terumo.

K. Kimura has received speakers' bureau/honoraria from MSD, Bayer Yakuhin, and Daiichi-Sankyo, and research funds from Toa Eiyo, Bayer Yakuhin, MSD, Astellas Pharma, AstraZeneca, Sanofi, Eli Lilly Japan, Research Institute for Production Development, Pfizer, Shionogi, Kowa Pharmaceutical, Daiichi-Sankyo, Mitsubishi Tanabe Pharma, Ono Pharmaceutical, Nippon Boehringer Ingelheim, Takeda Pharmaceutical, and Otsuka Pharmaceutical.

T.I. has received speakers' bureau/honoraria from Sanofi, Daiichi-Sankyo, AstraZeneca, Shionogi, Takeda Pharmaceutical, MSD, Astellas Pharma, Mochida Pharmaceutical, and Otsuka Pharmaceutical, and research funds from Takeda Pharmaceutical, Daiichi-Sankyo, Nippon Boehringer Ingelheim, Sanofi, Pfizer, and Mitsubishi Tanabe Pharma.

Y.M. has received speakers' bureau/honoraria and research grants from Sanofi, Daiichi-Sankyo, and Bayer Yakuhin.

H.D. has received speakers' bureau/honoraria from MSD, AstraZeneca, Kowa Pharmaceutical, Sanofi, GlaxoSmithKline, Shionogi, Daiichi-Sankyo, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, Pfizer, and Astellas Pharma, and research funds from Takeda Pharmaceutical, Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Astellas Pharma, Novartis Pharma, MSD, Sanofi, Otsuka Pharmaceutical, Dainippon Sumitomo Pharma, Pfizer, Kowa Pharmaceutical, Shionogi, AstraZeneca, Teijin, and Morinaga Milk Industry.

H.T. has received speakers' bureau/honoraria from MSD, Ono Pharmaceutical, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, Daiichi-Sankyo, Teijin, Nippon Boehringer Ingelheim, Bayer Yakuhin, Pfizer, and Bristol-Myers Squibb, research funds from Takeda Pharmaceutical, Nippon Boehringer Ingelheim, Mitsubishi Tanabe Pharma, and Daiichi-Sankyo, and consultation fees from Novartis Pharma, Ono Pharmaceutical, and Pfizer.

The other authors declare no conflicts of interest related to this article.

Grant

This study was supported by Sanofi, Tokyo Japan.

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