Table 1
Baseline clinical characteristics according to living arrangements

Variable	Living Alone (n = 515)	Not Living Alone (n = 3594)	p Value
Age (years)	68.5 ± 13.0	67.6 ± 12.1	0.11
Age ≥75 years*	196 (38%)	1097 (31%)	0.001
Men*	322 (63%)	2701 (75%)	<0.001
Body mass index (kg/m^2) <25.0*	390 (76%)	2586 (72%)	0.07
Hypertension*	407 (79%)	2826 (79%)	0.84
Diabetes mellitus	159 (31%)	1157 (32%)	0.55
On insulin therapy*	19 (3.7%)	160 (4.5%)	0.43
Current smoker*	206 (40%)	1430 (40%)	0.93
Heart failure*	188 (37%)	1093 (30%)	0.005
Multivessel coronary disease*	243 (47%)	1884 (52%)	0.03
Mitral regurgitation grade 3/4*	13 (2.5%)	115 (3.2%)	0.41
Prior myocardial infarction*	44 (8.5%)	307 (8.5%)	0.99
Prior percutaneous coronary intervention*	40 (7.8%)	316 (8.8%)	0.44
Prior stroke (symptomatic)*	50 (9.7%)	331 (9.2%)	0.72
Peripheral vascular disease*	17 (3.3%)	119 (3.3%)	0.99
eGFR (ml/min/1.73 m^2) <30, without hemodialysis*	27 (5.2%)	150 (4.2%)	0.26
Hemodialysis*	11 (2.1%)	52 (1.5%)	0.23
Atrial fibrillation*	53 (10%)	333 (9.3%)	0.46
Anemia (hemoglobin <11.0 g/dl)*	62 (12%)	338 (9.4%)	0.06
Thrombocytopenia (platelet count <100,000)*	11 (2.1%)	65 (1.8%)	0.61
Chronic obstructive pulmonary disease*	23 (4.5%)	113 (3.1%)	0.12
Liver cirrhosis*	20 (3.9%)	76 (2.1%)	0.02
Malignancy*	34 (6.6%)	293 (8.2%)	0.22

Categorical variables are expressed as number (%) unless otherwise indicated. Continuous variables are shown as mean ± SD or median (interquartile range).

eGFR = estimated glomerular filtration rate; SD = standard deviation.

* Potential independent variables selected for Cox proportional hazard models.

Table 2
Presentation and angiographic characteristics according to living arrangements

Variable	Living Alone (n = 515)	Not Living Alone (n = 3594)	p Value
ST-segment elevation myocardial infarction	453 (88%)	3162 (88%)	0.99
Hours from onset to presentation	3.1 (1.3–6.4)	2.4 (1.2–5.3)	0.001
≤2 hours	189 (39%)	1541 (45%)	0.01
Minutes from door to balloon	90 (60–138)	96 (66–138)	0.16
Hemodynamics:			
Killip class 1	365 (71%)	2682 (75%)	0.04
Killip class 2	59 (11%)	279 (7.8%)	
Killip class 3	14 (2.7%)	105 (2.9%)	
Killip class 4*	77 (15%)	528 (15%)	
Duration of hospitalization (days)	15 (10–22)	15 (10–23)	0.06
Infarct related coronary artery			
Left anterior descending	249 (48%)	1602 (45%)	0.32
Left circumflex	69 (13%)	471 (13%)	
Right	180 (35%)	1419 (40%)	
Left main	13 (2.5%)	85 (2.4%)	
Number of target coronary narrowings	1 (1–2)	1 (1–2)	0.76
Target of proximal left anterior descending coronary artery*	286 (56%)	1909 (53%)	0.30
Target of unprotected left main coronary artery*	19 (3.7%)	131 (3.6%)	0.96
Target of chronic total occlusion*	17 (3.3%)	122 (3.4%)	0.91
Target of bifurcation*	146 (28%)	956 (27%)	0.40
Side-branch stenting*	14 (2.7%)	122 (3.4%)	0.42
Total number of stents	1 (1–2)	1 (1–2)	0.97
Total stent length >28 mm*	207 (44%)	1422 (43%)	0.79
Minimum stent size <3.0 mm*	175 (37%)	1105 (34%)	0.13
Drug eluting stent use (culprit or other lesions)*	151 (32%)	1092 (33%)	0.60

Categorical variables are expressed as number (%) unless otherwise indicated. Continuous variables are shown as mean ± SD or median (interquartile range).

SD = standard deviation.

* Potential independent variables selected for Cox proportional hazard models.

guidelines of the Japanese Ministry of Health, Labour and Welfare.

The details on the design and patient enrollment of this registry have been described previously.[13] Of 5,429 patients enrolled in this registry, we excluded 9 patients who refused to participate in the study, 195 patients treated by coronary artery bypass grafting, 689 patients who underwent PCI beyond 24 hours after symptom onset, 30 patients whose symptom onset was unknown, 331 patients for whom the data on living arrangements was not available, and 66 patients who had previous coronary artery bypass grafting. Therefore, the study population for the current analysis consisted of 4,109 patients with AMI who underwent PCI within 24 hours of symptom onset and for whom the data on living arrangements were available (ST-segment elevation AMI: n = 3,615, non–ST-segment elevation AMI: n = 494).

Experienced clinical research coordinators from an independent clinical research organization (Research Institute for Production Development, Kyoto, Japan; Supplementary Appendix B) collected baseline clinical, angiographic, and procedural characteristics including living arrangement from hospital charts or hospital databases according to prespecified definitions. Collection of follow-up information was mainly conducted through review of 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, subsequent hospitalizations, and status of antiplatelet therapy. Death, myocardial infarction (MI), and stroke were adjudicated by the clinical event committee (Supplementary Appendix C). Median follow-up duration for the surviving patients was 1,844 days (interquartile range 1,508 to 2,163). Complete 1- and 3-year follow-up information was obtained in 98.3% and 96.2% of patients, respectively.

We defined the living alone group as comprising patients who did not live with their family or others, at the time of hospital admission. The detailed definitions of baseline clinical characteristics were described previously.[13,14] The primary outcome measure for the current analysis was

Table 3
Medications at discharge according to living arrangements

Variable	Living Alone (n = 515)	Not Living Alone (n = 3594)	p Value
Antiplatelet therapy			
Thienopyridine	495 (96%)	3427 (95%)	0.44
Ticlopidine	443 (90%)	3164 (92%)	0.03
Clopidogrel	51 (10%)	259 (7.6%)	0.03
Aspirin	508 (99%)	3545 (99%)	0.99
Cilostazol*	158 (31%)	1266 (35%)	0.04
Other medications			
Statins*	260 (50%)	1930 (54%)	0.17
Beta-blockers*	238 (46%)	1465 (41%)	0.02
ACE-I/ARB*	368 (71%)	2622 (73%)	0.47
Nitrates*	168 (33%)	1081 (30%)	0.24
Calcium channel blockers*	103 (20%)	769 (21%)	0.47
Nicorandil*	148 (29%)	1002 (28%)	0.69
Warfarin*	45 (8.7%)	385 (11%)	0.17
Proton pump inhibitors*	185 (36%)	1259 (35%)	0.69
H2-blockers*	167 (32%)	1155 (32%)	0.90

Categorical variables are expressed as number (%) unless otherwise indicated. Continuous variables are shown as mean ± SD or median (interquartile range).

ACE-I = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; SD = standard deviation.

* Potential independent variables selected for Cox proportional hazard models.

all-cause death. The secondary outcome measures included cardiac death, MI, stroke, hospitalization for congestive heart failure, and any coronary revascularization. Death was regarded as cardiac in origin unless obvious noncardiac causes could be identified. Any death during hospitalization for the index AMI was regarded as cardiac death. MI was defined according to the definition in the Arterial Revascularization Therapies Study.[15] Stroke was defined as ischemic or hemorrhagic stroke either occurring during the index hospitalization or requiring hospitalization with symptoms lasting >24 hours. Hospitalization for congestive heart failure was regarded as present when intravenous drug treatment was required for worsening heart failure. Any coronary revascularization was defined as either PCI or coronary artery bypass grafting for any reasons. Scheduled staged coronary revascularization procedures performed within 3 months of the initial procedure were not regarded as follow-up events but were included in the index procedure.

We present continuous variables as mean ± SD or median with interquartile range and categorical variables as numbers and percentages. We compared categorical variables with the chi-square test when appropriate; otherwise, we used Fisher's exact test. We compared continuous variables with the Student *t* test or the Wilcoxon rank sum test on the basis of the distributions.

We used the Kaplan-Meier method to estimate cumulative incidences of clinical event rates and assessed differences with the log-rank test. The effects of the living alone group relative to the not living alone group for individual end points were expressed as hazard ratios with 95% confidence intervals by multivariable Cox proportional hazard models adjusting for the 40 clinically relevant factors indicated in Tables 1, 2, and 3. Consistent with our previous reports, continuous variables were dichotomized using clinically meaningful reference values or median values. A subgroup analysis stratified by patients' age (≥75 years or <75 years) was also conducted. Statistical analyses were conducted using JMP 10.0 (SAS Institute Inc., Cary, North Carolina). All the statistical analyses were 2-tailed. We regarded p values <0.05 as statistically significant.

Results

Regarding the baseline clinical characteristics, the living alone group had significantly greater prevalence of patients with advanced age, female gender, history of heart failure, and liver cirrhosis (Table 1). The living alone group also had a significantly longer onset-to-presentation time compared with the not living alone group (Figure 1). However, there was no significant difference in the angiographic and procedural characteristics between the 2 groups except for the lower prevalence of multivessel coronary artery disease in the living alone group. Regarding medical treatment at discharge, β blockers were more often prescribed in the living alone group (Tables 2 and 3).

The cumulative incidence of all-cause death was not significantly different between the living alone and not living alone groups at 5 years (Figure 2). After adjustment for potential confounding factors, the risk for all-cause death in the living alone group remained to be comparable with that in the not living alone group. The unadjusted and adjusted risk for cardiac death, MI, stroke, and any coronary revascularization were also not different between the 2 groups (Figure 2, Supplementary Figure 1). However, the cumulative incidence of readmission for heart failure in the living alone group was significantly greater than that in the not living alone group, although the adjusted risk of the living alone group relative to the not living alone group for readmission for heart failure was not statistically significant (Table 4 and Supplementary Figure 1).

In the population of patients aged <75 years, the cumulative 5-year incidence of all-cause death was not different between the living alone and the not living alone group. The cumulative incidence of all the other clinical end points were also not different between the 2 groups in the subgroup of patients aged <75 years (Table 4). In contrast, the cumulative 5-year incidence of all-cause death and cardiac death in the living alone group was significantly lower than that in the not living alone group in the subgroup of patients aged ≥75 years. However, after adjusting for the confounders, lower risk of the living alone group relative to the not living alone group for all-cause death was no longer significant in the subgroup of patients aged ≥75 years, although the adjusted risk for cardiac death in the living alone group remained significant. Regarding the other clinical end points, the adjusted outcomes between the living alone group and the not living alone group were not significantly different in the subgroup of patients aged ≥75 years (Table 4).

Discussion

The main findings in this study were as follows: (1) living alone was not associated with higher long-term mortality in

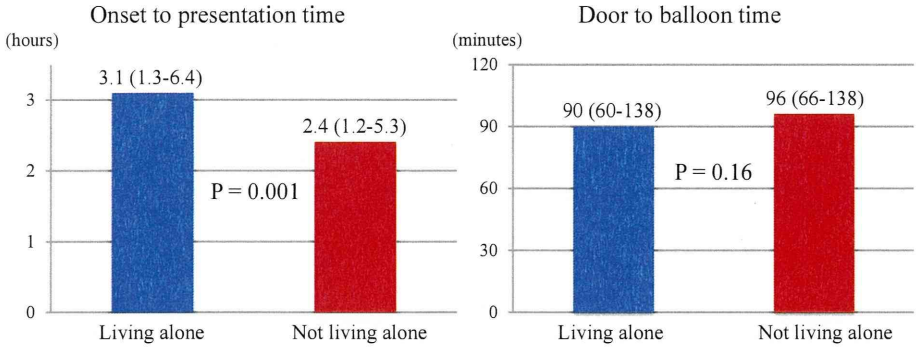
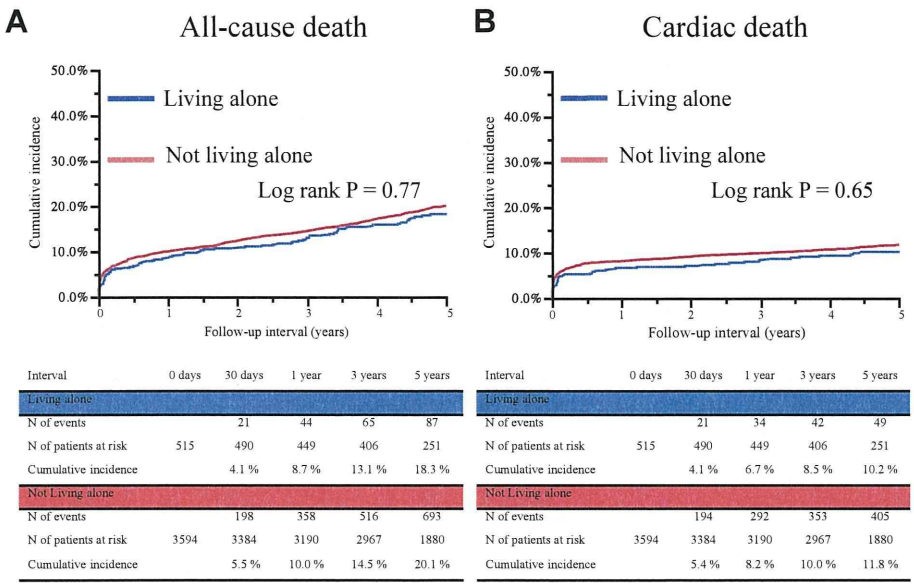


Figure 1. Onset-to-presentation time and door-to-balloon time according to living arrangements.



Interval	0 days	30 days	1 year	3 years	5 years
Living alone					
N of events		21	44	65	87
N of patients at risk	515	490	449	406	251
Cumulative incidence		4.1 %	8.7 %	13.1 %	18.3 %
Not Living alone					
N of events		198	358	516	693
N of patients at risk	3594	3384	3190	2967	1880
Cumulative incidence		5.5 %	10.0 %	14.5 %	20.1 %

Interval	0 days	30 days	1 year	3 years	5 years
Living alone					
N of events		21	34	42	49
N of patients at risk	515	490	449	406	251
Cumulative incidence		4.1 %	6.7 %	8.5 %	10.2 %
Not Living alone					
N of events		194	292	353	405
N of patients at risk	3594	3384	3190	2967	1880
Cumulative incidence		5.4 %	8.2 %	10.0 %	11.8 %

Figure 2. Clinical outcomes according to living arrangements. Cumulative incidences of all-cause death *(A)* and cardiac death *(B)* were compared between the living alone group and not living alone group.

patients with AMI who underwent PCI within 24 hours of symptom onset; (2) the risk of readmission for heart failure was also not significantly different between the living alone group and the not living alone group; and (3) these results were consistently observed regardless of patients' age.

Living alone in older patients is an important welfare issue in the rapidly aging societies. The Statistics Bureau of Japan reported that percentage of subjects living alone in Japan was 11.3% in 2005 and 13.1% in 2010 (12.5% in the present study).[16] However, little is known about the influence of living alone in older patients on the clinical outcome after AMI. In previous studies, living alone was reported to be associated with increased risk of cardiovascular disease[1–4] and poorer clinical outcomes after AMI.[5–10] However, most studies enrolled not only patients receiving primary PCI but also those with lytic therapy or those not receiving reperfusion therapy. Moreover, some of the recent studies reported no significant association between living alone and mortality after AMI.[11,12] Therefore, the association between living alone and long-term mortality after AMI in patients with PCI is controversial in the current real-world clinical practice.

In contrast to many previous reports, living alone was not associated with higher long-term mortality in patients with AMI who underwent PCI within 24 hours of symptom onset in the present study. One of the possible reasons for this discrepancy might be the difference in the baseline characteristics of the enrolled patients. The average of patients' age in the present study was much higher than those in other studies, and all the patients in the present study received PCI in the AMI setting. In older populations, patients living alone might be more likely to have good functional status, which has been reported to be a powerful predictor of survival in older subjects.[17–19] Another possible reason for the discrepancy between the present and previous studies might be the health insurance system in Japan, where public health insurance system covers everyone. Previous studies reported that patients living alone tended to have a higher unemployment rate and lower incomes,[3,8,11,20] and other studies also reported that lower income patients were less likely to receive primary PCI.[21,22] Indeed, the recent study evaluating living arrangement and mortality after AMI in Japan also reported no significant difference in long-term mortality between the living alone and not living alone patients.[23]

Table 4
Clinical outcomes in patients living alone compared with patients not living alone

Variable	Living Alone	Not Living Alone	Unadjusted		p Value	Adjusted		p Value
	N of Patients With Events	N of Patients With Events	Living Alone			Living Alone		
	(Cumulative Incidence)	(Cumulative Incidence)	HR	95% CI		HR	95% CI	
	(n = 515)	(n = 3594)						
All-cause death	87 (18%)	693 (20%)	0.97	(0.79–1.19)	0.77	0.82	(0.65–1.02)	0.08
Cardiac death	49 (10%)	405 (12%)	0.94	(0.70–1.23)	0.65	0.78	(0.57–1.04)	0.10
Myocardial infarction	26 (6.0%)	167 (5.3%)	1.11	(0.73–1.62)	0.62	0.99	(0.63–1.48)	0.95
Stroke	27 (6.0%)	204 (6.5%)	0.94	(0.62–1.35)	0.73	0.96	(0.63–1.41)	0.82
Readmission for heart failure	59 (14%)	262 (8.4%)	1.55	(1.16–2.04)	0.004	1.22	(0.88–1.65)	0.22
Any coronary revascularization	173 (38%)	1204 (38%)	1.00	(0.86–1.17)	0.99	1.11	(0.93–1.30)	0.24
Patients <75 years of age	(n = 319)	(n = 2497)						
All-cause death	33 (11%)	255 (11%)	1.11	(0.79–1.53)	0.53	0.75	(0.50–1.09)	0.13
Cardiac death	22 (7.2%)	156 (6.4%)	1.23	(0.80–1.82)	0.34	0.91	(0.55–1.43)	0.68
Myocardial infarction	13 (4.7%)	102 (4.4%)	1.07	(0.60–1.77)	0.81	1.05	(0.57–1.79)	0.88
Stroke	12 (4.2%)	108 (4.7%)	0.69	(0.48–1.52)	0.69	0.92	(0.48–1.61)	0.78
Readmission for heart failure	21 (7.2%)	111 (4.9%)	1.44	(0.88–2.23)	0.14	1.01	(0.59–1.66)	0.96
Any coronary revascularization	119 (41%)	918 (39%)	0.80	(0.84–1.23)	0.80	1.12	(0.91–1.36)	0.28
Patients ≥75 years of age	(n = 196)	(n = 1097)						
All-cause death	54 (30%)	438 (42%)	0.71	(0.54–0.92)	0.009	0.79	(0.59–1.04)	0.10
Cardiac death	27 (16%)	249 (25%)	0.64	(0.43–0.91)	0.01	0.65	(0.42–0.97)	0.04
Myocardial infarction	13 (8.2%)	65 (8.0%)	1.04	(0.55–1.82)	0.89	0.87	(0.43–1.62)	0.67
Stroke	15 (9.3%)	96 (12%)	0.82	(0.47–1.35)	0.45	0.96	(0.53–1.63)	0.87
Readmission for heart failure	38 (26%)	151 (18%)	1.32	(0.92–1.86)	0.13	1.29	(0.84–1.92)	0.24
Any coronary revascularization	54 (33%)	286 (33%)	1.00	(0.74–1.33)	0.98	1.12	(0.80–1.53)	0.49

Cumulative incidence was estimated by the Kaplan-Meier method.
Unadjusted and adjusted HR and 95% CI were estimated by the Cox proportional hazard models.
CI = confidence interval; HR = hazard ratio.

As mentioned before, older patients living alone might be more likely to have good functional status, which was a powerful predictor of survival in older subjects. In contrast, patients living alone might have difficulties in receiving social support. These 2 factors might have directionally opposite impact on the relation between living arrangement and clinical outcome after AMI.[19] Furthermore, the present study and previous studies could not evaluate the patients living alone who suffered from AMI and died before hospital arrival. Indeed, the time from symptom onset to arrival at the hospital was much longer in patients living alone than in patients not living alone in the present study. Total ischemic time was reported to be an important factor associated with long-term mortality in patients with ST-segment elevation AMI undergoing primary PCI.[13] In this point of view, it would be important to reinforce the social welfare system to support the patients living alone in emerging setting.

This study has several limitations. First, observational study design precluded definitive conclusions because of selection bias and unmeasured confounders. Second, we did not collect data on the changes in living arrangements after discharge from the index hospitalization, as well as functional, psychological, educational, and socioeconomic status, although those factors might be powerful predictors of mortality after AMI. Therefore, future well-conducted prospective studies in which those data are corrected will be desired. Third, practice style in Japan, such as longer length of hospital stay after AMI, is different from other countries.[24] Finally, patient demographics and clinical outcomes in patients with AMI living alone in Japan may be also different from those outside Japan. Therefore, generalizing these results to populations outside Japan should be done with caution.

Acknowledgment: We appreciate the assistance of the coinvestigators at the Coronary REvascularization Demonstrating Outcome Study in Kyoto AMI registry.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2014.05.029.

1. Capewell S, MacIntyre K, Stewart S, Chalmers JW, Boyd J, Finlayson A, Redpath A, Pell JP, McMurray JJ. Age, sex, and social trends in out-of-hospital cardiac deaths in Scotland 1986-95: a retrospective cohort study. *Lancet* 2001;358:1213–1217.
2. Udell JA, Steg PG, Scirica BM, Smith SC Jr, Ohman EM, Eagle KA, Goto S, Cho JI, Bhatt DL. Living alone and cardiovascular risk in outpatients at risk of or with atherothrombosis. *Arch Intern Med* 2012;172:1086–1095.
3. Wang H, Chen K, Pan Y, Jing F, Liu H. Associations and impact factors between living arrangements and functional disability among older Chinese adults. *PloS One* 2013;8:e53879.

4. Nielsen KM, Faergeman O, Larsen ML, Foldspang A. Danish singles have a twofold risk of acute coronary syndrome: data from a cohort of 138 290 persons. *J Epidemiol Community Health* 2006;60:721–728.
5. Case RB, Moss AJ, Case N, McDermott M, Eberly S. Living alone after myocardial infarction. *JAMA* 1992;267:515–519.
6. Schmaltz HN, Southern D, Ghali WA, Jelinski SE, Parsons GA, King KM, Maxwell CJ. Living alone, patient sex and mortality after acute myocardial infarction. *J Gen Intern Med* 2007;22:572–578.
7. Norekvål TM, Fridlund B, Rokne B, Segadal L, Wentzel-Larsen T, Nordrehaug JE. Patient-reported outcomes as predictors of 10-year survival in women after acute myocardial infarction. *Health Qual Life Outcomes* 2010;8:140.
8. Nielsen FE, Mard S. Single-living is associated with increased risk of long-term mortality among employed patients with acute myocardial infarction. *Clin Epidemiol* 2010;2:91–918.
9. Green P, Newman JD, Shaffer JA, Davidson KW, Maurer MS, Schwartz JE. Relation of patients living without a partner or spouse to being physically active after acute coronary syndromes (from the PULSE accelerometry substudy). *Am J Cardiol* 2013;111:1264–1269.
10. Lammintausta A, Airaksinen JK, Immonen-Räihä P, Torppa J, Kesäniemi AY, Ketonen M, Koukkunen H, Kärjä-Koskenkari P, Lehto S, Salomaa V. Prognosis of acute coronary events is worse in patients living alone: the FINAMI myocardial infarction register. *Eur J Prev Cardiol* Published Online First: 30 January 2013. http://dx.doi.org/10.1177/2047487313475893.
11. Bucholz EM, Rathore SS, Gosch K, Schoenfeld A, Jones PG, Buchanan DM, Spertus JA, Krumholz HM. Effect of living alone on patient outcomes after hospitalization for acute myocardial infarction. *Am J Cardiol* 2011;108:943–948.
12. O'Shea JC, Wilcox RG, Skene AM, Stebbins AL, Granger CB, Armstrong PW, Bode C, Ardissino D, Emanuelsson H, Aylward PE, White HD, Sadowski Z, Topol EJ, Califf RM, Ohman EM. Comparison of outcomes of patients with myocardial infarction when living alone versus those not living alone. *Am J Cardiol* 2002;90:1374–1377.
13. Shiomi H, Nakagawa Y, Morimoto T, Furukawa Y, Nakano A, Shirai S, Taniguchi R, Yamaji K, Nagao K, Suyama T, Mitsuoka H, Araki M, Takashima H, Mizoguchi T, Eisawa H, Sugiyama S, Kimura T. Association of onset to balloon and door to balloon time with long term clinical outcome in patients with ST elevation acute myocardial infarction having primary percutaneous coronary intervention: observational study. *BMJ* 2012;344:e3257.
14. Kimura T, Morimoto T, Furukawa Y, Nakagawa Y, Kadota K, Iwabuchi M, Shizuta S, Shiomi H, Tada T, Tazaki J, Kato Y, Hayano M, Abe M, Tamura T, Shirotani M, Miki S, Matsuda M, Takahashi M, Ishii K, Tanaka M, Aoyama T, Doi O, Hattori R, Tatami R, Suwa S, Takizawa A, Takatsu Y, Takahashi M, Kato H, Takeda T, Lee JD, Nohara R, Ogawa H, Tei C, Horie M, Kambara H, Fujiwara H, Mitsudo K, Nobuyoshi M, Kita T. Long-term safety and efficacy of sirolimus-eluting stents versus bare-metal stents in real world clinical practice in Japan. *Cardiovasc Interv Ther* 2011;26:234–245.
15. Serruys PW, Ong AT, van Herwerden LA, Sousa JE, Jatene A, Bonnier JJ, Schönberger JP, Buller N, Bonser R, Disco C, Backx B, Hugenholtz PG, Firth BG, Unger F. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol* 2005;46:575–581.
16. "Statistical Handbook of Japan 2013" by Statistics Bureau, Japan. Available at: *http://www.stat.go.jp/english/data/handbook/index.htm*. Accessed on April 11, 2014.
17. Singh M, Rihal CS, Lennon RJ, Spertus JA, Nair KS, Roger VL. Influence of frailty and health status on outcomes in patients with coronary disease undergoing percutaneous revascularization. *Circ Cardiovasc Qual Outcomes* 2011;4:496–502.
18. Sarwari AR, Fredman L, Langenberg P, Magaziner J. Prospective study on the relation between living arrangement and change in functional health status of elderly women. *Am J Epidemiol* 1998;147:370–378.
19. Gopinath B, Rochtchina E, Anstey KJ, Mitchell P. Living alone and risk of mortality in older, community-dwelling adults. *JAMA Intern Med* 2013;173:320–321.
20. Nihtila E, Martikainen P. Why older people living with a spouse are less likely to be institutionalized: the role of socioeconomic factors and health characteristics. *Scand J Public Health* 2008;36:35–43.
21. Casale SN, Auster CJ, Wolf F, Pei Y, Devereux RB. Ethnicity and socioeconomic status influence use of primary angioplasty in patients presenting with acute myocardial infarction. *Am Heart J* 2007;154:989–993.
22. Rosvall M, Chaix B, Lynch J, Lindström M, Merlo J. The association between socioeconomic position, use of revascularization procedures and five-year survival after recovery from acute myocardial infarction. *BMC Public Health* 2008;8:44.
23. Kitamura T, Sakata Y, Nakatani D, Suna S, Usami M, Matsumoto S, Hara M, Hamasaki T, Nanto S, Sato H, Hori M, Iso H, Komuro I. Living alone and risk of cardiovascular events following discharge after acute myocardial infarction in Japan. *J Cardiol* 2013;62:257–262.
24. Kinjo K, Sato H, Nakatani D, Mizuno H, Shimizu M, Hishida E, Ezumi A, Hoshida S, Koretsune Y, Hori M. Predictors of length of hospital stay after acute myocardial infarction in Japan. *Circ J* 2004;68:809–815.

Effect of Preinfarction Angina Pectoris on Long-term Survival in Patients With ST-Segment Elevation Myocardial Infarction Who Underwent Primary Percutaneous Coronary Intervention

Tomohiko Taniguchi, MD[a], Hiroki Shiomi, MD[a,*], Toshiaki Toyota, MD[a], Takeshi Morimoto, MD, MPH[b], Masaharu Akao, MD[c], Kenji Nakatsuma, MD[a], Koh Ono, MD[a], Takeru Makiyama, MD[a], Satoshi Shizuta, MD[a], Yutaka Furukawa, MD[d], Yoshihisa Nakagawa, MD[e], Kenji Ando, MD[f], Kazushige Kadota, MD[g], Minoru Horie, MD[h], and Takeshi Kimura, MD[a]

The influence of preinfarction angina pectoris (AP) on long-term clinical outcomes in patients with ST-segment elevation myocardial infarction (STEMI) who underwent primary percutaneous coronary intervention (PCI) remains controversial. In 5,429 patients with acute myocardial infarction (AMI) enrolled in the Coronary Revascularization Demonstrating Outcome Study in Kyoto AMI Registry, the present study population consisted of 3,476 patients with STEMI who underwent primary PCI within 24 hours of symptom onset and in whom the data on preinfarction AP were available. Preinfarction AP defined as AP occurring within 48 hours of hospital arrival was present in 675 patients (19.4%). Patients with preinfarction AP was younger and more often had anterior AMI and longer total ischemic time, whereas they less often had history of heart failure, atrial fibrillation, and shock presentation. The infarct size estimated by peak creatinine phosphokinase was significantly smaller in patients with than in patients without preinfarction AP (median [interquartile range] 2,141 [965 to 3,867] IU/L vs 2,462 [1,257 to 4,495] IU/L, p <0.001). The cumulative 5-year incidence of death was significantly lower in patients with preinfarction AP (12.4% vs 20.7%, p <0.001) with median follow-up interval of 1,845 days. After adjusting for confounders, preinfarction AP was independently associated with a lower risk for death (hazard ratio 0.69, 95% confidence interval 0.54 to 0.86, p = 0.001). The lower risk for 5-year mortality in patients with preinfarction AP was consistently observed across subgroups stratified by total ischemic time, initial Thrombolysis In Myocardial Infarction flow grade, hemodynamic status, infarct location, and diabetes mellitus. In conclusion, preinfarction AP was independently associated with lower 5-year mortality in patients with STEMI who underwent primary PCI. **(Am J Cardiol 2014;114:1179–1186)**

Preinfarction angina pectoris (AP) before the onset of ST-segment elevation myocardial infarction (STEMI) was reported to be associated with limited infarct size and improved clinical outcomes in patients with STEMI in the thrombolytic era in accordance with the previous experimental studies reporting the protective effect of brief episodes of ischemia before coronary occlusion on infarct size.[1–12] The prevalence of preinfarction AP in previous studies, however, varies widely from 11% to 69% according to the definitions of preinfarction AP.[10,13] Furthermore, the cardioprotective effects of preinfarction AP in patients with STEMI are still controversial in the primary percutaneous coronary intervention (PCI) era. The clinical significance of preinfarction AP was evaluated in several relatively small studies, and most of those studies evaluated infarct size instead of mortality with discordant results in those studies.[9,13,14] Therefore, we sought to assess the clinical significance of preinfarction AP on long-term mortality of patients with STEMI who underwent primary PCI in a large, multicenter acute myocardial infarction (AMI) registry in Japan.

Methods

The Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) AMI registry is a

[a]Department of Cardiovascular Medicine, Kyoto University, Shogoin, Sakyo-ku, Kyoto, Japan; [b]Division of General Medicine, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan; [c]Department of Cardiology, National Hospital Organization Kyoto Medical Center, Fushimi-ku, Kyoto, Japan; [d]Division of Cardiology, Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan; [e]Division of Cardiology, Tenri Hospital, Tenri, Nara, Japan; [f]Department of Cardiology, Kokura Memorial Hospital, Kitakyushu, Japan; [g]Department of Cardiology, Kurashiki Central Hospital, Kurashiki, Okayama, Japan; and [h]Department of Cardiovascular and Respiratory Medicine, Shiga University of Medical Science, Otsu, Shiga, Japan. Manuscript received May 22, 2014; revised manuscript received and accepted July 9, 2014.

This study was supported by the Ministry of Health, Labour and Welfare and the Pharmaceuticals and Medical Devices Agency in Japan.

See page 1185 for disclosure information.

*Corresponding author: Tel: (+81) 75-751-4255; fax: (+81) 75-751-3299.

E-mail address: hishiomi@kuhp.kyoto-u.ac.jp (H. Shiomi).

0002-9149/14/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2014.07.038

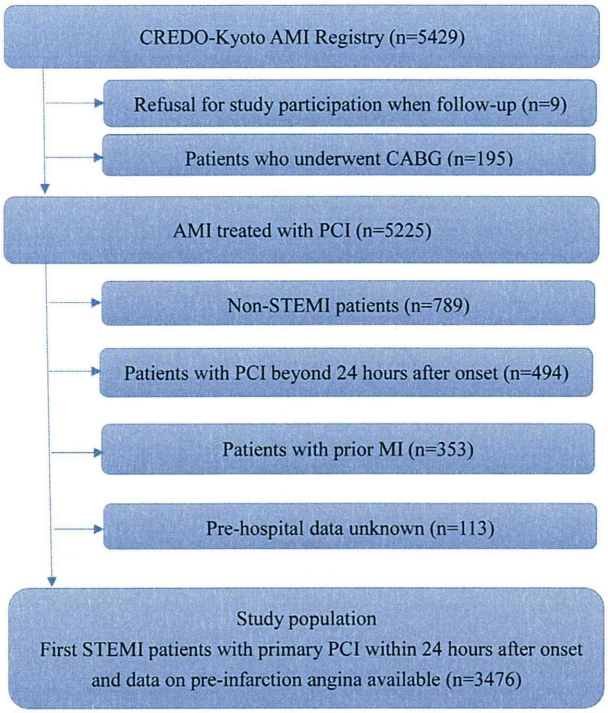


Figure 1. Study flow chart. CABG = coronary artery bypass grafting.

physician-initiated, non–company-sponsored multicenter registry that enrolled consecutive patients with AMI having coronary revascularization within 7 days of the onset of symptoms from January 2005 to December 2007 across 26 tertiary hospitals in Japan (Supplementary Appendix A).[15] The relevant review boards or ethics committees in all 26 participating centers approved the study protocol. Obtaining written informed consent from the patients was waived because of the retrospective study design. In 5,429 patients enrolled in the CREDO-Kyoto AMI registry, 9 patients were excluded because of their refusal to participate in the study when contacted at follow-up. We also excluded 195 patients who had coronary artery bypass grafting surgery, 789 patients with non-STEMI, 494 patients who received PCI beyond 24 hours after onset, 353 patients with previous myocardial infarction (MI), and 113 patients in whom data on the presence or absence of preinfarction AP were not available because their clinical histories before the onset of STEMI were not found in their charts or database (Figure 1). We excluded patients with previous MI because previous studies have reported that cardioprotective mechanism of ischemic preconditioning is impaired in patients with post-infarct left ventricular remodeling.[16,17] Therefore, the study population for the current analysis consisted of 3,476 patients with first STEMI who had primary PCI within 24 hours of onset and in whom data on the presence or absence of preinfarction AP were available.

Experienced clinical research coordinators in the 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 (Supplementary Appendix B).[18] They also collected data about symptoms within 48 hours before hospital arrival from the hospital charts or hospital databases.

Collection of follow-up information was mainly conducted 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, subsequent hospitalizations, and status of antiplatelet therapy. Serious adverse events, such as death, MI, stent thrombosis, and stroke, were adjudicated by the clinical event committee (Supplementary Appendix C). The median length of follow-up in this study was 1,845 (interquartile range [IQR]: 1,517 to 2,155) days.

Preinfarction AP was defined as typical AP, chest discomfort, or radiating pain persisting <30 minutes within 48 hours of hospital arrival for the index STEMI. Atypical chest pain or dyspnea was not included in preinfarction AP because it was difficult to assess whether those symptoms were representing myocardial ischemia. Those patients whose symptoms of preinfarction AP were not described in their charts or database despite available clinical information before hospital arrival were regarded as those without preinfarction AP. The detailed definitions of other baseline clinical characteristics were described previously.[15,18]

The primary outcome measure for this analysis was all-cause death. Death was regarded as cardiac in origin unless obvious noncardiac causes could be identified. Any death during the index hospitalization for AMI was regarded as cardiac death. As the secondary outcome measure, recurrent MI was also evaluated. MI was defined according to the definition in the Arterial Revascularization Therapy Study.[19]

We present continuous variables as the mean and SD or median and IQR and categorical variables as numbers and percentages. We compared continuous variables with the Student's *t* test or a Wilcoxon rank-sum test on the basis of the distributions. We compared categorical variables with the chi-square test when appropriate; otherwise, we used the Fisher's exact test. A multivariable logistic regression model was used to identify independent predictors of preinfarction AP.

We used the Kaplan-Meier method to estimate the cumulative incidences of clinical event and assessed the differences with the log-rank test. The effects of preinfarction AP for the primary outcome measure were expressed as hazard ratios with 95% confidence intervals by multivariable Cox proportional hazard models adjusting for the 36 clinically relevant factors indicated in Table 1. We did not use hemodynamic status, infarct size, and total ischemic time as covariates in the multivariable models because these factors could potentially be affected by the presence of preinfarction AP. We also computed the adjusted cumulative incidence curves of patients with and without preinfarction AP using a multivariable Cox proportional hazards model in conjunction with the methods described by Ghali et al.[20] Consistent with our previous reports, continuous variables were dichotomized using clinically meaningful reference values or median values. We also evaluated the effects of preinfarction AP on the primary outcome measure in several subgroups stratified by total ischemic

Table 1
Baseline characteristics of patients with and without preinfarction angina pectoris

Variable	Pre-infarction Angina Pectoris		p Value
	Yes (N = 675)	No (N = 2801)	
Age (years ± SD)	66.1 ± 11.7	67.5 ± 12.4	0.008
Age ≥ 75 years*	174 (26%)	866 (31%)	0.009
Male*	492 (73%)	2036 (73%)	0.92
Body mass index† (mean ± SD)	23.5 ± 3.4	23.7 ± 3.5	0.26
Body mass index <25 kg/m^2*	485 (72%)	2010 (72%)	0.96
Hypertension*	539 (80%)	2163 (77%)	0.14
Diabetes mellitus	196 (29%)	878 (31%)	0.24
On insulin therapy*	24 (3.6%)	120 (4.3%)	0.39
Current smoker*	290 (43%)	1145 (41%)	0.32
Prior heart failure*	4 (0.6%)	53 (1.9%)	0.02
Severe mitral regurgitation*	8 (1.2%)	79 (2.8%)	0.01
Prior stroke (symptomatic)*	53 (7.9%)	242 (8.6%)	0.51
Peripheral vascular disease*	17 (2.5%)	85 (3.0%)	0.48
eGFR‡ <30 ml/min/1.73 m^2, without dialysis*	18 (2.7%)	122 (4.4%)	0.045
Hemodialysis*	9 (1.3%)	39 (1.4%)	0.91
Atrial fibrillation*	40 (5.9%)	277 (9.9%)	0.001
Anemia (Hb < 11.0 g/dl)*	60 (8.9%)	260 (9.3%)	0.75
Thrombocytopenia (PLT <10*10^4)*	9 (1.3%)	54 (1.9%)	0.30
COPD*	30 (4.4%)	83 (3.0%)	0.051
Liver cirrhosis*	17 (2.5%)	65 (2.3%)	0.76
Malignancy*	48 (7.1%)	220 (7.9%)	0.52
Hours from onset to presentation	3.1 (1.3–7.4)	2.3 (1.1–4.9)	<0.001
Hours from onset to balloon	4.9 (3.1–9.1)	4.1 (2.8–6.9)	<0.001
≤3 hours from onset to balloon	145/595 (24%)	728/2460 (30%)	0.01
Minutes from door to balloon	90 (60–132)	90 (60–132)	0.66
Hemodynamics			
Killip class 1	567 (84%)	2061 (74%)	<0.001
Killip class 2	48 (7.1%)	227 (8.1%)	
Killip class 3	7 (1.0%)	79 (2.8%)	<0.001
Killip class 4 (cardiogenic shock)	53 (7.9%)	434 (15%)	<0.001
Killip class 2–4	108 (16%)	740 (26%)	
Location of MI			
Anterior wall	363 (54%)	1320 (47%)	<0.001
Inferior wall	224 (33%)	1161 (41%)	
Lateral wall	16 (2.4%)	86 (3.1%)	<0.001
Posterior wall	72 (11%)	234 (8.4%)	0.006
TIMI flow grade 0	367 (54%)	1687 (60%)	
Multivessel disease*	322 (48%)	1387 (50%)	0.40
Target of proximal LAD*	419 (62%)	1513 (54%)	<0.001
Target of unprotected LMCA*	24 (3.6%)	97 (3.5%)	0.91
Target of CTO*	14 (2.1%)	91 (3.3%)	0.11
Target of bifurcation*	197 (29%)	723 (26%)	0.07
Side-branch stenting*	22 (3.3%)	87 (3.1%)	0.84
Total stent length >28 mm*	272 (42%)	1082 (42%)	0.97
Minimum stent size <3.0 mm*	220 (34%)	799 (31%)	0.16
Medications at discharge			
Thienopyridine	657 (97%)	2663 (95%)	0.01
Aspirin	670 (99%)	2749 (98%)	0.04
Cilostazole*	254 (38%)	969 (35%)	0.14
Statin*	374 (55%)	1487 (53%)	0.28
Beta-blockers*	282 (42%)	1181 (42%)	0.86
ACE-I/ARB*	515 (76%)	2011 (72%)	0.02
Nitrates*	255 (38%)	780 (28%)	<0.001
Calcium channel blockers*	125 (19%)	550 (20%)	0.51
Nicorandil*	196 (29%)	777 (28%)	0.50
Warfarin*	62 (9.2%)	309 (11%)	0.16
Proton pump inhibitors*	242 (36%)	955 (34%)	0.39
H2-blockers*	235 (35%)	910 (32%)	0.25

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blockers; COPD = chronic obstructive pulmonary disease; CTO = chronic total occlusion; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; IQR = interquartile range; LAD = left anterior descending artery; LMCA = left main coronary artery; PLT = platelet; SD = standard deviation; TIMI = Thrombolysis In Myocardial Infarction.

* Potential independent variables selected for Cox proportional hazard models.

† Body mass index was calculated as weight in kilograms divided by height in meters squared.

‡ eGFR was calculated by the Modification of Diet in Renal Disease formula modified for Japanese patients.

Table 2
Predictors of preinfarction angina pectoris, univariate and multivariate analysis

Variable	Univariate Analysis				Multivariate Analysis		
	Pre-infarction Angina Pectoris		OR	p Value	OR	95% CI	p Value
	Yes (N = 675)	No (N = 2801)					
Age ≥ 75 years	174 (26%)	866 (31%)	0.78	0.008	0.86	0.71–1.04	0.13
Prior heart failure	4 (0.6%)	53 (1.9%)	0.31	0.008	0.42	0.13–1.04	0.06
Severe mitral regurgitation	8 (1.2%)	79 (2.8%)	0.41	0.008	0.51	0.22–1.01	0.053
eGFR* <30 ml/min/1.73 m^2, without dialysis	18 (2.7%)	122 (4.4%)	0.60	0.04	0.71	0.42–1.16	0.18
Atrial fibrillation	40 (5.9%)	277 (9.9%)	0.57	<0.001	0.65	0.46–0.93	0.01
Anterior wall MI	419 (62%)	1513 (54%)	1.39	<0.001	1.35	1.13–1.60	<0.001

CI = confidence interval; MI = myocardial infarction; OR = odds ratio.
* eGFR was calculated by the Modification of Diet in Renal Disease formula modified for Japanese patients.

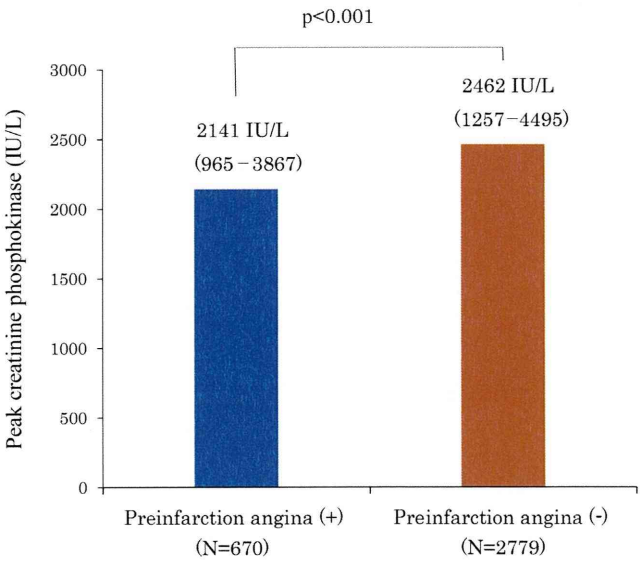


Figure 2. Peak creatinine phosphokinase value according to preinfarction AP. Data were presented as median (IQR). IQR = interquartile range.

time (≤3 hours, 3 to 6 hours, or 6 to 24 hours), Thrombolysis In Myocardial Infarction (TIMI) flow grade (0 or ≥1), hemodynamic status (Killip class I or Killip class II to IV), infarct location (anterior MI or nonanterior MI), and diabetes mellitus (diabetes mellitus or non-diabetes mellitus). For the subgroup analyses, we also developed the Cox proportional hazard models incorporating the same risk adjusting variables to estimate the effect of preinfarction AP for the primary outcome measure.

All statistical analyses were conducted using JMP, version 10.0.2 (SAS Institute Inc., Cary, North Carolina) or SAS, version 9.3 (SAS Institute Inc.). All reported p values were 2 tailed, and p values <0.05 were considered statistically significant.

Results

In the 3,476 patients with STEMI who underwent primary PCI, preinfarction AP within 48 hours of hospital arrival was present in 675 patients (19.4%). Baseline characteristics were significantly different in several aspects between the 2 groups of patients with or without preinfarction AP (Table 1). Independent predictors for preinfarction AP identified by a multivariate logistic regression model included anterior MI and absence of atrial fibrillation (Table 2).

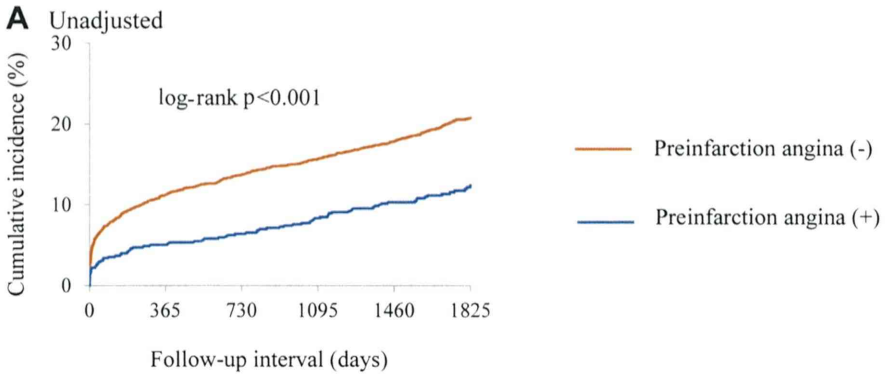
Regarding clinical presentation of STEMI, onset-to-admission time and total ischemic time as represented by onset-to-balloon time were significantly longer in patients with preinfarction AP, whereas door-to-balloon time was not different between the 2 groups. The prevalence of hemodynamic compromise as represented by Killip class II to IV was significantly lower in patients with preinfarction AP than in those without preinfarction AP (Table 1).

Regarding medications at hospital discharge, antiplatelet agents, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and nitrates were more often prescribed in patients with preinfarction AP than in those without preinfarction AP.

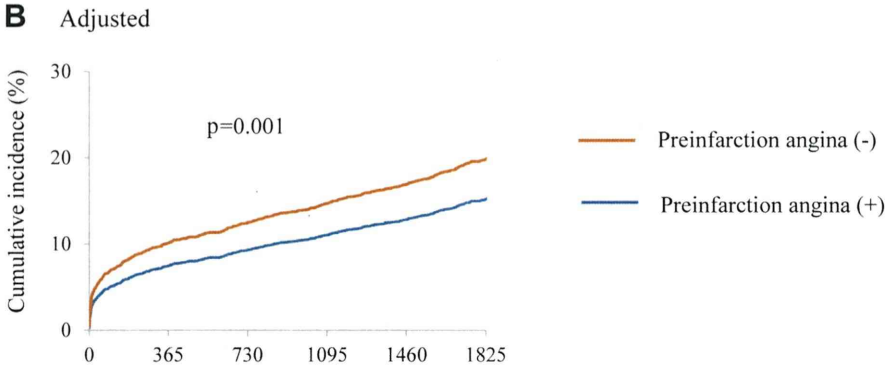
The infarct size estimated by peak creatinine phosphokinase (CPK) value was evaluated in the vast majority of patients (3,449 patients [99.2%]). The peak CPK value was significantly smaller in patients with preinfarction AP than in patients without preinfarction AP (median peak CPK [IQR]: 2,141 [965 to 3,867] IU/L vs 2,462 [1,1257 to 4,495] IU/L, p <0.001; Figure 2).

The cumulative 5-year incidence of all-cause death was significantly lower in patients with preinfarction AP than in patients without preinfarction AP (12.4% vs 20.7%, p <0.001; Figure 3). After adjusting for confounders, preinfarction AP was independently associated with a lower risk for all-cause death (adjusted hazard ratio 0.69, 95% confidence interval 0.54 to 0.86, p = 0.001; Figure 3).

The lower risk for 5-year mortality in patients with preinfarction AP was consistently observed across subgroups stratified by total ischemic time, initial TIMI flow grade, hemodynamic status, infarct location, and diabetes mellitus. There was no significant interaction between the subgroup factors and the effect of preinfarction AP on 5-year mortality in any of the subgroups evaluated (Figure 4). It was noteworthy that the 5-year mortality in patients with preinfarction AP was not affected by the total ischemic time (Figure 5).



Interval	0	30 days	1 year	3 years	5 years
Preinfarction angina (-)					
N. of patients with event		165	311	432	554
N. of patients at risk	2801	2622	2435	2247	1400
Cumulative incidence		6.0 %	11.2 %	15.6 %	20.7 %
Preinfarction angina (+)					
N. of patients with event		16	34	56	79
N. of patients at risk	675	657	638	606	402
Cumulative incidence		2.4 %	5.1 %	8.4 %	12.4 %



Interval	0	30 days	1 year	3 years	5 years
Preinfarction angina (-)					
Cumulative incidence		5.0 %	10.0 %	14.6 %	19.8 %
Preinfarction angina (+)					
Cumulative incidence		3.6 %	7.4 %	11.0 %	15.2 %

Figure 3. Unadjusted Kaplan-Meier curves for cumulative incidence of all-cause death *(A)* and adjusted curve for all-cause death *(B)*.

There was no significant difference in the cumulative incidence of MI between the 2 groups of patients with and without preinfarction AP (4.6% vs 5.8%, p = 0.21).

Discussion

The main findings of the present study are as follows: (1) the prevalence of preinfarction AP was 19.4% in a large, real-world consecutive series of patients with STEMI who underwent primary PCI within 24 hours of symptom onset; (2) the presence of preinfarction AP was independently associated with a lower risk for 5-year mortality; (3) the lower risk for 5-year mortality in patients with preinfarction AP was consistently observed across subgroups stratified by total ischemic time, initial TIMI flow grade, hemodynamic status, infarct location, and diabetes mellitus.

Murry et al[11] reported that brief, nonlethal episodes of myocardial ischemia paradoxically preconditioned the heart and profoundly reduced infarct size, proposing the concept named "preconditioning effect." Several mechanisms, such as accelerated thrombolysis,[3] reduced microvascular obstruction,[21] and opening of preexisting collateral channels,[22] have been proposed to explain the cardioprotective effects. After this report, many studies reported that