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Clinical Characteristics, Achievement of Secondary Prevention Goals, and Outcomes of Patients with Recurrent Acute Coronary Syndrome

Shuhei Tara[1], Takeshi Yamamoto[1], Shin Sakai[1], Tokuhiro Kimura[1], Kazuhiro Asano[1], Yuhi Fujimoto[1], Reiko Shiomura[1], Junya Matsuda[1], Kosuke Kadooka[1], Kenta Takahashi[1], Toshinori Ko[1], Hideto Sangen[1], Yoshiyuki Saiki[1], Jun Nakata[1], Yusuke Hosokawa[1], Hitoshi Takano[2] and Wataru Shimizu[1,2]

[1]Division of Cardiovascular Intensive Care, Nippon Medical School Hospital, Tokyo, Japan
[2]Department of Cardiovascular Medicine, Nippon Medical School, Tokyo, Japan

Background: Because development of acute coronary syndrome (ACS) worsens the prognosis of patients with coronary artery disease, preventing recurrent ACS is crucial. However, the degree to which secondary prevention treatment goals are achieved in patients with recurrent ACS is unknown.

Methods: 214 consecutive ACS patients were classified as having First ACS (n=182) or Recurrent ACS (n=32), and the clinical characteristics of these groups were compared. Fifteen patients died or developed cardiovascular (CV) events during hospitalization, and the remaining 199 patients were followed from the date of hospital discharge to evaluate subsequent CV events.

Results: Patients in the Recurrent ACS group were older than those in the First ACS group (76.8±10.8 years vs 68.8±13.4 years, p=0.002) and had a higher rate of diabetes mellitus (DM) (65.6% vs 36.8%, p= 0.003). The rate of achieving a low-density lipoprotein cholesterol (LDL-C) level of <70 mg/dL in the Recurrent ACS group was only 28.1%, even though 68.8% of these patients were taking statins. An HbA 1c level of <7.0% was achieved in 66.7% of patients with recurrent ACS who had been diagnosed with DM. Overall, 12.5% of patients with recurrent ACS had received optimal treatment for secondary prevention. CV events after hospital discharge were noted in 37.9% of the Recurrent ACS group and 21.2% of the First ACS group (log-rank test: p=0.004). However, recurrent ACS was not an independent risk factor for CV events (adjusted hazard ratio: 2.09, 95% confidence interval: 0.95 to 4.63, p=0.068).

Conclusion: Optimal treatment for secondary prevention was not achieved in some patients with recurrent ACS, and achievement of the guideline-recommended LDL-C goal for secondary prevention was especially low in this population. (J Nippon Med Sch 2021; 88: 432−440)

Key words: cardiovascular events, low-density lipoprotein cholesterol, optimal medical therapy, comprehensive risk factor control

Introduction

Despite advances in revascularization and optimal medical therapies, coronary artery disease (CAD) remains the leading cause of death worldwide[1]. Development of acute coronary syndrome (ACS) affects outcomes of patients with CAD, and ACS recurrence is related to worse mortality and morbidity rates, because of subsequent cardiovascular (CV) events[2]. Thus, secondary prevention interventions, including lifestyle modifications, optimal medical therapy, and risk factor management strategies, must be started immediately after an initial ACS event and then consistently maintained[3–6].

Patients with recurrent ACS have been assessed in the settings of pre-reperfusion, thrombolysis, and primary percutaneous coronary intervention[7–9]. However, the characteristics of patients with recurrent ACS are thought to be changing, because new ACS treatments and secondary prevention therapies are being developed. Furthermore,

guidelines recommending secondary prevention goals, especially reducing low-density lipoprotein cholesterol (LDL-C) levels, have also been updated in accordance with treatment advancements. Nevertheless, few studies have examined the extent to which patients with recurrent ACS achieve the goals recommended in recent guidelines. Furthermore, the prognostic significance is unclear in Japanese patients with recurrent ACS. The present study compared the clinical characteristics, the extent to which the goals advocated by risk factor guidelines were achieved, and outcomes of patients with recurrent and first ACS.

Methods

Study Design

We retrospectively reviewed the hospital records of 226 consecutive ACS patients who had been admitted to the cardiovascular care unit (CCU) in Nippon Medical School Hospital between January and December 2018. ACS included ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina, which had been diagnosed by using the Fourth Universal Definition of Myocardial Infarction[10]. Type 2 myocardial infarction (MI) was excluded from the study. NSTEMI and unstable angina were distinguished on the basis of high-sensitivity troponin T value. Recurrent ACS was defined as an ACS event that occurred later than 28 days after an established prior ACS[11]. Ultimately, 214 ACS patients were classified as having a first ACS event (First ACS; n=182) or recurrent ACS event (Recurrent ACS; n=32). ACS patients received standard therapy based on the guidelines during hospitalization. The medical ethics committee of Nippon Medical School reviewed and approved this clinical study (B-2020-156).

All patients were evaluated for clinical characteristics, including background characteristics, co-interventions during hospitalization, and in-hospital course. Achievement of risk factor management goals for secondary prevention was assessed and compared between the Recurrent ACS group and First ACS group. Specifically, lifestyle factors, including smoking status (never, former, and current), body mass index (BMI), medical therapies (statins, angiotensin-converting enzyme inhibitors [ACE-I]/ angiotensin II receptor blockers [ARB], β-blockers, and anti-platelet drugs) before admission, lipid control (LDL-C level), and glycemic control (HbA1c <7.0%) were determined. These variables were evaluated or examined at the time of admission or within 3 days of admission, if

assessment on admission was not possible. When patients did not receive the required examinations within the 3-day period, these values were not included in subsequent data analyses. Current smoking was defined based on smoking status during the month before admission. Blood pressure was not included among the risk factors evaluated in the present study because of the effects of ACS on hemodynamics.

For comprehensive evaluation of secondary prevention treatments in patients with recurrent ACS, a composite score (0 to 6 points) was calculated by summing the attainment scores for each measurement, i.e., non-current smoking (never smokers or former smokers), ACE-I/ARB use, β-blocker use, anti-platelet agent use, lipid control (LDL-C <70 mg/dL), and glycemic control (HbA1c <7.0%)-variables selected on the basis of guidelines and past reports[12,13]. Optimal secondary prevention treatment was defined as a composite secondary prevention score of 6 points.

Among the 214 ACS patients, 15 who died or experienced CV events (MI and stroke) during hospitalization were excluded from the time-to-event analysis (Kaplan-Meier analysis) and multivariate analysis (Cox proportional hazards modeling). The remaining 199 ACS patients were monitored from the date of hospital discharge. The outcome used for survival analysis was time to first event of a composite of major adverse CV events (all-cause mortality, non-fatal MI or stroke, or admission for heart failure, unstable angina, or other CV events).

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics version 25 software (SPSS Inc., Chicago, IL, USA). Dichotomous variables were tested using the chi-square test or, if not applicable, Fisher's exact test. Numeric values are presented as mean ± standard deviation or median (interquartile range) and were tested with Student's t test, or with the non-parametric Mann-Whitney U test when the data had a non-normal distribution. The Kaplan-Meier method was used to estimate cumulative incidences of outcomes, and differences were compared with the log-rank test. For multivariate analysis, hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of outcomes were determined by Cox proportional hazards modeling. Covariates-including recurrent ACS, chronic kidney disease (CKD) ≥G3b, peripheral artery disease, pre-existing heart failure, and length of CCU stay-were selected with the forced entry method, with a statistically significant difference in the unadjusted univariate analysis, in addition to age and sex. A P value of

<0.05 was considered to indicate statistical significance.

Results

Clinical Characteristics

We compared the background characteristics, co-interventions during hospitalization, and in-hospital course of the Recurrent ACS group and First ACS group (**Table 1**). Among the prior ACS events in the Recurrent ACS group, MI accounted for 93.8% of such events. The Recurrent ACS group was older than the First ACS group (76.8 ± 10.8 years vs 68.8 ± 13.4 years, p=0.002), had higher rates of DM (65.6% vs 36.8%, p=0.003) and hemodialysis use (12.5% vs 3.3%, p=0.045), and was more likely to have comorbidities involving peripheral arterial disease (18.8% vs 2.7%, p=0.002). In 93.8% of the Recurrent ACS patients, treatments for secondary prevention had been continued by primary physicians until hospital admission.

Patients with recurrent ACS had more NSTEMI than did first ACS patients (46.9% vs 25.3%, p=0.019), and less STEMI (37.5% vs 62.6%, p=0.011). Regarding severity, the left ventricular ejection fraction (LVEF) was significantly lower in the Recurrent ACS than in First ACS (44.6 ± 13.0% vs 50.0 ± 13.2%, p=0.033), and the rate of moderate to severe mitral regurgitation was higher (21.9% vs 7.7%, p=0.020). There was no significant difference between the two groups in the use of mechanical respiratory or circulatory support devices, including noninvasive positive pressure ventilation, respirators, intra-aortic balloon pumps, percutaneous cardiopulmonary support, and the Impella device. As to clinical course during hospitalization, the duration of CCU stay and in-hospital mortality rates did not differ significantly between the two groups.

Secondary Prevention Treatments

Lifestyle factors in patients with recurrent ACS-including smoking status, i.e., both former and current smokers, and BMI-are shown in **Table 1**. The proportions of patients treated with statins, ACE-I/ARB, β-blockers, or anti-platelet drugs before admission were higher in the Recurrent ACS group than in the First ACS group (**Table 1**). When the Recurrent ACS group was limited to those with low LVEF (≤40%) (n=13), ACE-I/ARB and β-blocker administration rates decreased (ACE-I/ARB: 62.5% to 53.8%; β-blocker: 53.1% to 46.2%, respectively). The rate of anti-platelet drug administration in the Recurrent ACS group was 75% (single anti-platelet therapy: 56.3%; dual anti-platelet therapy: 18.8%). Two of the eight patients (25%) in the Recurrent ACS group who were not treated with anti-platelet drugs were treated with warfarin to manage atrial fibrillation.

Although the LDL-C levels of patients in the Recurrent ACS group were lower than those in the First ACS group (93.0 ± 37.0 mg/dL vs 114.1 ± 35.9 mg/dL, p=0.003) (**Table 1**), the rate of achieving good control (LDL-C <70 mg/dL) was 28.1% in the Recurrent ACS group (**Fig. 1 A**). In the Recurrent ACS group, the LDL-C levels of patients were 81.4 ± 30.5 mg/dL with statin treatment and 118.4 ± 38.8 mg/dL without statin treatment. One patient in the Recurrent ACS group was given ezetimibe in addition to a statin, but none of the patients with recurrent ACS were prescribed a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. Among patients diagnosed with DM, HbA1c was less than 7.0% in 52.3% of the First ACS group and 66.7% of the Recurrent ACS group (p=0.62), (**Fig. 1B**).

The composite secondary prevention score for patients in the Recurrent ACS group is shown in **Figure 2**. All patients had scores of at least one; however, only 12.5% (4 of 32) were receiving optimal treatment (6 points) for secondary prevention. When the Recurrent ACS group was limited to patients with a low LVEF (≤40%) (n=13), the rate of optimal treatment increased to 15.4% (2 of 13).

Outcomes for Patients with Recurrent ACS

CV events after hospital discharge were identified in 37.9% (11 of 29) of the Recurrent ACS group and 21.2% (36 of 170) of the First ACS group at a median (interquartile range) follow-up duration of 375 (133-494) days. The cumulative incidence of CV events was higher in the Recurrent ACS group than in the First ACS group, as demonstrated by Kaplan-Meier analysis (log-rank: p=0.004) (**Fig. 3**). Evaluation of cardiovascular disease outcomes showed no significant difference between the two groups (all-cause mortality: 3.4% vs 4.1%, p=1.000; non-fatal MI or stroke: 0% vs 0%, p=NA; admission for heart failure: 10.3% vs 5.3%, p=0.388; unstable angina: 6.9% vs 0.6%, p=0.056; other CV events: 17.2% vs 10.6%, p=0.343).

Recurrent ACS was not an independent risk factor for subsequent CV events in multivariate analysis using Cox proportional hazards modeling (adjusted HR: 2.09; 95% CI: 0.95 to 4.63, p=0.068) (**Table 2**).

Discussion

This study focused on patients with recurrent ACS for whom secondary prevention failed. As to clinical characteristics, patients with recurrent ACS were older and had a higher rate of DM than did first ACS patients. Lipid control with LDL-C lowering was the worst-managed risk factor for secondary prevention. Comprehensive sec-

Table 1   Clinical Characteristics of Patients

	Recurrent ACS (n=32)	First ACS (n=182)	P value
Age (years)	76.8 ± 10.8	68.8 ± 13.4	0.002*
Male, n (%)	24 (75.0)	142 (78.0)	0.654
Body mass index (kg/m²)	23.3 ± 3.2	25.1 ± 12.1	0.398
Smoking status, n (%)			
Never smoker	11 (34.4)	64 (35.2)	1.000
Former smoker	16 (50.0)	85 (46.7)	0.848
Current smoker	5 (15.6)	33 (18.1)	1.000
History of MI, n (%)	30 (93.8)	NA	NA
Risk factors, n (%)			
Diabetes mellitus	21 (65.6)	67 (36.8)	0.003
Hypertension	28 (87.5)	141 (77.5)	0.245
Dyslipidemia	24 (75.0)	118 (64.8)	0.314
Hyperuricemia	11 (34.4)	36 (19.8)	0.103
CKD (stage ≥G3b)	6 (18.8)	23 (12.6)	0.402
Hemodialysis	4 (12.5)	6 (3.3)	0.045
HbA1c (%)	6.5 ± 1.0	6.3 ± 1.2	0.336
Lipid profiles (mg/dL)			
LDL-C	93.0 ± 37.0	114.1 ± 35.9	0.003
HDL-C	46.3 ± 13.3	44.6 ± 13.0	0.496
Triglyceride	102.2 ± 60.1	123.4 ± 80.7	0.160
Comorbidities, n (%)			
Peripheral artery disease	6 (18.8)	5 (2.7)	0.002
Previous cerebral infarction	5 (15.6)	22 (12.1)	0.569
Care by primary physician until admission, n (%)	30 (93.8)	132 (72.5)	0.007
Medications before admission, n (%)			
Statin	22 (68.8)	39 (21.7)	<0.001
ACE-I/ARB	20 (62.5)	58 (32.4)	0.002
β-blocker	17 (53.1)	26 (14.5)	<0.001
Anti-platelet drugs	24 (75.0)	33 (18.1)	<0.001
ACS classification, n (%)			
STEMI	12 (37.5)	114 (62.6)	0.011
NSTEMI	15 (46.9)	46 (25.3)	0.019
UA	5 (15.6)	22 (12.1)	0.567
Severity on admission			
OHCA, n (%)	1 (3.1)	4 (2.2)	0.871
CPAOA, n (%)	0 (0.0)	7 (3.8)	0.598
Shock vital, n (%)	1 (3.1)	18 (9.9)	0.320
GRACE risk score (score)	163.6 ± 36.6	160.8 ± 49.0	0.752*
Pre-existing heart failure, n (%)	9 (28.1)	7 (3.8)	<0.001
NT pro-BNP (pg/mL)	1,051 [162.5, 2,448.3]	539 [129.3, 2,333.8]	0.340†
LVEF (%)	44.6 ± 13.0	50.0 ± 13.2	0.033*
MR (moderate-severe), n (%)	7 (21.9)	14 (7.7)	0.020
Treatments during hospitalization, n (%)			
PCI	23 (71.9)	137 (75.3)	0.664
CABG	3 (9.4)	22 (12.1)	1.000
NPPV	6 (18.8)	31 (17.0)	0.802
Mechanical ventilator	2 (6.3)	24 (13.2)	0.383
CHDF	5 (15.6)	14 (7.7)	0.173
HD	4 (12.5)	5 (2.7)	0.030
IABP	4 (12.5)	38 (20.9)	0.340
PCPS	1 (3.1)	6 (3.3)	1.000
Impella	0 (0.0)	8 (4.4)	0.609

Table 1 Clinical Characteristics of Patients (continued)

	Recurrent ACS (n=32)	First ACS (n=182)	P value
Length of CCU stay (days)	5 [4-7]	5 [3-7]	0.860†
In-hospital mortality, n (%)	2 (6.3)	9 (4.9)	1.000

Data are presented as means ± SD, n (%), or median [interquartile range].
* Compared by Student t-test; † Compared by Mann-Whitney U-test.
CKD (stage G3b), based on estimated glomerular filtration rate <30 mL/min/1.73 m².
ACS, acute coronary syndrome; MI, myocardial infarction; CKD, chronic kidney disease; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; UA, unstable angina; OHCA, out-of-hospital cardiac arrest; CPAOA, cardiopulmonary arrest on arrival; GRACE, global registry of acute coronary events; NT pro-BNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; NPPV, non-invasive positive pressure ventilation; CHDF, continuous hemodiafiltration; HD, hemodialysis; IABP, intra-aortic balloon pump; PCPS, percutaneous cardiopulmonary support; CCU, cardiovascular care unit; NA, not applicable.
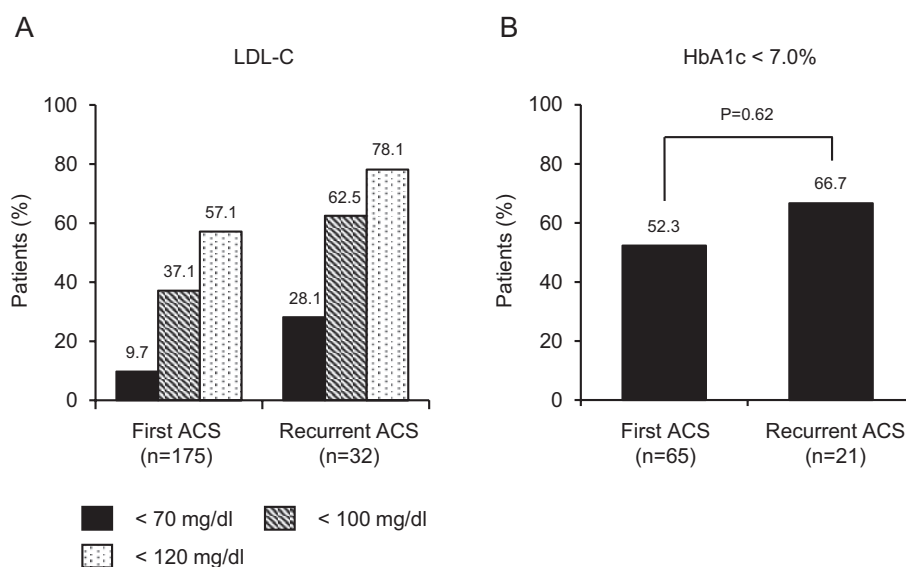

Fig. 1 Risk factor goals for achievement of (A) lipid control (staged LDL-C level) and (B) glycemic control (HbA1c<7.0%).
LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; ACS; acute coronary syndrome.

ondary prevention has not yet reached a satisfactory level for patients with recurrent ACS. Recurrent ACS was not an independent risk factor for subsequent CV events.

Our results indicate that optimal medical therapy was not achieved for some patients with recurrent ACS. After MI, treatment with ACE-I/ARB and β-blockers is used to lower blood pressure and the risk of subsequent CV events[4,14,15]. These drugs are highly effective for patients with reduced systolic LV function (LVEF ≤40%) and are administered unless contraindicated[16,17]. However, fewer than 70% of the present Recurrent ACS patients were treated with an ACE-I/ARB or β-blocker, even though more than 90% of these patients had a prior MI. Furthermore, patients with recurrent ACS with a low LVEF (≤40%) were less often treated with ACE-I/ARB and β-blockers than were those without a low LVEF. Although anti-platelet therapy has a pivotal role in secondary prevention of ACS, 25% of the present patients with recurrent ACS did not receive anti-platelet drugs. Although the duration of dual anti-platelet agent therapy is ad-

justed in relation to bleeding risk, lifetime single anti-platelet therapy with low-dose aspirin or clopidogrel after dual anti-platelet agent therapy is usually recommended. We did not analyze why ACE-I/ARB, β-blockers, and anti-platelet drugs were not prescribed for more than 30% of patients with recurrent ACS; however, administration rates of these drugs in the present study were lower than those in randomized studies[12,13].

Only 28% of the patients with recurrent ACS achieved the LDL-C goal of <70 mg/dL, despite guidelines advocating lowering LDL-C to <70 mg/dL with high-intensity statin therapy for secondary prevention of ACS[6,18,19], based

on evidence that very low LDL-C levels are related to lower risk for CV events[20–22]. Although a meta-analysis of data from eight randomized controlled studies showed that more than 50% of participants treated with high-intensity statin therapy reached an LDL-C level of <70 mg/dL[21], real-world data from Japan showed that only 27% of ACS patients achieved an LDL-C concentration of <70 mg/dL within a 12-month period after onset of ACS[23]. In addition, a cross-sectional survey of patients with CAD and DM in Europe showed that 28% achieved an LDL-C concentration of <70 mg/dL[24]. In conjunction with our dataset, in which about 70% of patients with recurrent ACS received statin treatment but had LDL-C levels of >80 mg/dL, existing evidence indicates that LDL-C lowering with statins is insufficient. In addition to starting statin administration for patients not being treated with these agents, the statin dose should be increased unless there is a history of intolerance to high-intensity statin therapy or other clinical factors that could influence safety[5,18]. The addition of ezetimibe or a PCSK9 inhibitor to high-intensity statin therapy reduced recurrent CV events[25–27], although only one patient (3.1%) was given ezetimibe in our study. Thus, treatment with ezetimibe and PCSK9 inhibitors should be considered when the LDL-C goal is not achieved after ACS, despite high-intensity statin therapy, or when patients cannot tolerate statin therapy[6,19].

Over 60% of DM patients in the Recurrent ACS group had adequate blood glucose control, as indicated by an HbA1c of <7.0%. Strict glucose control-i.e., achieving a nearly normal HbA1c of <7.0%-is recommended for prevention of atherosclerotic cardiovascular disease (ASCVD) in DM patients[19,28]. However, it is unclear
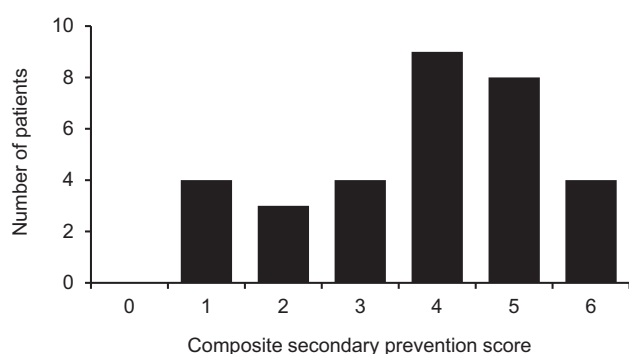

Fig. 2   The composite secondary prevention score was calculated for patients in the Recurrent ACS group. The maximum score, 6 points, was given to patients who satisfied the following criteria: non-current smoker, ACE-I/ARB use, β-blocker use, anti-platelet agent use, achievement of LDL-C of <70 mg/dL, and HbA1c of <7.0%.
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c.
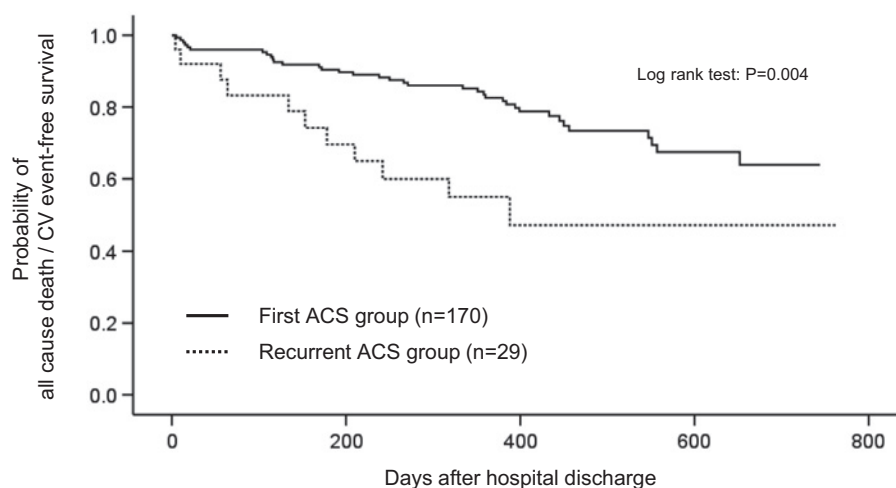

Fig. 3   Cumulative incidences of CV events, as estimated by Kaplan–Meier analysis.

Table 2 Associations of Risk Factors with Subsequent Cardiovascular Events

	Unadjusted Results		Adjusted Results	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	1.01 (0.99-1.04)	0.348	1.01 (0.98-1.03)	0.676
Female sex	1.02 (0.51-2.06)	0.956	1.07 (0.51-2.24)	0.857
Recurrent ACS	2.64 (1.34-5.21)	0.005	2.09 (0.95-4.63)	0.068
Diabetes mellitus	1.15 (0.64-2.08)	0.635		
Hypertension	1.59 (0.71-3.56)	0.262		
Dyslipidemia	0.73 (0.40-1.33)	0.308		
CKD (≥ G3b)	3.04 (1.51-6.13)	0.002	2.65 (1.23-5.70)	0.013
Peripheral artery disease	4.89 (1.89-12.69)	0.001	2.52 (0.85-7.44)	0.094
Care by primary physician until admission	1.11 (0.56-2.18)	0.768		
STEMI	1.00 (0.57-1.78)	0.990		
GRACE risk score	1.00 (1.00-1.01)	0.173		
Pre-existing heart failure	3.41 (1.34-8.68)	0.010	2.51 (0.92-6.85)	0.073
LVEF	1.00 (0.98-1.03)	0.824		
MR (moderate-severe)	1.89 (0.80-4.50)	0.148		
Hemodialysis during hospitalization	2.55 (0.79-8.23)	0.118		
Length of CCU stay (days)	1.04 (1.02-1.06)	0.001	1.04 (1.02-1.06)	0.001

Subsequent cardiovascular events were defined as the first event of all-cause mortality, non-fatal myocardial infarction or stroke, or admission for heart failure, unstable angina, or other cardiovascular events, after hospital discharge.

HR, hazard ratio; CI, confidence interval; ACS, acute coronary syndrome; CKD, chronic kidney disease; STEMI, ST elevation myocardial infarction; GRACE, global registry of acute coronary events; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; CCU, cardiac care unit.

whether maintaining HbA1c at this level reduces CV events[29], because macrovascular complications such as MI are less closely associated than microvascular complications with hyperglycemia[30]. Thus, a recent guideline placed less emphasis on strict glycemic management based on HbA1c goals and indicated that HbA1c targets after ACS must be individualized by taking into account age, duration of DM, organ damage, and risk of hypoglycemia[19,28]. Because metformin, glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors are less likely to induce hypoglycemia and help prevent CV events in DM patients[31-33], they are recommended for DM patients with ASCVD, heart failure, and CKD, regardless of HbA1c level[28]. The proportion of DM patients was higher in the present Recurrent ACS group than in the First ACS group, and a past report showed that DM patients developing ACS were at greater risk of relapse of CV events[34]. However, the risk of subsequent CV events was lower in patients with ASCVD and DM when target secondary-prevention measurements were comprehensively achieved[12,13]. To achieve secondary prevention, ACS patients with DM must be strictly managed for multiple risk factors, regardless of HbA1c level.

Although more than 90% of patients with recurrent ACS in this study continued to receive medical treatments prescribed by their primary physicians until admission, only 12.5% of patients with recurrent ACS received optimal comprehensive management, i.e., treatment that achieved all secondary prevention goals, including smoking cessation, optimal medical therapy with ACE-I/ARB, β-blocker, or anti-platelet drugs, lipid control, and glycemic control. Because ACS patients have a very high risk of subsequent CV events[6], risk factors must be strictly controlled[12,13]. However, real-world data, including the present results, reveal a gap between the goals recommended by guidelines and their achievement in clinical practice[23,24]. This gap is likely attributable to therapeutic inertia at several levels[35]. At the patient level, there are drug side-effects, too many drugs, and the high cost of some drugs. At the level of the clinician/health care provider, relevant factors include failure to initiate treatment and failure to individualize dosing to meet goals. At the healthcare system level, management is affected by lack of clinical guidelines and inadequate coordination of care. Physicians usually focus on the clinician/health care provider level when managing risk factors. However, effective interventions at each level are required in order to close the aforementioned gap and achieve optimal comprehensive risk factor control.

Recurrent ACS was not an independent risk factor for

subsequent CV events in this study, although the cumulative incidence of CV events was higher in the Recurrent ACS than in the First ACS group, when analyzed with the Kaplan-Meier method and log-rank test. In contrast, CKD ≥G3b and longer CCU stay were independent risk factors for subsequent CV events. CKD is a major risk factor for CV complications after ACS[36,37], and a prolonged stay in an intensive care unit is related to poor in-hospital and long-term prognosis[38,39]. Thus, these are important prognostic markers for ACS patients. ACS patients with CKD or prolonged CCU stay should be carefully treated for secondary prevention because of their higher risk of CV events.

Study Limitations

This study has several limitations owing to its retrospective design and the small number of patients analyzed, all of whom were from a single center. We evaluated the degree to which patients with recurrent ACS achieved the goals recommended in recent guidelines but did not assess the extent to which the degree of these achievements reduced the risk of ACS recurrence in the present study. Therefore, our results do not show whether achieving secondary prevention goals reduces the risk of ACS recurrence. A further large-scale prospective study is required for this purpose.

We evaluated variables for secondary prevention at admission for ACS. Each variable was potentially affected by the clinical condition and severity of ACS and thus did not reflect daily control. Because blood pressure is directly influenced by hemodynamics in patients with ACS, as demonstrated in 30 patients who developed cardiac arrest or shock on admission, blood pressure was not examined in this study. However, hypertension is reportedly another important and unmanaged risk factor for CAD[13].

More than 90% of patients with recurrent ACS were treated by primary physicians before admission. However, the cause of insufficient prior treatment by primary physicians could not be ascertained in this retrospective study. Future prospective studies will investigate therapeutic inertia in the secondary prevention of ACS.

In the present study, we used a composite secondary prevention score to evaluate the achievement of goals for control of risk factors in each patient. However, no comprehensive scoring system for secondary prevention has yet been established. Residual risk factors such as hypertriglyceridemia, hyperuricemia, and inflammation are secondary prevention challenges that are yet to be adequately studied. We did not evaluate the relationship be-

tween comprehensive risk factor management and subsequent CV events in this study, because the number of patients with recurrent ACS was small, and the measurements for secondary prevention were obtained only at the time of admission.

Conclusion

As compared with first ACS patients, patients with recurrent ACS were older and had a higher rate of DM. Secondary prevention was suboptimal for some patients with recurrent ACS, and the rate of achieving the guideline recommendation of an LDL-C level of <70 mg/dL was low. Recurrent ACS was not an independent risk factor for subsequent CV events.

Conflict of Interest: The authors declare no conflicts of interest associated with this manuscript.

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