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Original Article

Prodromal symptoms and the care-seeking behavior in patients with acute ST-segment elevation myocardial infarction

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ABSTRACT

Background: The prodromal symptoms perceived by patients before the onset of acute myocardial infarction (AMI) are diverse and not necessarily limited to the typical symptoms of angina.

Methods: Among 3959 consecutive patients with ST-segment elevation myocardial infarction (STEMI) who underwent primary percutaneous coronary intervention within 24 h of the onset of AMI enrolled in the CREDO-Kyoto AMI registry wave-2, the patients were categorized into 3 groups by the symptoms before the onset and within 48 h before the index hospital presentation: (1) prodromal symptoms typical of angina ($N = 865$, 21.8 %), (2) atypical prodromal symptoms only ($N = 156$, 3.9 %), and (3) no prodromal symptoms ($N = 2938$, 74.2 %). We investigated the association between the types of the prodromal symptoms and long-term clinical outcomes as well as the prevalence of seeking medical care for the prodromal symptoms.

Results: As compared with patients with no prodromal symptoms, those with typical prodromal symptoms had a lower mortality risk [adjusted hazard ratio (HR): 0.69, 95 % confidence interval (CI): 0.58–0.83, $p = 0.0001$], whereas those with atypical prodromal symptoms only had a higher mortality risk (HR: 1.53, 95 % CI: 1.17–2.00, $p = 0.002$). Regarding healthcare-seeking behavior, 162 out of 1021 patients (15.9 %) with the prodromal symptoms sought medical care for the prodromal symptoms. There was no significant difference in the rate of seeking medical care between the patients with typical prodromal symptoms and atypical prodromal symptoms only (15.5 % and 17.9 %, $p = 0.44$).

Conclusions: Compared to patients with no prodromal symptoms before STEMI, long-term mortality outcome was better in patients with typical prodromal symptoms, but worse in those with atypical prodromal symptoms.

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Introduction

Acute myocardial infarction (AMI) is often preceded by a range of prodromal symptoms, not limited to those typical for angina pectoris.

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Previous research has predominantly focused on the typical angina symptoms called pre-infarction angina, which was reported to be associated with reduced infarct size [1–4], less left ventricular remodeling [5], and better prognosis [3,4,6–10]. On the other hand, there is a paucity of studies examining the atypical prodromal symptoms before the onset of AMI [11,12]. Moreover, a subset of patients experiencing prodromal symptoms might have sought medical care before the onset of AMI. However, the extent of this behavior remained unclear.

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Furthermore, it is also unclear whether the impact of the prodromal symptoms on long-term clinical outcomes could be different between the typical and atypical symptoms. To ensure clarity in the timing of symptom onset, we included only patients with ST-segment elevation myocardial infarction (STEMI) in this study, as the onset of symptoms in non-STEMI is often uncertain, making it difficult to distinguish between prodromal symptoms and the symptoms of the infarction itself. Therefore, we investigated the prodromal symptoms preceding acute STEMI, and assessed their impact on the long-term prognosis using a large Japanese observational database of patients with AMI.

Methods

Study population and data collection

The Coronary Revascularization Demonstrating Outcome Study in Kyoto Acute Myocardial Infarction (CREDO-Kyoto AMI) Registry Wave-2 is a physician-initiated, noncompany-sponsored, multicenter registry that enrolled consecutive 6470 patients with AMI who underwent coronary revascularization within 7 days of the onset of symptoms between January 2011 and December 2013 in 22 participating centers

in Japan (Online Appendix A) [13–15]. The relevant institutional review boards at all participating centers approved the study protocol and written informed consent for this study was substituted by the opt-out method because of the retrospective nature of the study. This strategy was concordant with the guidelines of the Ministry of Health, Labor, and Welfare of Japan.

The present study population consisted of 3959 patients who underwent percutaneous coronary intervention (PCI) for STEMI within 24 h of onset, after excluding those patients who refused study participation ($N = 21$), those who received coronary artery bypass grafting ($N = 221$), those who were diagnosed as non-STEMI ($N = 1603$), those whose onset of AMI was unknown ($N = 20$), and those who underwent PCI beyond 24 h after onset ($N = 646$) (Fig. 1).

Experienced clinical research coordinators in an independent research organization (Research Institute for Production Development, Kyoto, Japan) collected demographic, angiographic, and procedural data from the hospital charts or hospital databases according to the prespecified definitions (Online methods). From the hospital charts or hospital databases, we also collected data about prodromal symptoms before the onset of AMI and within 48 h before the index hospital presentation. The 48-h window for defining prodromal symptoms was

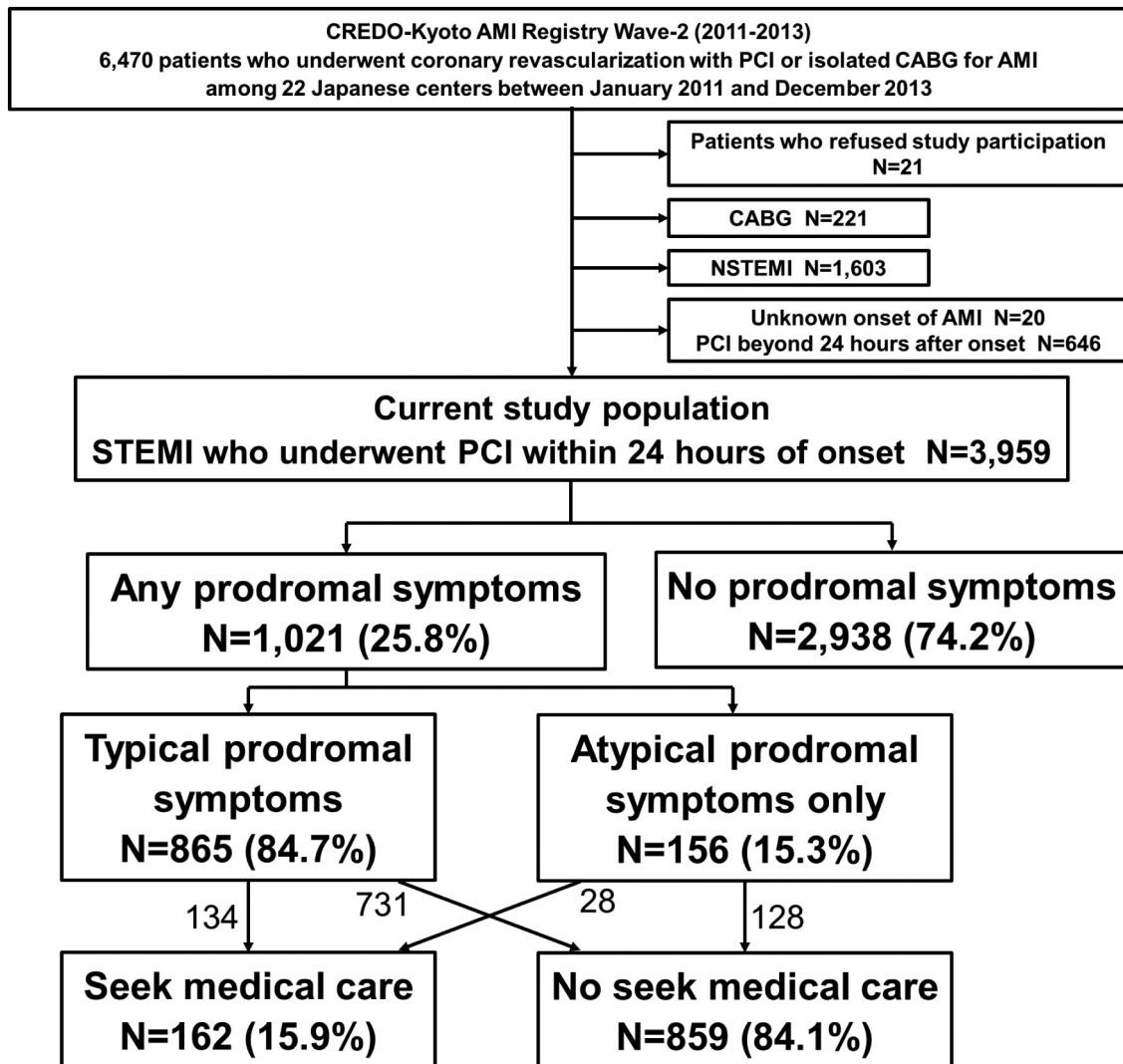


Fig. 1. Study flow chart illustrating patient disposition for the types of prodromal symptoms and the status of seeking medical care.

Patients who had both typical and atypical symptoms were included in those with typical prodromal symptoms.

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CREDO-Kyoto AMI Registry Wave-2, Coronary Revascularization Demonstrating Outcome study in Kyoto AMI Registry Wave-2; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

adopted in accordance with our previous report, which examined the clinical impact of pre-infarction angina using the same timeframe [10]. In addition, we collected data on whether they sought medical care for the prodromal symptoms before the onset of AMI and before the index hospitalization.

Collection of follow-up information was mainly through review of the inpatient and outpatient hospital charts by the clinical research coordinators, and additional follow-up information was collected through contact with patients, relatives, and/or referring physicians by sending mail with questions regarding vital status and subsequent hospitalizations.

Definitions and clinical outcome measures

In this study, the onset of AMI was defined as the onset of symptoms that sustained until the index hospital presentation including those that were waxing and waning. Prodromal symptoms were defined as any symptoms before the onset of AMI and within 48 h before the index hospital presentation. Typical prodromal symptoms were defined as symptoms typical of angina such as chest pain, chest oppression, chest discomfort, and symptoms in epigastrium, shoulder, back, throat, neck, jaw, and arm as well as cold sweats or perspiration, while other symptoms were defined as atypical prodromal symptoms [16]. Patients who had both typical and atypical symptoms were included in those with typical prodromal symptoms.

We also investigated whether patients had sought medical care for the prodromal symptoms. Seeking medical care for the prodromal symptoms was defined as any medical consultation before the onset of AMI that did not lead to the index hospitalization. We did not regard a regular outpatient visit without any symptoms as the seeking of medical care for the prodromal symptoms.

The primary outcome measure in the present study was all-cause death. The secondary outcome measures included cardiovascular death, myocardial infarction, and hospitalization for heart failure (HF). Death of unknown causes and any death during the index hospitalization for AMI were regarded as cardiac death. Cardiovascular death included cardiac death and other vascular death related to stroke, renal disease, and vascular disease. The definitions of baseline characteristics and other endpoints are described in the Online methods. Death and myocardial infarction were adjudicated by the independent clinical event committee (Online Appendix C).

Statistical analyses

We present continuous variables as the mean and standard deviation or median and interquartile range (IQR), and categorical variables as numbers and percentages. We compared continuous variables with the Student's *t*-test or the Wilcoxon rank-sum test based on the distributions. We compared categorical variables with the chi square test when appropriate; otherwise, we used the Fisher's exact test. We used the Kaplan-Meier method to estimate the cumulative incidences of clinical events and assessed the differences with the log-rank test. Assigning dummy codes to typical and atypical prodromal symptoms only, the hazard ratios (HRs) with 95 % confidence intervals (CIs) of the typical prodromal symptoms versus the no prodromal symptoms and the atypical prodromal symptoms only versus the no prodromal symptoms for the clinical outcome measures were estimated by the multivariable Cox proportional hazard models adjusting for the 23 clinically relevant factors selected from the 28 risk-adjusting variables used in the previous studies in this registry [13–15]. We removed five risk-adjusting variables including multivessel disease, proximal left anterior descending coronary artery target, left main coronary artery target, anterior wall myocardial infarction, and cardiogenic shock, because these factors were closely related to the severity of AMI and might also potentially be linked to the presence of the prodromal symptoms. Consistent with our previous reports, continuous variables were dichotomized using

clinically meaningful reference values or median values [17]. As a sensitivity analysis, the same analysis was conducted excluding patients with cardiopulmonary arrest or cardiogenic shock on admission, in whom serious conditions might have impeded effective interviewing, and certain prodromal symptoms that might be left undetected by the physicians. We also compared the baseline characteristics and clinical outcomes between the two groups of patients with and without seeking medical care among patients with prodromal symptoms.

All statistical analyses were conducted using JMP, version 16.2.0 (SAS Institute Inc., Cary, NC, USA). All reported *p*-values were two-tailed, and values of *p* < 0.05 were considered statistically significant.

Results

Baseline characteristics and prodromal symptoms

Among 3959 STEMI patients who underwent primary PCI within 24 h of onset, 865 (21.8 %) patients had typical prodromal symptoms, 156 (3.9 %) patients had atypical prodromal symptoms only, and 2938 (74.2 %) patients had no prodromal symptoms (Fig. 1). Dominant typical prodromal symptoms included chest pain, chest oppression, and chest discomfort, while dominant atypical prodromal symptoms included dyspnea, nausea or vomiting, feeling of unwellness, and fatigue (Table 1).

Baseline characteristics were significantly different in several aspects across the 3 groups of patients classified by the prodromal symptoms (Table 2). Patients with typical prodromal symptoms were younger, and had fewer cardiovascular co-morbidities such as previous myocardial infarction, HF, atrial fibrillation, and renal failure than those with no prodromal symptoms. On the other hand, patients with atypical prodromal symptoms only were older, and had more cardiovascular co-morbidities than those with no prodromal symptoms (Table 2). Men

Table 1
Types of prodromal symptoms.

	Among patients with any prodromal symptoms (N = 1021)	
Typical prodromal symptoms		
Chest pain	445	43.6 %
Chest pressure or tightness	188	18.4 %
Chest discomfort	153	15.0 %
Back pain or discomfort	57	5.6 %
Shoulder pain or discomfort	50	4.9 %
Sweating	44	4.3 %
Epigastric pain or discomfort	21	2.1 %
Neck pain or discomfort	15	1.5 %
Pharynx pain or discomfort	14	1.4 %
Arm pain or discomfort	12	1.2 %
Mandible pain	1	0.1 %
Atypical prodromal symptoms		
Dyspnea	96	9.4 %
Nausea or vomiting	37	3.6 %
Feeling of unwellness	34	3.3 %
Fatigue	29	2.8 %
Heartburn or anorexia	14	1.4 %
Palpitation	11	1.1 %
Abdominal pain or discomfort	10	1.0 %
Syncope	7	0.7 %
Head pain or discomfort	6	0.6 %
Lightheadedness or dizziness	6	0.6 %
Cough	6	0.6 %
Tooth pain or discomfort	4	0.4 %
Patients with typical prodromal symptoms	865	84.7 %
Patients with atypical prodromal symptoms	238	23.3 %
Patients with atypical prodromal symptoms only	156	15.3 %

Some patients had multiple symptoms, and therefore, the types of symptoms were not mutually exclusive.

Among 865 patients with typical prodromal symptoms, 82 patients also had atypical prodromal symptoms.

Table 2

Baseline characteristics and hemodynamic status according to the types of the prodromal symptoms.

	Overall	Typical prodromal symptoms	Atypical prodromal symptoms only	No prodromal symptoms	P-Value
N	3959	865 (21.8 %)	156 (3.9 %)	2938 (74.2 %)	
Clinical characteristics					
Age (years)	68.4 ± 12.7	66.7 ± 12.2	69.5 ± 14.5	68.9 ± 12.7	<0.0001
Age ≥ 75 years ^a	1377 (34.8 %)	237 (27.4 %)	62 (39.7 %)	1078 (36.7 %)	<0.0001
Men ^a	2996 (75.7 %)	659 (76.2 %)	106 (67.9 %)	2231 (75.9 %)	0.07
Body mass index (kg/m ²)	23.7 ± 3.6	23.9 ± 3.4	23.5 ± 4.1	23.6 ± 3.6	0.09
Body mass index <25.0 kg/m ^{2a}	2731 (69.0 %)	579 (66.9 %)	109 (69.9 %)	2043 (69.5 %)	0.34
Hypertension ^a	3154 (79.7 %)	690 (79.8 %)	118 (75.6 %)	2346 (79.9 %)	0.44
Diabetes ^a	1363 (34.4 %)	321 (37.1 %)	64 (41.0 %)	978 (33.3 %)	0.02
On insulin therapy	207 (5.2 %)	44 (5.1 %)	13 (8.3 %)	150 (5.1 %)	0.21
Current smoking ^a	1470 (37.1 %)	331 (38.3 %)	45 (28.8 %)	1094 (37.2 %)	0.08
Prior heart failure ^a	84 (2.1 %)	8 (0.9 %)	6 (3.8 %)	70 (2.4 %)	0.01
Prior PCI	456 (11.5 %)	82 (9.5 %)	19 (12.2 %)	355 (12.1 %)	0.10
Prior CABG	52 (1.3 %)	7 (0.8 %)	3 (1.9 %)	42 (1.4 %)	0.29
Prior myocardial infarction ^a	370 (9.3 %)	57 (6.6 %)	21 (13.5 %)	292 (9.9 %)	0.002
Prior stroke (symptomatic) ^a	412 (10.4 %)	72 (8.3 %)	20 (12.8 %)	320 (10.9 %)	0.06
Peripheral vascular disease ^a	165 (4.2 %)	30 (3.5 %)	8 (5.1 %)	127 (4.3 %)	0.45
eGFR <30 mL/min per 1.73 m ² , without hemodialysis ^a	221 (5.6 %)	26 (3.0 %)	22 (14.1 %)	173 (5.9 %)	<0.0001
Hemodialysis ^a	102 (2.6 %)	13 (1.5 %)	4 (2.6 %)	85 (2.9 %)	0.08
eGFR <30 mL/min per 1.73 m ² or hemodialysis	323 (8.2 %)	39 (4.5 %)	26 (16.7 %)	258 (8.8 %)	<0.0001
Prior atrial fibrillation ^a	343 (8.7 %)	54 (6.2 %)	18 (11.5 %)	271 (9.2 %)	0.01
Anemia (hemoglobin <11.0 g/L) ^a	421 (10.6 %)	57 (6.6 %)	28 (18.0 %)	336 (11.4 %)	<0.0001
Thrombocytopenia (platelet <100 × 10 ⁹ /L) ^a	95 (2.4 %)	11 (1.3 %)	7 (4.5 %)	77 (2.6 %)	0.02
Chronic obstructive pulmonary disease ^a	140 (3.5 %)	25 (2.9 %)	7 (4.5 %)	108 (3.7 %)	0.44
Liver cirrhosis ^a	85 (2.1 %)	14 (1.6 %)	5 (3.2 %)	66 (2.2 %)	0.35
Malignancy ^a	435 (11.0 %)	92 (10.6 %)	19 (12.2 %)	324 (11.0 %)	0.84
Presentation					
Current heart failure	1263 (31.9 %)	212 (24.5 %)	83 (53.2 %)	968 (32.9 %)	<0.0001
Killip classification					<0.0001
Killip I	2712 (68.5 %)	663 (76.6 %)	71 (45.5 %)	1978 (67.3 %)	
Killip II	473 (11.9 %)	113 (13.1 %)	29 (18.6 %)	331 (11.3 %)	
Killip III	100 (2.5 %)	14 (1.6 %)	11 (7.1 %)	75 (2.6 %)	
Killip IV (cardiogenic shock)	674 (17.0 %)	75 (8.7 %)	45 (28.8 %)	554 (18.9 %)	
Cardiopulmonary arrest	188 (4.7 %)	23 (2.7 %)	9 (5.8 %)	156 (5.3 %)	0.005
Baseline CK	149 (91–386)	162 (98.5–404.5)	189 (92.3–610.8)	144 (89–360)	0.001
Baseline CKMB	14 (7–33.6)	15 (8–35)	15 (8–58)	13 (7–32)	0.006
Maximum CK	2094 (963–3941)	1914 (854–3785)	2295 (1065.5–4165)	2136 (1000–3960)	0.01
Maximum CKMB	176 (76–345)	156 (60.8–323.3)	171.5 (90.1–341.3)	181 (78.3–349.6)	0.008
Angiographic characteristics					
Infarct related artery location					0.02
Left anterior descending coronary artery	1820 (46.0 %)	443 (51.2 %)	64 (41.0 %)	1313 (44.7 %)	
Left circumflex coronary artery	382 (9.6 %)	79 (9.1 %)	17 (10.9 %)	286 (9.7 %)	
Right coronary artery	1612 (40.7 %)	312 (36.1 %)	66 (42.3 %)	1234 (42.0 %)	
Left main coronary artery	122 (3.1 %)	28 (3.2 %)	7 (4.5 %)	87 (3.0 %)	
Multivessel disease	2168 (54.8 %)	438 (50.6 %)	79 (50.6 %)	1651 (56.2 %)	0.009
Procedural characteristics					
Onset-to-presentation time (min)	142 (70–283)	147 (77–295)	144 (74–275)	141 (68–280)	0.52
Onset-to-balloon time (min)	240 (160–396)	242.5 (162–406)	269.5 (178.5–393.5)	238 (159–394)	0.49
Door-to-balloon time (min)	79 (59–110)	78.5 (58–109)	89.5 (65.8–130.8)	79 (59–109)	0.02
Baseline medications					
Thienopyridine	3826 (96.6 %)	846 (97.8 %)	145 (93.0 %)	2835 (96.5 %)	0.006
Aspirin	3880 (98.0 %)	854 (98.7 %)	147 (94.2 %)	2879 (98.0 %)	0.001
Cilostazol	97 (2.5 %)	16 (1.9 %)	4 (2.6 %)	77 (2.6 %)	0.43
Statins ^a	3294 (83.2 %)	750 (86.7 %)	109 (69.9 %)	2435 (82.9 %)	<0.0001
Beta blockers ^a	2136 (54.0 %)	484 (56.0 %)	82 (52.6 %)	1570 (53.4 %)	0.40
ACE inhibitors/ARB ^a	3024 (76.4 %)	688 (79.5 %)	93 (59.6 %)	2243 (76.3 %)	<0.0001
Nitrates	722 (18.2 %)	151 (17.5 %)	23 (14.7 %)	548 (18.7 %)	0.37
Calcium channel blockers ^a	772 (19.5 %)	176 (20.4 %)	27 (17.3 %)	569 (19.4 %)	0.64
Nicorandil	787 (19.9 %)	169 (19.5 %)	20 (12.8 %)	598 (20.4 %)	0.07
Warfarin	458 (11.6 %)	87 (10.1 %)	18 (11.5 %)	353 (12.0 %)	0.29
DOAC	52 (1.3 %)	10 (1.2 %)	2 (1.3 %)	40 (1.4 %)	0.90
PPI	2960 (74.8 %)	654 (75.6 %)	113 (72.4 %)	2193 (74.6 %)	0.67
Histamine type 2 receptor blockers	452 (11.4 %)	95 (11.0 %)	12 (7.7 %)	345 (11.7 %)	0.27
PPI or histamine type 2 receptor blockers ^a	3401 (85.9 %)	748 (86.5 %)	125 (80.1 %)	2528 (86.0 %)	0.10

p-values are results from comparison among 3 groups.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; CABG, coronary artery bypass grafting; CK, creatine kinase; CKMB, creatine kinase isoenzyme MB; DOAC, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; PPI, proton pump inhibitors.

^a Risk-adjusting variables selected for the Cox proportional hazard models.

were less prevalent in patients with atypical prodromal symptoms only than in those with no prodromal symptoms. In terms of hemodynamic status, cardiopulmonary arrest, cardiogenic shock, and HF on admission

were less frequent in patients with typical prodromal symptoms and more frequent in those with atypical prodromal symptoms only than in those with no prodromal symptoms.

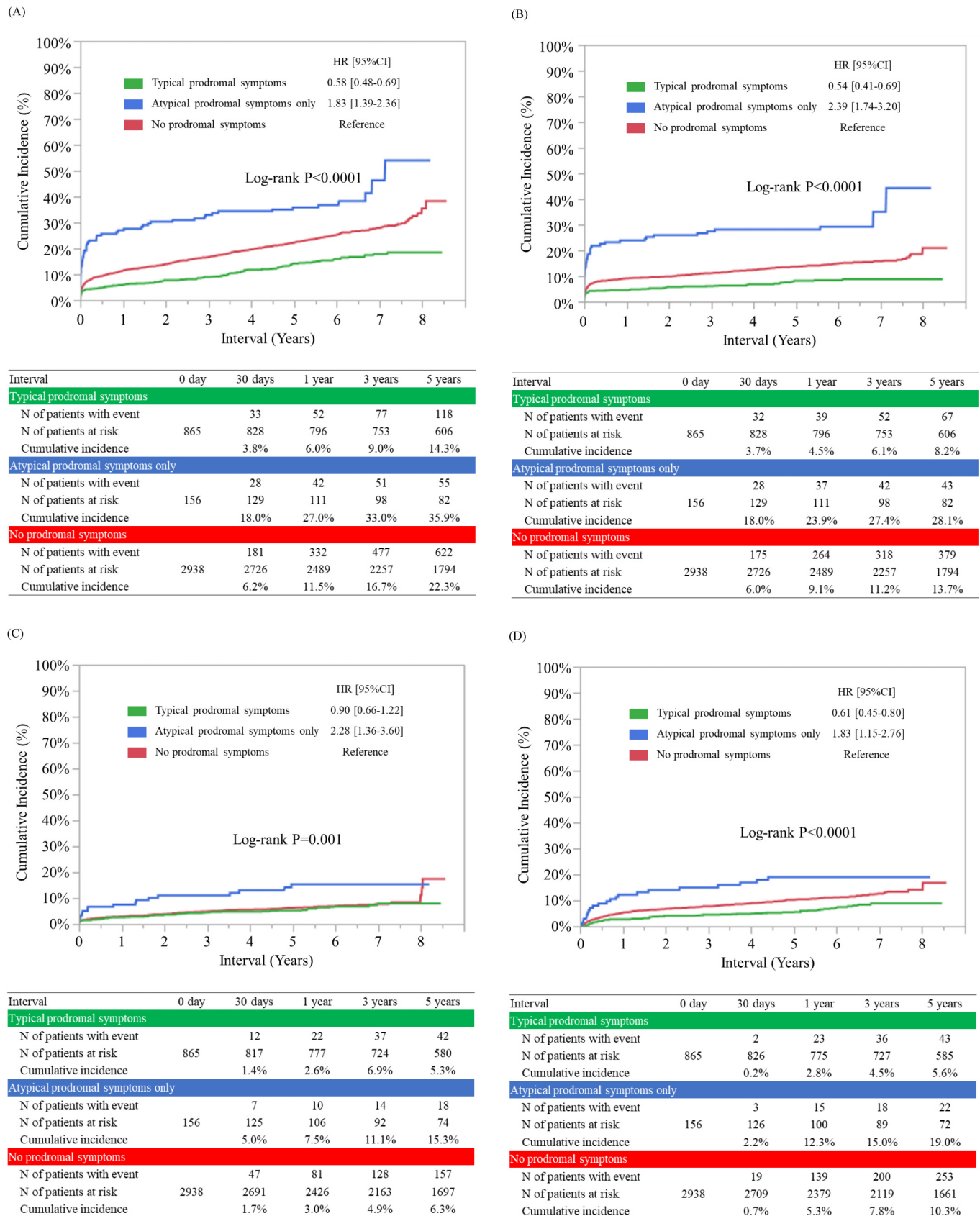


Fig. 2. Kaplan-Meier curves for the clinical outcomes according to the types of prodromal symptoms.

(A) All-cause death, (B) cardiovascular death, (C) myocardial infarction, and (D) hospitalization for heart failure.

Crude HRs and 95 % CIs of patients with typical prodromal symptoms and atypical prodromal symptoms only are indicated with reference to patients with no prodromal symptoms. CI, confidence interval; HR, hazard ratio.

Long-term clinical outcomes according to the types of the prodromal symptoms

Complete 1-, 3-, and 5-year clinical follow-up data were obtained in 96.5 %, 93.8 %, and 82.8 % of the patients, respectively, without difference across the three groups according to the prodromal symptoms (98.0 %, 96.0 %, and 83.7 % in the typical prodromal symptoms group; 98.1 %, 95.5 %, and 87.8 % in the atypical prodromal symptoms only group; 96.0 %, 93.1 %, and 82.2 % in the no prodromal symptoms group). During the median 5.6 years (IQR: 4.2 to 6.6 years) follow-up, the cumulative 5-year incidence of all-cause death was lower in those patients with typical prodromal symptoms, and higher in those with atypical prodromal symptoms only than in those with no prodromal symptoms (14.3 %, 35.9 %, and 22.3 %, log-rank $p < 0.0001$) (Fig. 2). Even after adjusting confounders, the lower mortality risk of the typical prodromal symptoms relative to the no prodromal symptoms remained significant (HR, 0.69; 95 % CI, 0.58–0.83; $p = 0.0001$), while the higher mortality risk of the atypical prodromal symptoms relative to the no prodromal symptoms remained significant (HR, 1.53; 95 % CI, 1.17–2.00; $p = 0.002$) (Table 3). The lower adjusted risks of the typical prodromal symptoms relative to the no prodromal symptoms were significant for cardiovascular death and hospitalization for HF (HR, 0.66; 95 % CI, 0.51–0.85; $p = 0.002$, and HR, 0.71; 95 % CI 0.53–0.95; $p = 0.02$, respectively) (Fig. 2, Table 3). The higher adjusted risks of the atypical prodromal symptoms relative to the no prodromal symptoms were significant for cardiovascular death, myocardial infarction, and hospitalization for HF (HR, 1.63; 95 % CI 1.19–2.23; $p = 0.002$, HR, 2.21; 95 % CI, 1.35–3.60; $p = 0.002$, and HR, 1.60; 95 % CI 1.03–2.48; $p = 0.04$, respectively) (Fig. 2, Table 3). In a sensitivity analysis excluding those patients with cardiopulmonary arrest or cardiogenic shock on admission, the results were consistent with the results in the entire cohort (Online Table 1, and Online Fig. 1).

Healthcare-seeking behavior for the prodromal symptoms

Regarding healthcare-seeking behavior in patients with the prodromal symptoms, a total of 162 patients (15.9 %) had sought medical care for the prodromal symptoms before the onset of AMI and within 48 h before hospital presentation, but were returned home without hospitalization (Fig. 1). Patients who had sought medical care were older, and more often had malignancy, prior atrial fibrillation, and dialysis (Table 4). The rate of seeking medical care was not significantly different between the patients with typical prodromal symptoms and those with atypical prodromal symptoms only (15.5 % and 17.9 %, $p = 0.44$). Long-term mortality was significantly higher in the patients seeking medical care than those not seeking medical care (22.9 % and 16.5 %,

log-rank $p = 0.02$) (Fig. 3). However, after adjusting the confounders, the higher mortality risk of those seeking medical care relative to those not was no longer significant (HR, 1.23; 95 % CI, 0.85–1.76; $p = 0.27$) (Table 5). The adjusted risks of those seeking medical care relative to those without were also not significant for the secondary endpoints such as cardiovascular death, myocardial infarction and hospitalization for HF (Table 5).

Discussion

The main findings of this study investigating the types of the prodromal symptoms and care-seeking behavior for the prodromal symptoms and their relationship with long-term clinical outcomes in STEMI patients who underwent primary PCI were as follows: (1) There were 21.8 % of patients with typical prodromal symptoms and 3.9 % of patients with atypical prodromal symptoms only before the onset of AMI and within 48 h before the index hospital presentation; (2) Compared with patients without prodromal symptoms before AMI, those with typical prodromal symptoms were associated with better long-term outcomes, whereas those with atypical prodromal symptoms were associated with poorer long-term outcomes; (3) 15.9 % of the patients with prodromal symptoms sought medical care before the onset of AMI and within 48 h before the index hospital presentation, but were returned to home without hospitalization.

Previous studies on the prodromal symptoms preceding AMI have concentrated primarily on symptoms typical of angina. Such typical prodromal symptoms were often referred to as pre-infarction angina and were reported to be associated with reduction of the infarct size [1–4], inhibition of left ventricular remodeling [5], and better prognosis [3,4,6–10] in numerous studies. In most of those previous studies, pre-infarction angina was defined as typical symptoms of angina occurring within 24 or 48 h before the onset of AMI, and atypical prodromal symptoms were mostly excluded from pre-infarction angina. In our previous report on pre-infarction angina in Japan [10], its prevalence was found to be 19.4 %, and patients with pre-infarction angina demonstrated a better long-term prognosis as compared with those without. The present study demonstrated consistent results in terms of the prevalence of typical prodromal symptoms (21.8 %) and its relationship with a better prognosis.

On the other hand, there have been only a few reports on atypical prodromal symptoms before AMI, which described only the frequency and gender differences. In a survey involving 914 consecutive patients admitted to a coronary care unit with suspected AMI, it was reported that 62 % of them had experienced symptoms other than chest pain in the week before admission [11]. It has been reported that women more often experienced atypical symptoms [11,12], a finding consistent

Table 3
Clinical outcomes according to the types of the prodromal symptoms.

End points	Types of prodromal symptoms	N of patients with event (cumulative 5-year incidence)	Crude HR [95 % CI]	p-Value	Adjusted HR [95 % CI]	p-Value
All-cause death	Typical prodromal symptoms	135 (14.3 %)	0.58 [0.48–0.69]	<0.0001	0.69 [0.58–0.83]	0.0001
	Atypical prodromal symptoms only	60 (35.9 %)	1.83 [1.39–2.36]	<0.0001	1.53 [1.17–2.00]	0.002
	No prodromal symptoms	724 (22.3 %)	Reference		Reference	
Cardiovascular death	Typical prodromal symptoms	70 (8.2 %)	0.54 [0.41–0.69]	<0.0001	0.66 [0.51–0.85]	0.002
	Atypical prodromal symptoms only	46 (28.1 %)	2.39 [1.74–3.20]	<0.0001	1.63 [1.19–2.23]	0.002
	No prodromal symptoms	414 (13.7 %)	Reference		Reference	
Myocardial infarction	Typical prodromal symptoms	52 (5.3 %)	0.90 [0.66–1.22]	0.51	0.99 [0.72–1.35]	0.94
	Atypical prodromal symptoms only	18 (15.3 %)	2.28 [1.36–3.60]	0.0009	2.21 [1.35–3.60]	0.002
	No prodromal symptoms	178 (6.3 %)	Reference		Reference	
Hospitalization for heart failure	Typical prodromal symptoms	57 (5.6 %)	0.61 [0.45–0.80]	0.0007	0.71 [0.53–0.95]	0.02
	Atypical prodromal symptoms only	22 (19.0 %)	1.83 [1.15–2.76]	0.006	1.60 [1.03–2.48]	0.04
	No prodromal symptoms	283 (10.3 %)	Reference		Reference	

Cumulative 5-year incidence was estimated by the Kaplan-Meier method.

Number of patients with event and HRs with 95 % CIs were estimated throughout the entire follow-up period by the Cox proportional hazard models.

CI, confidence interval; HR, hazard ratio.

Table 4

Baseline characteristics and hemodynamic status according to the status of seeking medical care.

	Any prodromal symptoms	Seeking medical care within 48 h before index hospital presentation following the onset of AMI		
		Yes	No	p-value
N	1021	162 (15.9 %)	859 (84.1 %)	
Clinical characteristics				
Age (years)	67.1 ± 12.6	69.1 ± 12.8	66.7 ± 12.6	0.03
Age ≥ 75 years	299 (29.3 %)	61 (37.7 %)	238 (27.7 %)	0.01
Men	765 (74.9 %)	111 (68.5 %)	654 (76.1 %)	0.04
Body mass index (kg/m ²)	23.8 ± 3.5	23.9 ± 3.5	23.8 ± 3.5	0.80
Body mass index <25 kg/m ²	688 (67.4 %)	104 (64.2 %)	584 (68.0 %)	0.35
Hypertension	808 (79.1 %)	126 (77.8 %)	682 (79.4 %)	0.64
Diabetes	385 (37.7 %)	69 (42.6 %)	316 (36.8 %)	0.16
On insulin therapy	57 (5.6 %)	14 (8.6 %)	43 (5.0 %)	0.06
Current smoking	376 (36.8 %)	55 (34.0 %)	321 (37.4 %)	0.41
Prior heart failure	14 (1.4 %)	3 (1.9 %)	11 (1.3 %)	0.57
Prior PCI	101 (9.9 %)	20 (12.4 %)	81 (9.4 %)	0.25
Prior CABG	10 (1.0 %)	3 (1.9 %)	7 (0.8 %)	0.22
Prior myocardial infarction	78 (7.6 %)	16 (9.9 %)	62 (7.2 %)	0.24
Prior stroke (symptomatic)	92 (9.0 %)	18 (11.1 %)	74 (8.6 %)	0.31
Peripheral vascular disease	38 (3.7 %)	7 (4.3 %)	31 (3.6 %)	0.66
eGFR <30 mL/min per 1.73 m ² , without hemodialysis	48 (4.7 %)	10 (6.2 %)	38 (4.4 %)	0.33
Hemodialysis	17 (1.7 %)	6 (3.7 %)	11 (1.3 %)	0.03
eGFR <30 mL/min per 1.73 m ² or hemodialysis	65 (6.4 %)	16 (9.9 %)	49 (5.7 %)	0.046
Prior atrial fibrillation	72 (7.1 %)	19 (11.7 %)	53 (6.2 %)	0.01
Anemia (hemoglobin <11.0 g/L)	85 (8.3 %)	16 (9.9 %)	69 (8.0 %)	0.44
Thrombocytopenia (platelet <100 × 10 ⁹ /L)	18 (1.8 %)	4 (2.5 %)	14 (1.6 %)	0.46
Chronic obstructive pulmonary disease	32 (3.1 %)	9 (5.6 %)	23 (2.7 %)	0.054
Liver cirrhosis	19 (1.9 %)	5 (3.1 %)	14 (1.6 %)	0.21
Malignancy	111 (10.9 %)	27 (16.7 %)	84 (9.8 %)	0.01
Prodromal symptoms				0.44
Typical prodromal symptoms	865 (84.7 %)	134 (82.7 %)	731 (85.1 %)	
Atypical prodromal symptoms only	156 (15.3 %)	28 (17.3 %)	128 (14.9 %)	
Presentation				
Current heart failure	295 (28.9 %)	53 (32.7 %)	242 (28.2 %)	0.24
Killip classification				0.41
Killip I	734 (71.9 %)	114 (70.4 %)	620 (72.2 %)	
Killip II	142 (13.9 %)	23 (14.2 %)	119 (13.9 %)	
Killip III	25 (2.4 %)	7 (4.3 %)	18 (2.1 %)	
Killip IV (cardiogenic shock)	120 (11.8 %)	18 (11.1 %)	102 (11.9 %)	
Cardiopulmonary arrest	32 (3.1 %)	5 (3.1 %)	27 (3.1 %)	0.97
Baseline CK	165 (97.5–442.5)	169 (96.5–475)	163 (98–422.3)	0.54
Baseline CKMB	15 (8–36)	18 (9.1–58.5)	15 (8–34)	0.06
Maximum CK	1940.5 (878–3906)	1820.5 (787–3502.8)	1982 (899–4010.3)	0.12
Maximum CKMB	159.5 (64.7–329.5)	152.2 (69.1–304.2)	162 (64.4–337.5)	0.65
Angiographic characteristics				
Infarct related artery location				0.65
Left anterior descending coronary artery	507 (49.9 %)	73 (45.1 %)	434 (50.5 %)	
Left circumflex coronary artery	96 (9.5 %)	17 (10.5 %)	79 (9.2 %)	
Right coronary artery	378 (37.2 %)	65 (40.1 %)	313 (36.4 %)	
Left main coronary artery	35 (3.4 %)	5 (3.1 %)	30 (3.5 %)	
Multivessel disease	517 (50.6 %)	75 (46.3 %)	442 (51.5 %)	0.23
Procedural characteristics				
Onset-to-presentation time (min)	146 (76–290)	150 (73–310)	145.5 (77–288.3)	0.85
Onset-to-balloon time (min)	246 (165–404)	257 (161–465)	243 (165–390)	0.36
Door-to-balloon time (min)	80 (59–112)	89 (72–112.3)	77 (57–111)	0.003

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CK, creatine kinase; CKMB, creatine kinase isoenzyme MB; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention.

with the present study. However, there was no previous study that assessed the impact of atypical prodromal symptoms on long-term clinical outcomes. The present study showed that patients with atypical prodromal symptoms, in contrast to those with typical ones, were older, had more cardiovascular co-morbidities, and experienced higher mortality, even after adjustment for confounders including age, renal failure, and prior HF. A few studies on the symptoms of AMI itself reported that atypical symptoms, such as shortness of breath [18,19] and syncope [19], were associated with increased long-term mortality rates. Atypical presentation of acute coronary syndrome (ACS), particularly dyspnea, was reported as an independent predictor of in-hospital mortality [20]. In our study, atypical prodromal symptoms could be the symptoms of HF associated with evolving ACS. Indeed, patients with atypical prodromal symptoms had a high prevalence of HF on

admission, which likely contributed to their worse prognosis. This finding highlights the clinical relevance of identifying such symptoms, as they may indicate a more serious underlying condition requiring timely management.

In the present study, 15.9 % of patients with the prodromal symptoms sought medical care before the onset of AMI. There also were limited data on the rate of medical consultation before the onset of AMI. A previous study reported that 15.9 % of patients with ACS sought medical care for at least one prodromal symptom in the 90 days before ACS presentation [21]. A survey of coronary care unit patients reported that 59 % of those with prodromal symptoms of suspected AMI had wanted to contact a physician, and 33 % actually did so in the week before admission [11]. According to the report from the VIRGO Study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients), 29.5 % of women and

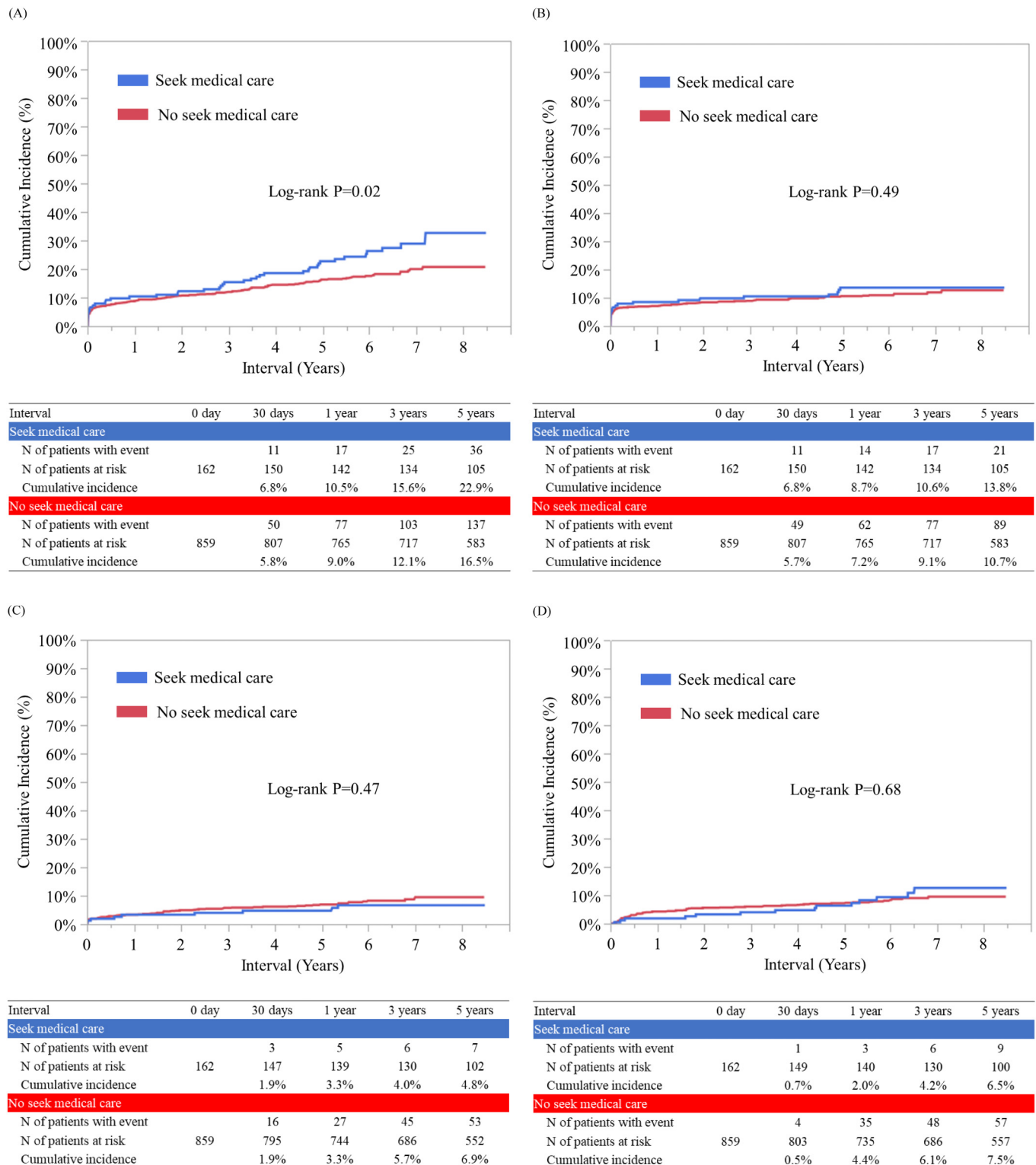


Fig. 3. Kaplan-Meier curves for the clinical outcomes according to the status of seeking medical care.
(A) All-cause death, (B) cardiovascular death, (C) myocardial infarction, and (D) hospitalization for heart failure.

22.1 % of men sought medical care for some forms of symptoms before hospitalization for AMI; however, 53 % of women said that their physician did not consider their symptoms to be heart-related [12].

We did not have detailed clinical information at the time of the medical consultation before AMI in the present study. Nevertheless, we might reasonably expect a considerable number of the patients to have already had some signs suggestive of ACS at the time of the

medical consultation before AMI, in whom appropriate medical response could have led to prevention or earlier treatment of AMI. Earlier presentation and faster revascularization in STEMI are known to result in better myocardial salvage and improved long-term outcomes [22,23].

The findings of this study would serve as an important alert for medical practitioners involved in emergency care and primary care. A substantial number of patients who were returned to home after seeking medical

Table 5

Clinical outcomes according to the status of seeking medical care.

End points	Status of seeking medical care	N of patients with event (cumulative 5-year incidence)	Unadjusted HR [95 % CI]	p-Value	Adjusted HR [95 % CI]	p-Value
All-cause death	Seek medical care	43 (22.9 %)	1.50 [1.06–2.08]	0.02	1.23 [0.85–1.76]	0.27
	No seek medical care	152 (16.5 %)	Reference		Reference	
Cardiovascular death	Seek medical care	21 (13.8 %)	1.18 [0.72–1.85]	0.49	1.15 [0.70–1.91]	0.58
	No seek medical care	95 (10.7 %)	Reference		Reference	
Myocardial infarction	Seek medical care	9 (4.8 %)	0.77 [0.36–1.48]	0.47	0.59 [0.29–1.22]	0.16
	No seek medical care	61 (6.9 %)	Reference		Reference	
Hospitalization for heart failure	Seek medical care	14 (6.5 %)	1.13 [0.61–1.95]	0.68	0.73 [0.39–1.36]	0.32
	No seek medical care	65 (7.5 %)	Reference		Reference	

Cumulative 5-year incidence was estimated by Kaplan-Meier method.

Number of patients with event and HRs with 95 % CIs were estimated throughout the entire follow-up period by the Cox proportional hazard models.

CI, confidence interval; HR, hazard ratio.

care with typical angina symptoms had AMI within 48 h. It would be important to recognize that angina symptoms in patients with unplanned hospital visits should not be regarded as “stable” angina, but should be regarded as angina potentially related to ACS. Prompt evaluation with electrocardiogram, echocardiography, and high-sensitivity troponin measurement in all patients as well as coronary computed tomography angiography [24–26] in selected patients would be important to facilitate adequate treatment to prevent progression to AMI. Moreover, while it was often emphasized that typical symptoms such as chest pressure often signaled a high probability of coronary artery disease, atypical symptoms might have been underappreciated due to a relatively lower likelihood of coronary artery disease. However, as demonstrated in the present study, 15 % of patients with prodromal symptoms before AMI had atypical symptoms only, and those patients with atypical prodromal symptoms had poorer prognosis after AMI compared to those without prodromal symptoms. Therefore, in patients presenting with atypical symptoms—particularly those who are older or have multiple cardiovascular co-morbidities and are thus at high risk for coronary artery disease—it is crucial to diligently assess the possibility of both HF and ACS.

Limitations

This study has several limitations. First, the information on the prodromal symptoms and care-seeking behaviors was confined to what was documented in the medical records, which were not necessarily comprehensive. The attending physicians often tended to record those symptoms that were considered relevant to myocardial infarction, thereby introducing a potential acquisition bias. Consequently, atypical prodromal symptoms and the corresponding care-seeking behaviors might be underrepresented in the documentation. Second, due to the reliance on patient interviews for information about the prodromal symptoms, serious conditions such as cardiopulmonary arrest or shock on admission might have impeded effective interview, possibly leaving certain prodromal symptoms undetected by the physicians. Therefore, there was a potential for underestimation on the prevalence of the prodromal symptoms and on the event rates in patients with the prodromal symptoms. To mitigate this bias, we conducted the sensitivity analyses where patients presenting with cardiopulmonary arrest or cardiogenic shock on admission were excluded, and confirmed the robustness of our study results. Third, this study solely analyzed patients who eventually developed STEMI. We had no information on those patients with chest pain and unplanned hospital visit who received appropriate diagnosis and treatment to prevent progression to AMI. Additionally, we did not have detailed clinical data at the medical visit before the onset of AMI, nor information on whether the patient visited a clinic or hospital, or which department they consulted. Fourth, we did not systematically classify the symptoms at the onset of STEMI. Although most of the cases were expected to have had typical symptoms at the onset, a minority of patients might have

presented with only atypical symptoms such as HF or cardiogenic shock, which could influence diagnostic timing and outcomes. Fifth, we did not collect data on symptoms more than 48 h before hospital presentation. Finally, it was not always easy to pinpoint the onset of AMI, particularly in those patients who had insidious onset or intermittent symptoms. Symptoms of AMI could have mistakenly been interpreted as the prodromal symptoms, while the prodromal symptoms could have mistakenly been regarded as the onset of AMI.

Conclusions

Compared to patients with no prodromal symptoms before STEMI, long-term mortality outcome was better in patients with typical prodromal symptoms, but worse in those with atypical prodromal symptoms.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jjcc.2025.09.006>.

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SUPPLEMENTARY MATERIAL

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Wave-2

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Online Methods

Definition of baseline characteristics and endpoints

Baseline clinical characteristics, such as hypertension, current smoking, heart failure, prior myocardial infarction, atrial fibrillation, and chronic obstructive pulmonary disease were regarded as present when these diagnoses were recorded in hospital charts. Diabetes mellitus was defined as treatment with oral hypoglycemic agents or insulin, prior clinical diagnosis of diabetes, glycated hemoglobin level $\geq 6.5\%$, or non-fasting blood glucose level ≥ 200 mg/dL. Prior stroke was defined as ischemic or hemorrhagic stroke with neurological symptoms lasting >24 hours. Peripheral vascular disease was regarded as present when carotid, aortic, or other peripheral vascular diseases were being treated or scheduled for surgical or endovascular interventions. Renal function was expressed as estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease formula modified for Japanese patients [1].

Myocardial infarction and stent thrombosis were adjudicated according to the Academic Research Consortium (ARC) definition [2]. Stroke was defined as ischemic or hemorrhagic stroke either requiring hospitalization with symptoms lasting >24 hours, or occurring during hospitalization for other reasons. Hospitalization for heart failure was regarded as present when intravenous drug treatment was required for worsening heart failure. Bleeding was adjudicated according to the Bleeding Academic Research Consortium (BARC) classification [3]. BARC type 3 or 5 bleeding was regarded as major bleeding. Any coronary revascularization was defined as either PCI or CABG for any reasons.

Online Table 1 Clinical outcomes according to the types of prodromal symptoms: Sensitivity analysis.

Endpoints	Types of prodromal symptoms	N of patients with event (cumulative 5-year incidence)		Unadjusted HR [95%CI]	p-value	Adjusted HR [95% CI]	p-value
All-cause death	Typical prodromal symptoms	105	(11.6%)	0.62 [0.50-0.77]	<0.0001	0.72 [0.58-0.89]	0.002
	Atypical prodromal symptoms only	35	(26.2%)	1.65 [1.17-2.33]	0.004	1.65 [1.16-2.34]	0.005
	No prodromal symptoms	477	(16.9%)	Reference		Reference	
Cardiovascular death	Typical prodromal symptoms	44	(5.5%)	0.56 [0.40-0.77]	0.0005	0.66 [0.47-0.91]	0.01
	Atypical prodromal symptoms only	24	(17.7%)	2.37 [1.55-3.61]	<0.0001	2.04 [1.32-3.15]	0.001
	No prodromal symptoms	225	(8.7%)	Reference		Reference	
Myocardial infarction	Typical prodromal symptoms	48	(5.0%)	0.91 [0.65-1.25]	0.57	1.00 [0.72-1.40]	0.98
	Atypical prodromal symptoms only	17	(16.7%)	2.60 [1.52-4.17]	0.0002	2.49 [1.49-4.14]	0.0005
	No prodromal symptoms	149	(6.0%)	Reference		Reference	
Hospitalization for heart failure	Typical prodromal symptoms	55	(5.6%)	0.66 [0.49-0.88]	0.006	0.74 [0.55-1.0008]	0.051
	Atypical prodromal symptoms only	20	(19.3%)	2.02 [1.24-3.10]	0.003	1.73 [1.08-2.77]	0.02
	No prodromal symptoms	232	(9.5%)	Reference		Reference	

In this sensitivity analysis, we excluded those patients with cardiopulmonary arrest or cardiogenic shock on arrival.

Cumulative incidence was estimated by the Kaplan-Meier method.

Number of patients with event and HRs with 95% CIs were estimated throughout the entire follow-up period by the Cox proportional hazard models.

CI, confidence interval; HR, hazard ratio.

Online Figure 1 Kaplan-Meier curves for the clinical outcomes according to the types of prodromal symptoms: Sensitivity analysis.

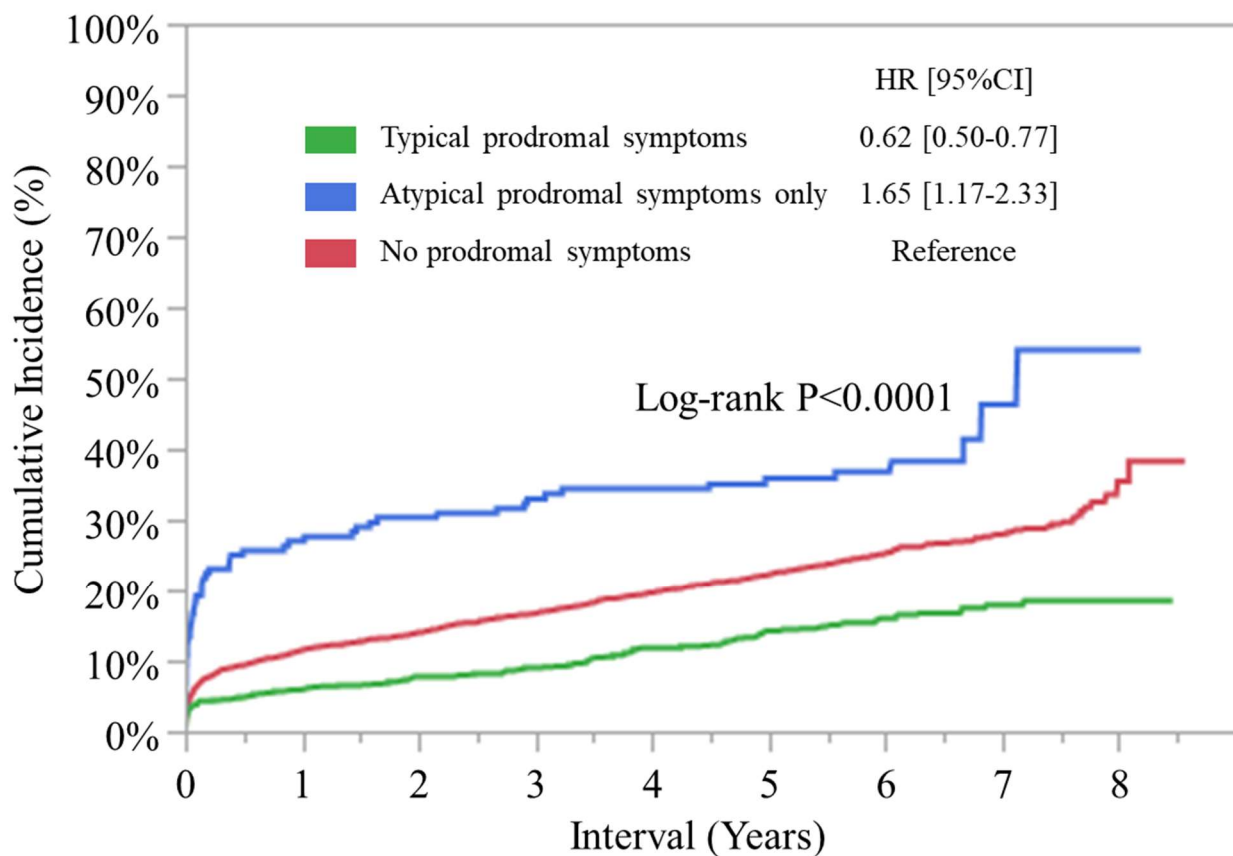
(A) All-cause death, (B) Cardiovascular death, (C) Myocardial infarction, and (D) Hospitalization for heart failure.

In this sensitivity analysis, we excluded those patients with cardiopulmonary arrest or cardiogenic shock on arrival.

Crude HRs and 95% CIs of patients with typical prodromal symptoms and atypical prodromal symptoms only were indicated with reference to patients with no prodromal symptoms.

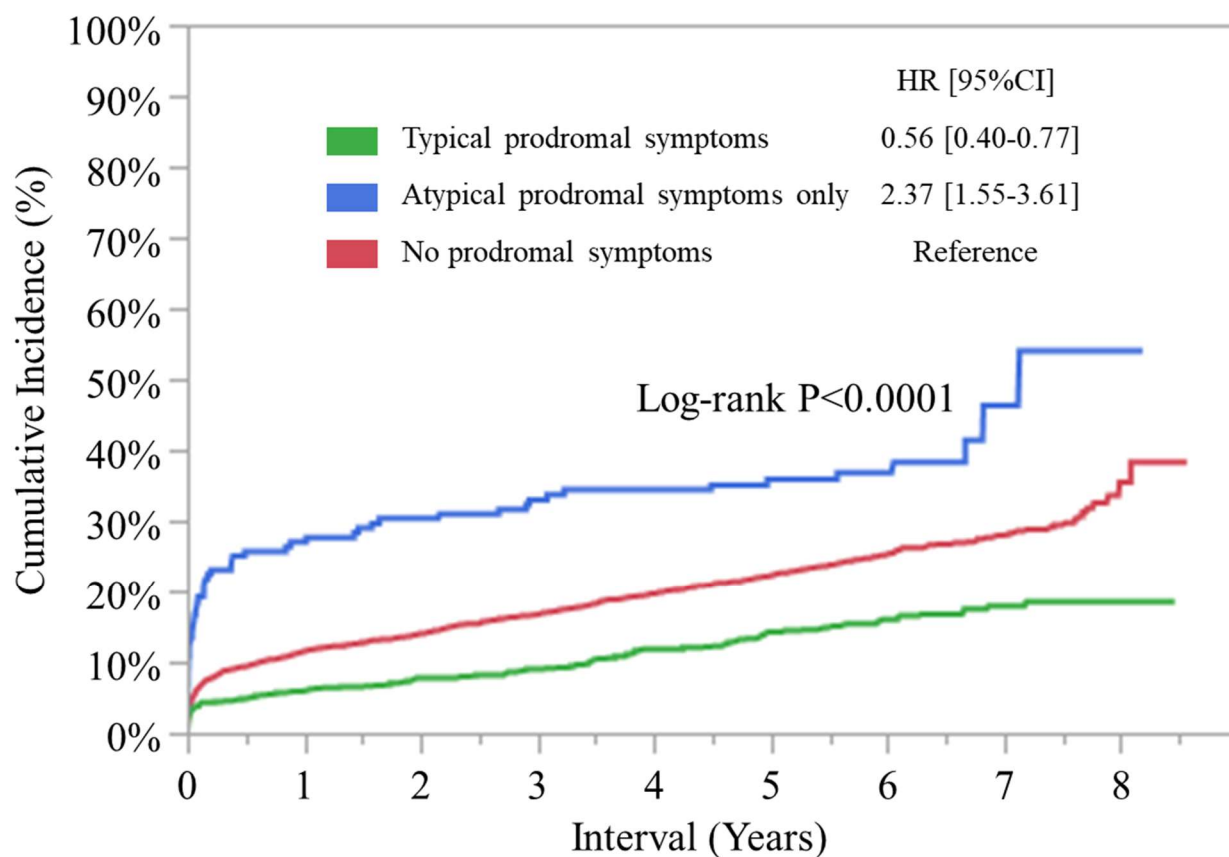
CI, confidence interval; HR, hazard ratio.

(A) All-cause death.



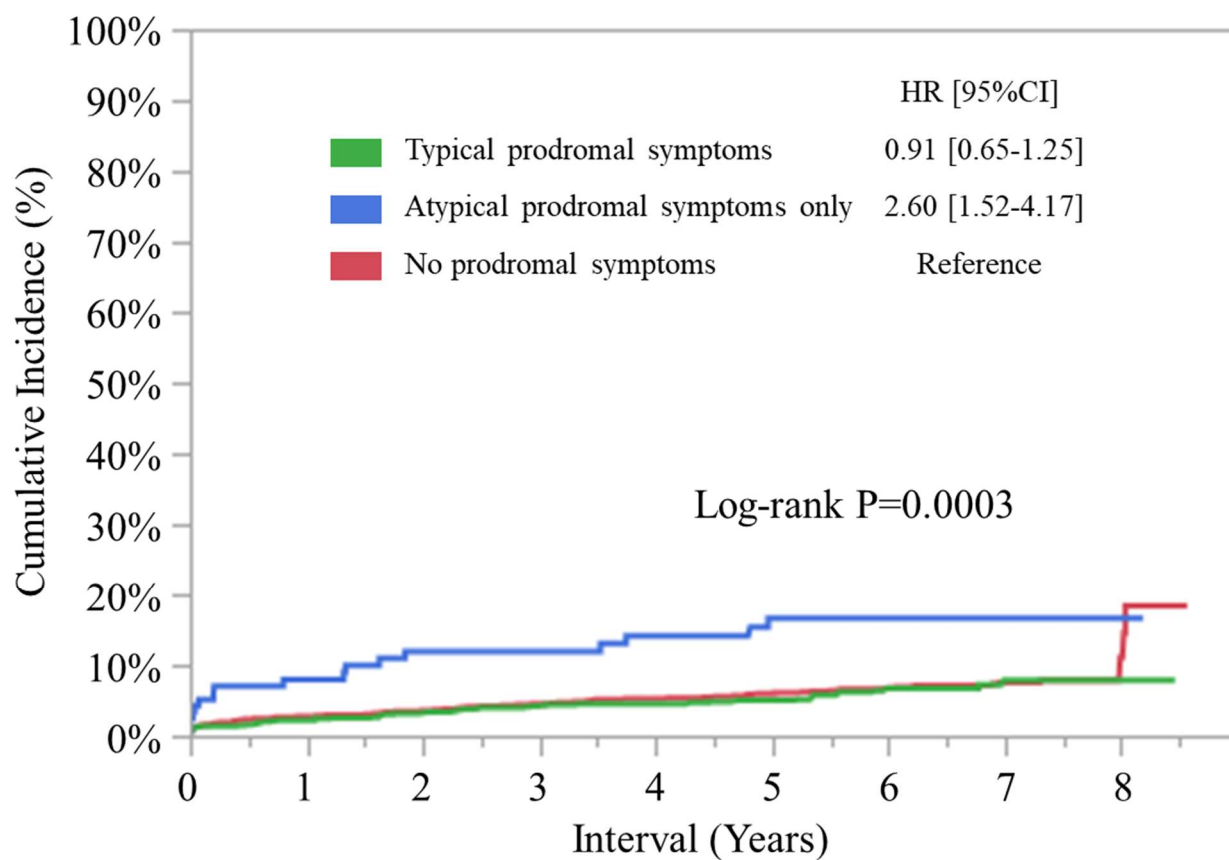
Interval	0 day	30 days	1 year	3 years	5 years
Typical prodromal symptoms					
N of patients with event		13	26	48	88
N of patients at risk	802	786	763	724	581
Cumulative incidence		1.6%	3.3%	6.1%	11.6%
Atypical prodromal symptoms only					
N of patients with event		10	19	28	31
N of patients at risk	121	111	100	88	74
Cumulative incidence		8.3%	15.7%	23.4%	26.2%
No prodromal symptoms					
N of patients with event		64	165	274	391
N of patients at risk	2451	2362	2196	2013	1606
Cumulative incidence		2.6%	6.8%	11.6%	16.9%

(B) Cardiovascular death.



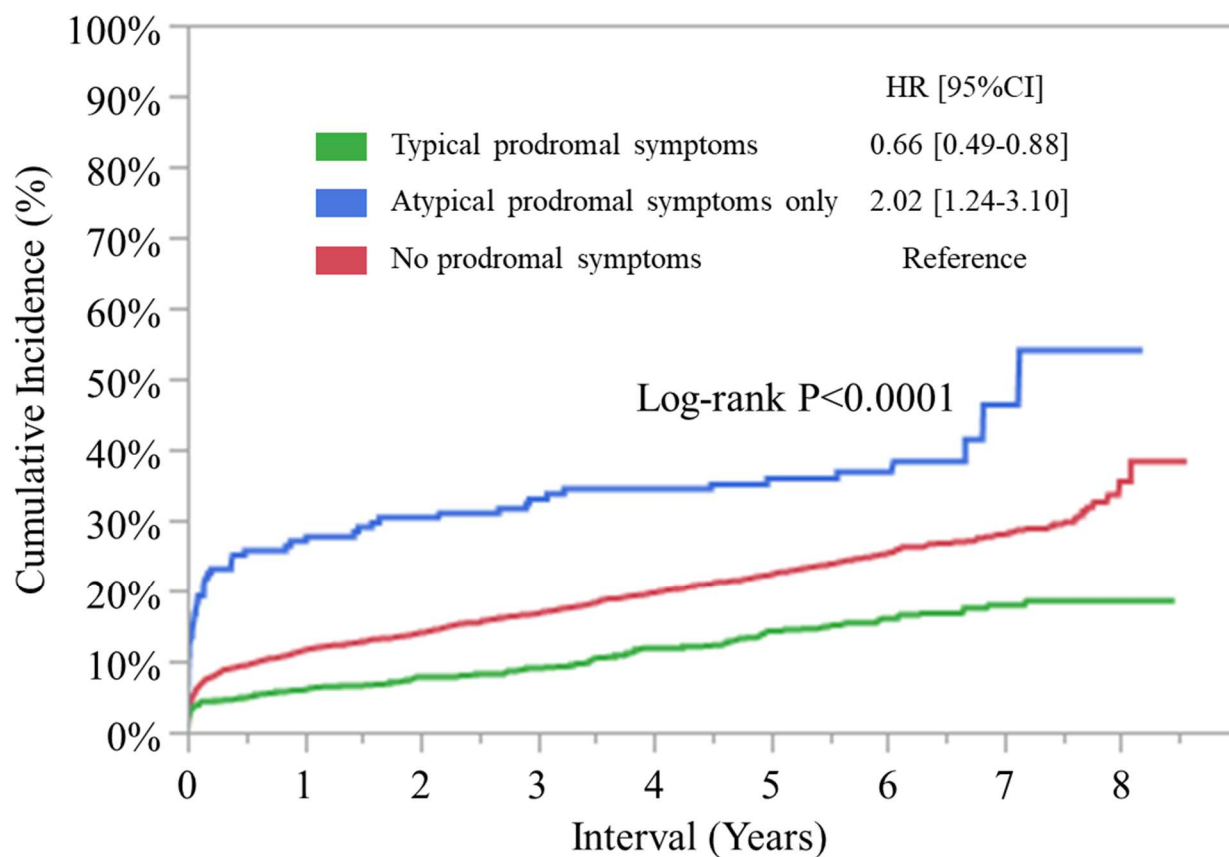
Interval	0 day	30 days	1 year	3 years	5 years
Typical prodromal symptoms					
N of patients with event		12	16	26	41
N of patients at risk	802	786	763	724	581
Cumulative incidence		1.5%	2.0%	3.3%	5.5%
Atypical prodromal symptoms only					
N of patients with event		10	16	21	21
N of patients at risk	121	111	100	88	74
Cumulative incidence		8.3%	13.3%	17.7%	17.7%
No prodromal symptoms					
N of patients with event		60	110	145	197
N of patients at risk	2451	2362	2196	2013	1603
Cumulative incidence		2.5%	4.6%	6.1%	8.7%

(C) Myocardial infarction.



Interval	0 day	30 days	1 year	3 years	5 years
Typical prodromal symptoms					
N of patients with event		10	18	33	38
N of patients at risk	802	777	748	699	559
Cumulative incidence		1.3%	2.3%	4.3%	5.0%
Atypical prodromal symptoms only					
N of patients with event		6	9	13	17
N of patients at risk	121	107	95	82	66
Cumulative incidence		5.2%	8.0%	11.9%	16.7%
No prodromal symptoms					
N of patients with event		37	65	103	130
N of patients at risk	2451	2332	2142	1930	1517
Cumulative incidence		1.5%	2.8%	4.6%	6.0%

(D) Hospitalization for heart failure.



Interval	0 day	30 days	1 year	3 years	5 years
Typical prodromal symptoms					
N of patients with event		2	21	34	42
N of patients at risk	802	784	744	700	562
Cumulative incidence		0.3%	2.7%	4.4%	5.6%
Atypical prodromal symptoms only					
N of patients with event		3	14	16	20
N of patients at risk	121	108	90	81	66
Cumulative incidence		2.6%	13.0%	15.0%	19.3%
No prodromal symptoms					
N of patients with event		17	112	158	204
N of patients at risk	2451	2347	2108	1904	1502
Cumulative incidence		0.7%	4.9%	7.0%	9.5%

Online References

- [1] Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;53:982-92.
- [2] Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344-51.
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