Elevated Cystatin-C Levels Are Associated with Increased Mortality in Acute Coronary Syndrome Patients: An HIJ-PROPER Sub-Analysis

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Keywords

Cystatin-C · Mortality · Cardiovascular events · Acute coronary syndrome

Abstract

Background and Aims: We investigated the association between serum cystatin-C (Cys-C) levels and cardiovascular events in patients with acute coronary syndrome (ACS). **Methods:** Data of 1,100 patients from the prospective parent study were included. Patients hospitalized for ACS were divided into 4 groups based on quartiles (Q) of Cys-C levels (mg/L) within 24 h of admission: Q1, ≤ 0.82 ; Q2, $0.82 < \text{estimated level} \leq 0.95$; Q3, $0.95 < \text{estimated level} \leq 1.12$; and Q4, > 1.12 . The primary endpoint of this study was all-cause mortality, and the secondary endpoint was composite of all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, unstable angina pectoris, or ischemia-driven revascularization. **Results:** During a median observation period of 4.0 years, the primary endpoint was noted in 5, 12, 18, and 36 patients in Q1–Q4, respectively, with corresponding incidence rates of 1.8%, 4.4%, 6.5%, and 13.5%, respectively ($p < 0.0001$ for difference among 4 groups). This association persisted even after adjusting for patient characteristics and other laboratory results at baseline ($p = 0.04$). A stepwise increase in the incidence rate of the secondary endpoint with

an incline in Cys-C levels was observed in the nonadjusted model (26.6%, 33.3%, 32.3%, and 39.1% in Q1–Q4, respectively; $p = 0.01$) but not in the adjusted model ($p = 0.3$). No difference was observed in the incidence rate of nonfatal myocardial infarction ($p = 0.89$), nonfatal stroke ($p = 0.3$), unstable angina pectoris ($p = 0.49$), and ischemia-driven revascularization ($p = 0.47$) with an incline in Cys-C levels. **Conclusion:** Elevated Cys-C levels were associated with increased all-cause mortality but not cardiovascular events other than mortality in ACS patients.

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Introduction

Cystatin-C (Cys-C) is a protease inhibitor enzyme produced by almost all human nucleated cells and exists freely in blood without binding to any other protein [1–3]. It is filtered into the renal glomerulus and is almost completely metabolized to amino acids in the proximal tubule. The serum Cys-C level strongly reflects the glomerular filtration rate (GFR) and is considered an indicator of renal

Clinical trial registration No. UMIN000002742, registered as an international standard randomized controlled trial. Registry URL: <https://www.umin.ac.jp>.

function. Several studies have reported that elevated Cys-C levels were strongly associated with poor clinical outcomes in patients with coronary artery disease [4–6]. Further, studies have shown how Cys-C is associated with mortality in patients with acute coronary syndrome (ACS) [7–12]. While several studies have analyzed the association between Cys-C and mortality, few studies have compared the relationship between Cys-C levels and cardiovascular events other than mortality [10]. Moreover, some studies analyzing the relationship between Cys-C levels and cardiovascular events in patients with coronary artery disease have collected data over a couple of decades before [7, 9], but these findings have been inconsistent across studies. In our previous, prospective, randomized controlled study of the Heart Institute of Japan-PROper level of lipid-lowering with Pitavastatin and Ezetimibe in acute coRonary syndrome (HIJ-PROPER), we compared outcomes of the standard therapy to those of intensive lipid-lowering therapy [13]. The aims of the present subgroup analysis of the HIJ-PROPER study were to examine (1) the distribution of Cys-C levels at baseline, (2) association between Cys-C levels and mortality, and (3) association between Cys-C levels and cardiovascular events other than mortality in ACS patients treated using contemporary measures.

Methods

Patients

We conducted a retrospective sub-analysis of data collected in the parent HIJ-PROPER study. Briefly, the HIJ-PROPER study was a multicenter, prospective, randomized controlled trial that compared outcomes of two lipid-lowering treatments and included participants from 19 Japanese hospitals [13]. In total, 1,734 patients diagnosed with ACS were randomized into 2 groups. One group received intensive lipid-lowering therapy (pitavastatin + ezetimibe therapy) and the other group received conventional lipid-lowering therapy (pitavastatin monotherapy) between January 2010 and April 2013. Following the loss of 13 patients to follow-up, the prospective data of 1,721 patients were finally analyzed in the original study. In the present study, we enrolled those patients whose serum Cys-C levels had been determined at baseline, which was defined as within 24 h of hospitalization with ACS.

Laboratory Investigations

All the HIJ-PROPER study participants had been hospitalized for the management of ACS, and samples for laboratory testing were collected within 24 h of admission. Biochemical analyses were exclusively performed at SRL Inc. (Hachioji, Tokyo, Japan), an external laboratory. Values of the estimated GFR (eGFR) used in this study were calculated by applying equations developed by the Japanese Society of Nephrology (male, $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ and female, $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$) [14].

Analysis and Outcome Measures

The primary endpoint of the current study was all-cause mortality. The secondary endpoint was the same as that in the original HIJ-PROPER study: a composite endpoint of the first occurrence of all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, unstable angina pectoris, or ischemia-driven revascularization. Patients were divided into 4 groups as per quartiles (Q) of Cys-C levels at baseline.

Patient characteristics were compared among these groups. We also examined whether Cys-C levels affected the incidence of the primary and secondary endpoints in patients diagnosed with ACS during a median observation period of 4.0 years.

Statistical Analysis

Continuous variables were reported as the mean and standard deviation. Nonnormally distributed data are reported as medians and interquartile ranges, while categorical data are presented as absolute values and percentages. Welch's *t* test and the Mann-Whitney U test were used to analyze normally and nonnormally distributed data, respectively. Pearson's χ^2 test was used for the analysis of categorical data. Among the 4 groups, the time interval until the first occurrence of endpoint events was analyzed using the Kaplan-Meier method along with the log-rank test. The conventional Cox proportional hazard regression model to assess how well quartiles of Cys-C could predict the mortality and cardiovascular events was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for each endpoint. Multivariable regression analyses were performed after adjusting for variables including age, sex, comorbidities' prevalence (hypertension and diabetes mellitus), current smoking habit, and revascularization history. Variables included in the multivariable analyses were selected based on the imbalance of the patient characteristics and clinical meaningfulness. Due to the small number of endpoints in the current study, we included selected potential confounders. Multivariable analysis with confounders including Cys-C as a continuous variable was evaluated to identify independent risk factors for the primary endpoint. The area under the curve (AUC) according to receiver operating characteristic curve (ROC) analysis was used to examine the cutoff value of Cys-C or the eGFR to predict the occurrence of all-cause mortality. A *p* value of <0.05 was considered statistically significant unless stated otherwise. All statistical analyses were performed using the software JMP Pro (Ver. 15; SAS Institute Inc., Cary, NC, USA).

This study was conducted in accordance with the principles of the 1975 Declaration of Helsinki. The Institutional Review Board of each participating medical center or the relevant Ethics Committee approved the protocol, and all patients provided written informed consent for trial enrollment.

Results

A total of 1,721 patients were enrolled in the original analysis of the HIJ-PROPER study. Cys-C values were unavailable for 621/1,721 patients analyzed in the parent HIJ-PROPER study. Therefore, a total of 1,100 patients were finally included in the current study. Figure 1 shows the flow chart of the current sub-study. Patients excluded

Fig. 1. Study flowchart. ACS, acute coronary syndrome.

Fig. 2. Distribution of Cys-C ($N = 1,100$).

from the study were comparable to those included in the study in terms of the majority of the baseline characteristics (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000522412). However, a different distribution of the clinical classification of ACS was observed between patients included in the study and those excluded from the study. In addition, the prevalence of hypertension was more common in patients excluded from the analysis.

The mean level of Cys-C in this sub-analysis was 0.95 (interquartile range; 0.82–1.12) mg/L (Fig. 2). Patients were divided into 4 groups as per quartiles of Cys-C levels at baseline: Q1, ≤ 0.82 mg/L; Q2, from 0.83 to 0.95 mg/L; Q3, from 0.96 to 1.12 mg/L; and Q4 > 1.12 mg/L.

The numbers of patients assigned into Q1–4 were 282 (25.6%), 273 (24.8%), 279 (25.4%), and 266 (24.2%), re-

spectively. Baseline clinical characteristics of the 4 groups are summarized in Table 1. Median (interquartile range) of Cys-C levels for patients in Q1–4 were 0.75 (0.68, 0.79), 0.89 (0.86, 0.93), 1.03 (0.99, 1.06), and 1.3 (1.2, 1.5) mg/L, respectively. Older patients tended to show higher Cys-C values. Concurrent hypertension and diabetes mellitus or history of revascularization were commonly noted in those with high Cys-C levels. Conversely, such patients were less likely to have a current smoking habit. Patients with elevated levels of Cys-C commonly used renin-angiotensin system inhibitors and calcium channel blockers. Levels of low-density lipoprotein cholesterol and high-density lipoprotein cholesterol were low in patients with elevated Cys-C levels. With regard to angiographical characteristics, patients with elevated levels of Cys-C had high frequency of multivessel lesions.

Incidence of the Primary Endpoint (All-Cause Mortality)

During a median observation period of 4.0 years (range 0–6.2), the primary endpoint was noted in 5, 12, 18, and 36 patients in Q1–Q4, corresponding to an incidence rate of 1.8%, 4.4%, 6.5%, and 13.5%, respectively ($p < 0.0001$ for difference among 4 groups) (Table 2). A Kaplan-Meier curve demonstrated that higher levels of Cys-C were associated with increased all-cause mortality ([HR: 2.74, 95% CI: 1.02–8.62, $p = 0.005$, for Q2 vs. Q1] [HR: 4.15, 95% CI: 1.66–12.6, $p = 0.002$, for Q3 vs. Q1] [HR: 9.50, 95% CI: 4.07–27.7, $p < 0.0001$, for Q4 vs. Q1]) (Fig. 3). A Cox multivariable proportional hazard regression analysis performed after making necessary adjustments for baseline variables also showed a stepwise increase in HRs for all-cause mortality across all 4 quartiles of Cys-C ($p =$

Table 1. Baseline clinical characteristics of 4 groups based on Cys-C quartiles (mg/L)

	All (N = 1,100)	Q1 ≤0.82 (N = 282)	Q2 0.83–0.95 (N = 273)	Q3 0.96–1.122 (N = 279)	Q4 >1.12 (N = 266)	p value
Age, years	65.8±11.7	59.9±11.2	63.4±10.5	67.1±10.3	73.0±10.4	<0.0001
Male	835 (75.9)	197 (69.9)	209 (76.6)	225 (80.7)	204 (76.7)	<0.0001
Body mass index, kg/m ²	24.2±3.5	24.2±4.0	24.2±3.6	24.2±3.1	24.3±3.3	0.99
eGFR, mL/min/1.73 m ²	72.5±18.9	85.9±16.2	77.8±15.7	70.5±14.3	54.9±14.4	<0.0001
Statin-naïve	898 (81.6)	240 (85.1)	221 (90.0)	231 (82.8)	206 (77.4)	0.13
Hypertension	731 (66.5)	166 (58.9)	171 (62.6)	181 (64.9)	213 (80.1)	<0.0001
Diabetes mellitus	313 (28.5)	88 (31.2)	67 (24.5)	64 (22.9)	94 (35.3)	0.004
Current smoker	387 (35.2)	114 (40.4)	102 (37.4)	104 (37.3)	67 (25.2)	0.001
Previous myocardial infarction	86 (7.8)	17 (6.0)	25 (9.2)	16 (5.7)	28 (10.5)	0.09
Previous revascularization	108 (9.8)	20 (7.1)	26 (9.5)	24 (8.6)	38 (14.3)	0.03
History of heart failure	19 (1.7)	4 (1.4)	1 (0.4)	8 (2.9)	6 (2.3)	0.08
Clinical presentation of ACS						
STEMI	527 (47.9)	145 (51.4)	124 (45.4)	137 (49.1)	121 (45.5)	
Non-STEMI	116 (10.5)	27 (9.6)	27 (9.9)	30 (10.8)	32 (12.0)	0.72
Unstable angina pectoris	457 (41.5)	110 (39.0)	122 (44.7)	112 (40.1)	113 (42.5)	
PCI for culprit lesion	1,032 (93.8)	266 (94.3)	256 (93.8)	260 (93.2)	250 (94.0)	0.33
Narrowed vessel*						
Right coronary artery	521 (47.4)	124 (44.0)	116 (42.5)	129 (46.2)	152 (57.1)	0.003
Left main trunk	46 (4.2)	3 (1.1)	9 (3.3)	16 (5.7)	18 (6.8)	0.001
LAD	831 (75.5)	215 (76.2)	204 (74.7)	213 (76.3)	199 (74.8)	0.95
Circumflex artery	515 (46.8)	105 (37.2)	123 (45.1)	132 (47.3)	155 (58.3)	<0.0001
Bypass graft	6 (0.5)	0 (0)	1 (0.4)	1 (0.4)	4 (1.5)	0.09
Randomization for adding ezetimibe	548 (49.8)	151 (53.6)	140 (51.3)	139 (49.8)	118 (44.4)	0.17
Medication						
Use of beta blocker	107 (9.7)	19 (6.7)	25 (9.2)	30 (10.8)	33 (12.4)	0.13
Use of ACEIs/ARBs	330 (30.0)	62 (22.0)	76 (27.8)	75 (26.9)	117 (44.0)	<0.0001
Use of a calcium channel blocker	317 (28.8)	61 (21.6)	71 (26.0)	76 (27.2)	109 (41.0)	<0.0001
Cholesterol metabolism						
LDL-C, mg/dL	129 [113, 150]	133 [116, 157]	131 [115, 149]	129 [115, 152]	122 [110, 143]	<0.0001
HDL-C, mg/dL	47 [39, 56]	48 [40, 57]	48 [41, 57]	46 [38, 55]	45 [37, 54]	0.0004
Triglyceride, mg/dL	117 [83, 170]	115 [80, 181]	111 [83, 163]	118 [88, 174]	117 [80, 161]	0.88
Cys-C, mg/L	0.95 [0.82, 1.12]	0.75 [0.68, 0.79]	0.89 [0.86, 0.93]	1.03 [0.99, 1.06]	1.3 [1.2, 1.5]	<0.0001
High-sensitivity CRP, mg/L	8.1 [2.6, 24.1]	9.0 [2.6, 24.3]	6.9 [2.0, 23.4]	8.0 [2.8, 20.8]	9.1 [2.9, 29.2]	0.30

Data are expressed as mean ± SD, median [interquartile range], or number (percentage). ACEIs, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARBs, angiotensin II receptor blockers; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LAD, left anterior descending artery; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; SD, standard deviation. * About 1,100 participants enrolled in the current sub-analysis had a total of 1,919 narrowed vessels, which were considered to indicate significant stenosis with a narrowing of more than 50%.

0.04, for difference among the 4 groups) (Table 2). A multivariable analysis which was analyzed with Cys-C as a continuous variable revealed that higher levels of Cys-C and older age were independent predictors of primary endpoints (HR, 2.95, 95% CI, 1.49–5.33, $p = 0.001$ for Cys-C; HR, 1.07, 95% CI, 1.04–1.10, $p < 0.0001$ for age; online suppl. Table 2).

Incidence of the Secondary Endpoint

The secondary endpoint was noted in 75, 91, 90, and 104 patients in Q1–Q4, corresponding to an incidence rate of 26.6%, 33.3%, 32.3%, and 39.1%, respectively ($p = 0.01$ for difference among 4 groups) (Table 2) (online suppl. Fig. 1). A Cox multivariable proportional hazard regression analysis showed no stepwise increase in HRs for secondary endpoint across all 4 quartiles of Cys-C ($p = 0.32$, for difference among the 4 groups). Though,

Table 2. Distribution of individual components of the primary and secondary endpoints among 4 groups

	Q1 ≤0.82 mg/L (n = 282)	Q2 >0.82 mg/L (n = 273)	Q3 >0.95 mg/L (n = 279)	Q4 >1.12 mg/L (n = 266)	p value
Primary endpoint (all-cause mortality)					
N (%)	5 (1.8)	12 (4.4)	18 (6.5)	36 (13.5)	
HR (95% CI)					
Nonadjusted	Reference	2.74 (1.02–8.62)	4.15 (1.66–12.6)	9.50 (4.07–27.7)	<0.0001
Adjusted	Reference	2.21 (0.78–6.33)	2.48 (0.90–6.83)	3.87 (1.43–10.5)	0.04
Secondary endpoint*					
N (%)	75 (26.6)	91 (33.3)	90 (32.3)	104 (39.1)	
HR (95% CI)					
Nonadjusted	Reference	1.37 (1.01–1.87)	1.29 (0.95–1.76)	1.65 (1.23–2.23)	0.01
Adjusted	Reference	1.29 (0.94–1.76)	1.14 (0.83–1.57)	1.32 (0.94–1.84)	0.30
Nonfatal MI					
N (%)	3 (1.1)	3 (1.1)	4 (1.4)	4 (1.5)	
HR (95% CI)					
Nonadjusted	Reference	1.15 (0.21–6.22)	1.54 (0.34–7.83)	1.76 (0.39–9.02)	0.89
Adjusted	Reference	0.94 (0.18–4.78)	1.30 (0.27–6.25)	0.92 (0.18–4.87)	0.96
Nonfatal stroke					
N (%)	3 (1.1)	4 (1.5)	7 (2.5)	7 (2.6)	
HR (95% CI)					
Nonadjusted	Reference	1.51 (0.33–7.66)	2.66 (0.74–12.4)	3.02 (0.83–14.1)	0.30
Adjusted	Reference	1.30 (0.29–5.87)	1.93 (0.48–7.82)	1.82 (0.41–8.12)	0.78
Unstable angina pectoris					
N (%)	9 (3.2)	8 (2.9)	14 (5.0)	8 (3.0)	
HR (95% CI)					
Nonadjusted	Reference	0.97 (0.37–2.50)	1.71 (0.74–3.96)	1.06 (0.41–2.75)	0.49
Adjusted	Reference	0.87 (0.33–2.29)	1.58 (0.65–3.80)	0.80 (0.28–2.26)	0.39
Ischemia-driven revascularization					
N (%)	68 (24.1)	74 (27.1)	65 (23.3)	72 (27.1)	
HR (95% CI)					
Nonadjusted	Reference	1.21 (0.87–1.68)	1.01 (0.72–1.42)	1.22 (0.88–1.70)	0.47
Adjusted	Reference	1.21 (0.87–1.70)	1.01 (0.70–1.43)	1.19 (0.82–1.72)	0.55
Cardiovascular mortality					
N (%)	3 (1.1)	7 (2.6)	6 (2.2)	22 (8.3)	
HR (95% CI)					
Nonadjusted	Reference	2.64 (0.68–10.2)	2.29 (0.57–9.18)	9.56 (2.85–32.1)	<0.0001
Adjusted	Reference	2.29 (0.59–8.94)	1.59 (0.39–6.53)	4.63 (1.27–16.9)	0.03

Adjusted model was adjusted by age, sex, prevalence of hypertension and diabetes mellitus, history of smoking, and revascularization. CI, confidence interval; HR, hazard ratio. * Secondary endpoint is defined as a composite endpoint of all-cause death, nonfatal myocardial infarction, nonfatal stroke, unstable angina pectoris, or ischemia-driven revascularization.

a stepwise increase in the incidence rate for all-cause mortality and cardiovascular mortality ($p < 0.0001$) with an incline in Cys-C levels was observed, no difference was observed in the incidence rate for nonfatal myocardial infarction ($p = 0.89$), nonfatal stroke ($p = 0.3$), unstable angina pectoris ($p = 0.49$), and ischemia-driven revascularization ($p = 0.47$) with an incline in Cys-C levels.

All-Cause Mortality according to Age, Sex, and BMI

Online supplementary Table 3 summarizes results of the Cox proportional hazards regression subgroup analysis of all-cause mortality, based on age (<65 years or ≥65 years), sex (male/female), and BMI (<25 kg/m² or ≥25 kg/m²) of study participants. A stepwise increase in HR for all-cause mortality was observed among the subgroups regardless of differences in age, sex, and BMI (online suppl. Fig. 2).

Fig. 3. Association between Cys-C quartiles and all-cause mortality. CI, confidence interval; HR, hazard ratio; Q, quartile.

Predictive Status of Cys-C or the eGFR in All-Cause Mortality

The receiver operating characteristic curve analysis indicated that the cutoff point of Cys-C or the eGFR to predict the occurrence of all-cause mortality were 1.03 mg/L (Fig. 4a) and 65.0 mL/min/1.73 m² (Fig. 4b), respectively. The AUC value of Cys-C to predict all-cause mortality was 0.71, which was comparable with the AUC value of the eGFR (0.69).

The frequency of all-cause mortality was significantly higher in patients with Cys-C ≥ 1.03 mg/L than in patients with Cys-C ≤ 1.03 mg/L (HR: 4.39; 95% CI: 2.64–7.27; $p < 0.0001$).

Discussion

This sub-analysis of the HIJ-PROPER suggests the following: (1) among ACS patients, the median levels of Cys-C were 0.95 mg/L; (2) Cys-C levels estimated during the early hospitalization period in ACS patients treated using contemporary measures could independently predict all-cause mortality; (3) but they cannot predict cardiovascular events other than mortality; and (4) the cutoff value of

Cys-C to predict the occurrence of all-cause mortality was 1.03 mg/L. Several studies have reported the association of Cys-C levels with mortality in patients diagnosed with ACS [7–12]. Most studies suggested that elevated Cys-C levels were independently associated with higher all-cause mortality after adjusting for patients' baseline characteristics and laboratory test results. The SOLID-TIMI 52 sub-analysis revealed that the elevated Cys-C levels were not related to increased all-cause mortality in the adjusted model [10]. However, the aforementioned sub-analysis differed from the other studies, with the most notable difference being the timing of Cys-C estimation. In the SOLID-TIMI 52 sub-analysis, blood samples were obtained at a median 14-day time interval after the ACS onset. Conversely, blood samples for Cys-C estimation were obtained at the time of hospital admission during other similar trials, including the present study. The biomarker status of Cys-C as a predictor of mortality might be affected by the timing of obtaining the blood sample.

Treatment strategy for ACS has changed with the trend moving toward early invasive treatment [15–18]. In the previous studies on Cys-C, the frequency of invasive treatment during hospitalization for ACS varied widely from 16 to 76%. Patients enrolled in the current study received con-

Fig. 4. The AUC according to ROC analysis was used to examine the Cys-C and eGFR cutoff value to predict the occurrence of all-cause mortality (Cys-C (a), eGFR (b)). The ROC curve analysis indicated that the Cys-C and eGFR cutoff points were 1.03 mg/L and 65.0 mL/min/1.73 m², respectively. After dividing patients

into 2 groups based on the cutoff point, the incidence rate of all-cause mortality was compared between the 2 groups. AUC, area under the curve; Cys-C, cystatin-C; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval; ROC, receiver operating characteristic curve.

temporary ACS treatment. More than 90% of patients underwent percutaneous coronary intervention during the acute, initial phase of hospitalization in the original HIJ-PROPER study. Further, enrolled patients had received optimal medical therapy (online suppl. Table 4) and were continuously monitored during the follow-up period. Our result suggested that the Cys-C levels estimated during the early hospitalization period in ACS patients treated using contemporary measures could predict all-cause mortality.

When the analysis was calculated for the relationship between the levels of Cys-C and cardiovascular event other than mortality, the difference in events among the 4 groups disappeared in the current study. The correlation between the levels of Cys-C and the incidence rate for myocardial infarction and stroke in ACS patients remains controversial [6–10]. Some studies reported a positive correlation in Cys-C levels with an incidence rate for myocardial infarction and stroke in patients after ACS in the nonadjusted model, but no association was observed after the adjusted model [7, 10]. To the best of our knowledge, there is only 1 study that has demonstrated a posi-

tive correlation between Cys-C levels and incidence of myocardial infarction even with multivariable analysis [9]. Considering the past reports and the current analysis, the correlation in Cys-C levels with myocardial infarction and stroke is not strong. Few past reports have reported an association between Cys-C levels and the incidence of unstable angina pectoris or ischemia-driven percutaneous coronary intervention in ACS patients. In this respect, the data of this study are meaningful. The Cys-C levels might not predict cardiovascular events other than mortality, including the incidence of myocardial infarction, stroke, unstable angina pectoris, and ischemia-driven percutaneous coronary intervention.

Cys-C is considered a biomarker of renal function and is not influenced by muscle volume and body mass. In this study, the mortality rate was found to show a stepwise increase with rising Cys-C levels, regardless of differences in age, sex, and BMI. Serum Cys-C levels are known to be less influenced by age and individual muscle mass and are related more strongly with all-cause mortality than serum creatinine values [19, 20]. Further, its predictive status ap-

pears to be independent of differences in baseline patient characteristics, including age, sex, and BMI. Risk stratification for predicting all-cause mortality could be performed by estimating the Cys-C level during the early hospitalization period, among ACS patients in contemporary practice.

This study had certain limitations. First, this was a nested, retrospective, subgroup analysis that utilized data from the prospective, parent study. Second, our study population consisted entirely of Japanese patients with ACS, which could affect the generalizability of our findings to non-Japanese participants. Third, only baseline data for Cys-C within 24 h of hospitalization were available in the current study. We could not assess how did the acute kidney injury, which occurred after admission, affect the value of Cys-C and cardiovascular events. Fourth, there was no information on the change in kidney function or kidney damage in this study. Fifth, the AUC value of Cys-C to predict all-cause mortality was slightly higher than those of the eGFR in the current study. However, it has not been clarified whether which biomarker of renal function is better to predict mortality in ACS patients. In conclusion, elevated Cys-C levels were associated with increased all-cause mortality but not associated with cardiovascular events other than mortality in ACS patients.

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Statement of Ethics

Patients or the public were not involved in the design or conduct or reporting or dissemination plans of our research. The study protocol conforms to the ethical guidelines laid within the 1975 Declaration of Helsinki, as reflected in a priori approval provided by the institutional review board or the relevant Ethics Com-

mittee of each participating medical center. Before enrollment in the parent trial, written informed consent was obtained from all patients, parents, and/or legal guardians if the participants were under 18 years old. This sub-analysis is nested within the original HIJ-PROPER study, which is registered in the UMIN Registry as an international standard randomized controlled trial (trial No. UMIN000002742, registry URL: <https://www.umin.ac.jp>).

Conflict of Interest Statement

The authors have the following disclosures: All members of the HIJ-PROPER study group have received research support to perform clinical trials, from the Japan Research Promotion Society for Cardiovascular Diseases, which is sponsored by the Abbott Vascular Japan Co., Ltd.; AstraZeneca K.K.; Bayer Yakuhin Ltd.; Boston Scientific Corporation; Bristol-Myers K.K.; Daiichi Sankyo Co., Ltd.; Kowa Pharmaceutical Co., Ltd.; Mochida Pharmaceutical Co., Ltd.; MSD K.K.; Nippon Boehringer Ingelheim Co., Ltd.; Novartis Pharma K.K.; Pfizer Japan Inc.; Sanofi K.K.; and Takeda Pharmaceutical Co., Ltd. N.H. reports receiving honoraria from Bristol-Myers K.K. and Nippon Boehringer Ingelheim Co., Ltd., and grants from Astellas Pharma Inc.; Daiichi Sankyo Co., Ltd.; Eisai Co., Ltd.; Mitsubishi Tanabe Pharma Corporation; Otsuka Pharmaceutical Co., Ltd.; Shionogi & Co., Ltd.; and Takeda Pharmaceutical Co., Ltd. J.Y. belongs to the Clinical Research Division for Cardiovascular Catheter Intervention, which is financially maintained by donations from Abbott Vascular, Boston Scientific, Medtronic, and Terumo. The HIJ-PROPER Steering Committee has full access to all data of the present study and were responsible for the decision to submit the study for publication.

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Author Contributions

H.A., J.Y., H.O., and N.H. conceptualized and designed the original study. H.A. collected data and enrolled and followed up with patients. T.S. and H.A. analyzed and interpreted the collected data. T.S. and H.A. drafted and wrote the manuscript. F.M., J.Y., H.O., and N.H. reviewed the manuscript. All the authors, external and internal, had full access to all data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and accuracy of the analysis.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material Files. Further inquiries can be directed to the corresponding author.

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