Impact of Age on Gender Difference in Long-term Outcome of Patients With Acute Myocardial Infarction (from J-MINUET)

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Although gender difference in long-term outcomes after acute myocardial infarction have been shown previously, impact of age on gender difference is still controversial. This study focused on the association between age and gender difference in long-term outcome. We analyzed data from 3,283 consecutive patients who were included in a prospective, nationwide, multicenter registry (Japan Registry of Acute Myocardial Infarction Diagnosed by Universal Definition) from 2012 to 2014. The primary end point was the major adverse cardiovascular event (MACE), which was defined as a composite of death, myocardial infarction, stroke, heart failure, and revascularization for unstable angina during 3 years. Patients were divided into 4 strata according to age: those with age <65 years (group 1: n = 1161), 65 to 74 years (group 2: n = 954), 75 to 84 years (group 3: n = 866) and 84< years (group 4: n = 302). Although the crude incidence of 3-year MACE was significantly higher in women than men (36.4% vs. 28.5%, p <0.001), there was not significant gender difference in each group (group 1, 19.6% vs 19.0%, p = 0.74; group 2, 33.1% vs 28.3%, p = 0.25; group 3,

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38.9% vs 39.6%, p = 0.54; and group 4, 54.0% vs 56.8%, p = 0.24). In conclusion, although women had higher crude incidence of 3-year MACE than men, there was no gender difference in each group. **(Am J Cardiol 2021;142:5−13)**

Previous studies have consistently reported that women patients with acute myocardial infarction (MI) had worse outcomes than men.[1-8] Women patients have advanced age, more complex baseline characteristics, more atypical symptom and less opportunity to receive optimal management. Among these factors, advanced age is an important predictor for outcomes. The J-MINUET (Japan Registry of Acute Myocardial Infarction Diagnosed by Universal Definition) is a registry that included 3283 patients with acute MI who received contemporary management. To assess whether gender could affect outcomes after MI independent from age, we stratified these patients into 4 groups according to their age and compared outcomes between men and women in each group.

Methods

The J-MINUET is a prospective, observational multicenter registry of Japanese patients hospitalized for acute MI (UMIN000010037). A total of 3,283 consecutive patients who were admitted at 28 Japanese medical institutions within 48 hours of the onset of MI were enrolled between July 2012 and March 2014. The study protocol has been previously reported.[9] In brief, diagnosis of MI was based on the ESC and/or ACC Foundation and/or AHA and/or World Heart Federation Task Force for the Universal Definition of Myocardial Infarction.[10] Only type 1 (spontaneous MI related to ischemia due to primary coronary event) and type 2 (MI secondary to ischemia because of either increased oxygen demand or decreased supply) were included in this registry. Type of cTn measured (cTnT or cTnI) depended on the attending physician, and the cutoff value of each institution was applied. In patients in whom creatine kinase (CK) was elevated more than twice the upper limit of normal, cTn measurement might not be required. Frequency and time interval data of cTn and CK measurements were not prespecified but left to the physicians' decision.

Patients were evaluated at baseline for demographic and clinical characteristics. Clinical follow-up after the index MI was performed through a review of medical records, telephone contact and mailed questionnaire. The primary end point in the present study was the major adverse cardiovascular event (MACE), defined as a composite of death, MI, stroke, heart failure, and revascularization for unstable angina.

Patients were divided into 4 strata according to age: those with age <65 years (group 1), 65 to 74 years (group 2), 75 to 84 years (group 3) and 84< years (group 4).

This study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained for all patients. The protocol was approved by the ethics committees of each participating institution.

All continuous variables are expressed as median (25th to 75th percentiles) and unpaired *t* tests were used to compare groups. If the variables were not distributed normally, signed-rank tests were used. Noncontinuous and categorical variables are presented as percentages and were compared using the chi-square test.

Event curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox regression models were used to calculate hazards ratios (HR) for all events and 95% confidence

Table 1
Baseline characteristics

	Men	Women	p value
Variable	(n = 2470)	(n = 813)	
Follow-up duration (days)	783 (391-1001)	725 (285-981)	<0.001
Age (years)	66.6±12.3	74.5±11.8	<0.001
Hypertension	1615/2449 (66.0%)	550/808 (68.1%)	0.27
Diabetes mellitus	921/2426 (38.0%)	250/795 (31.5%)	<0.001
Dyslipidemia	1275/2440 (52.3%)	411/807 (50.9%)	0.51
Chronic kidney disease	1048/2469 (42.5%)	421/812 (51.9%)	<0.001
Current smoker	995/2392 (41.6%)	86/786 (10.9%)	<0.001
AF	130/2437 (5.3%)	65/802 (8.1%)	0.004
PAD	103/2242 (4.6%)	35/736 (4.8%)	0.86
Previous MI	328/2455 (13.4%)	67/810 (8.3%)	<0.001
Previous stroke	243/2277 (10.7%)	100/758 (13.2%)	0.058
STEMI	1737/2470 (70.3%)	525/813 (64.6%)	0.002
Type 2 MI	102/2237 (4.6%)	53/752 (7.1%)	0.008
Spasm-related MI	57/2237 (2.6%)	30/752 (4.0%)	0.042
Symptom	1877/2313 (81.2%)	566/772 (73.3%)	<0.001
Killip class ≧ 2	567/2459 (23.1%)	229/804 (28.5%)	0.002
Max CK (IU/L)	1604 (577-3394)	1129 (380-2335)	<0.001
Time from onset to door (min)	148 (66-363)	180 (80-460)	0.002

AF = atrial fibrillation; CK = creatine kinase; MI = myocardial infarction; PAD = peripheral artery disease; STEMI = ST-elevated myocardial infarction.

Table 2
Management

	Men	Women	p value
Variable	(n = 2470)	(n = 813)	
Urgent CAG	2318/2466 (94.0%)	735/813 (90.4%)	<0.001
Initial TIMI 2/3 flow	891/2303 (38.7%)	309/730 (42.3%)	0.08
Multi-vessel disease	1016/2310 (44.0%)	311/730 (42.6%)	0.51
Urgent PCI	2139/2317 (92.3%)	649/735 (88.4%)	0.001
Time from door to balloon (min)	73 (51-118)	80 (58-135)	0.09
Time from onset to balloon (min)	248 (150-504)	293 (179-645)	0.004
Final TIMI 3 flow	1957/2128 (92.0%)	590/647 (91.2%)	0.53
Prescriptions at discharge			
Antiplatelet agent	1685/2187 (77.1%)	491/698 (70.3%)	<0.001
ACE inhibitor/ARB	1727/2176 (79.4%)	543/691 (78.6%)	0.66
β-blocker	1516/2177 (69.6%)	444/689 (64.4%)	0.011
Statin	1917/2184 (87.8%)	591/701 (84.3%)	0.018

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CAG = coronary angiography; PCI = percutaneous coronary intervention; TIMI = thrombolysis in myocardial infarction.

intervals (CI). Multivariable analyses were performed using covariates established as prognostic risk factors for cardiac events. Multiple imputation was used to replace each missing value with 2 or more acceptable values, representing a distribution of possibilities of covariates.[11] The multiple imputation method has been described previously.[12] All statistical tests were 2-sided and p values <0.05 were regarded as significant. Statistical analysis was performed with JMP, version 14.0.0 (SAS Institute Inc., Cary, North Carolina).

Results

There were 2470 men (75%) and 813 women (25%). Baseline characteristics are shown in Table 1. The median age was 75 years in women and 67 years in men (p <0.001). Women had more chronic kidney disease, atrial fibrillation, type 2 MI and Killip class ≥2 than men. Spasm-related MI was also more frequent in women than men. Women had less diabetes mellitus, current smoking, previous MI and ST-elevated MI than men. Typical symptom was also less frequent in women than men. Table 2 shows management in the entire study patients. Urgent coronary angiography (CAG) and subsequent PCI were performed less frequently in women compared with men (90.4% vs 94.0%, p <0.001; and 88.4% vs 92.3%, p <0.001). The median time from symptom onset to balloon was shorter in men compared with women (248 min vs 293 min, p = 0.004). At the time of hospital discharge, prescriptions of guideline recommended drugs, including antiplatelet agents, β−blockers and statins were less frequent in women than men.

The percentage of women patients in each group stratified by age is shown in Figure 1. There was a liner increase in the prevalence of women from group 1 to group 4 (p <0.001). Table 3 shows baseline characteristics in each

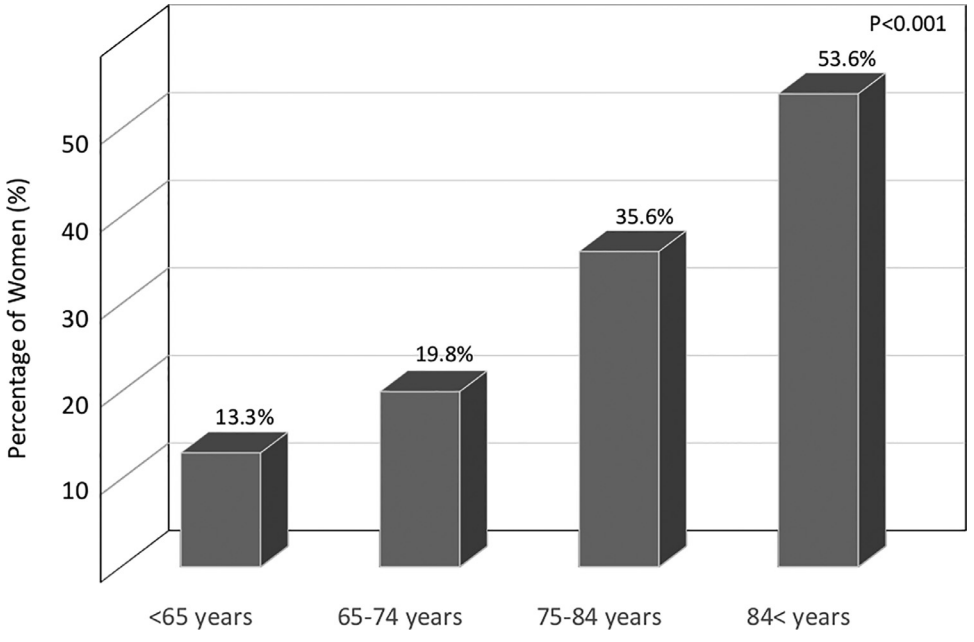

Figure 1. The percentage of women patients in each group stratified by age.

Table 3
Baseline characteristics in each group stratified by age

	<65 Years			65-74 Years			75-84 Years			84< Years		
	Men	Women	p value	Men	Women	p value	Men	Women	P value	Men	Women	P value
Variable	(n=1007)	(n=154)		(n=765)	(n=189)		(n=558)	(n=308)		(n=140)	(n=162)	
Follow-up duration (days)	803 (472-1009)	833 (455-1064)	0.23	800 (497-1012)	786 (365-1009)	0.24	746 (326-992)	707 (275-954)	0.31	533 (149-871)	382 (41-769)	0.13
Age (years)	54.6±7.7	55.9±8.5		69.4±2.9	69.6±2.6		79.0±2.8	79.7±2.9		88.1±3.5	88.3±2.9	
Hypertension	591/995 (59.4%)	93/154 (60.4%)	0.82	507/759 (66.8%)	121/189 (64.0%)	0.47	414/556 (74.5%)	220/306 (71.9%)	0.41	103/139 (74.1%)	116/159 (73.0%)	0.82
Diabetes mellitus	367/986 (37.2%)	54/150 (36.0%)	0.77	301/754 (39.9%)	65/187 (34.8%)	0.20	208/548 (38.0%)	83/301 (27.6%)	0.002	45/138 (32.6%)	48/157 (30.6%)	0.71
Dyslipidemia	562/991 (56.7%)	79/153 (51.6%)	0.24	395/756 (52.3%)	106/189 (56.1%)	0.35	261/554 (47.1%)	161/307 (52.4%)	0.13	57/139 (41.0%)	65/158 (41.1%)	0.98
Chronic kidney disease	270/1007 (26.8%)	46/154 (29.9%)	0.43	348/764 (45.6%)	81/189 (42.9%)	0.51	335/558 (60.0%)	176/307 (57.3%)	0.44	95/140 (67.9%)	118/162 (72.8%)	0.34
Current smoker	577/980 (58.9%)	40/150 (26.7%)	<0.001	275/747 (36.8%)	25/182 (13.7%)	<0.001	121/533 (22.7%)	19/298 (6.4%)	<0.001	22/132 (16.7%)	2/156 (1.3%)	<0.001
AF	20/996 (2.0%)	2/152 (1.3%)	0.76	43/758 (5.7%)	16/186 (8.6%)	0.14	51/548 (9.3%)	25/304 (8.2%)	0.60	16/135 (11.9%)	22/160 (13.8%)	0.63
PAD	12/913 (1.3%)	6/141 (4.3%)	0.012	42/692 (6.1%)	11/167 (6.6%)	0.80	41/514 (8.0%)	12/282 (4.3%)	0.044	8/123 (6.5%)	6/146 (4.1%)	0.38
Previous MI	93/1001 (9.3%)	17/153 (11.1%)	0.48	118/762 (15.5%)	11/189 (5.8%)	0.001	90/555 (16.2%)	24/307 (7.8%)	0.001	27/137 (19.7%)	15/161 (9.3%)	0.01
Previous stroke	45/924 (4.9%)	9/146 (6.2%)	0.51	73/707 (10.3%)	22/175 (12.6%)	0.39	106/521 (20.4%)	42/286 (14.7%)	0.047	19/125 (15.2%)	27/151 (17.9%)	0.55
STEMI	757/1007 (75.2%)	106/154 (68.8%)	0.093	549/765 (71.8%)	121/189 (64.0%)	0.037	343/558 (61.5%)	200/308 (64.9%)	0.31	88/140 (62.9%)	98/162 (60.5%)	0.67
Type 2 MI	47/908 (5.2%)	19/145 (13.1%)	<0.001	24/691 (3.5%)	12/171 (7.0%)	0.038	29/516 (5.6%)	15/283 (5.3%)	0.85	2/122 (1.6%)	7/153 (4.6%)	0.17
Spasm-related MI	38/908 (4.2%)	15/145 (10.3%)	0.002	9/691 (1.3%)	6/171 (3.5%)	0.093	9/516 (1.7%)	8/283 (2.8%)	0.31	1/122 (0.8%)	1/153 (0.7%)	1
Symptom	792/941 (84.2%)	119/144 (82.6%)	0.64	576/717 (80.3%)	131/178 (73.6%)	0.050	417/528 (79.0%)	218/295 (73.9%)	0.096	92/127 (72.4%)	98/155 (63.2%)	0.10
Killip class =>2	197/1004 (19.6%)	23/152 (15.1%)	0.19	167/760 (22.0%)	47/186 (25.3%)	0.34	152/557 (27.3%)	96/304 (31.6%)	0.18	51/138 (37.0%)	63/162 (38.9%)	0.73
Max CK (IU/L)	2055 (694-4046)	1071 (438-2289)	<0.001	1495 (598-3232)	1083 (335-2356)	0.57	1227 (438-2569)	1185 (399-2497)	0.10	1119 (489-2847)	1135 (346-2165)	0.29
Time from onset to door (min)	130 (60-320)	147 (70-356)	0.17	152 (70-368)	137 (60-457)	0.26	166 (76-404)	198 (88-455)	0.35	190 (90-590)	201 (90-609)	0.41

AF = atrial fibrillation; CK = creatine kinase; MI = myocardial infarction; PAD = peripheral artery disease; STEMI = ST-elevated myocardial infarction.

Table 4
Management in each group stratified by age

	<65 Years			65-74 Years			75-84 Years			84< Years		
	Men	Women	p value	Men	Women	p value	Men	Women	p value	Men	Women	p value
Variable	(n = 1,007)	(n = 154)		(n = 765)	(n = 189)		(n = 558)	(n = 308)		(n = 140)	(n = 162)	
Urgent CAG	961/1006 (95.5%)	142/154 (92.2%)	0.076	725/764 (94.9%)	179/189 (94.7%)	0.92	512/556 (92.1%)	282/308 (91.6%)	0.79	120/140 (85.7%)	132/162 (81.5%)	0.32
Initial TIMI 2/3 flow	311/954 (32.6%)	53/142 (37.3%)	0.27	283/722 (39.2%)	75/177 (42.4%)	0.44	244/507 (48.1%)	123/280 (43.9%)	0.26	53/120 (44.2%)	58/131 (44.3%)	0.99
Multi-vessel disease	346/956 (36.2%)	50/141 (35.5%)	0.87	330/722 (45.7%)	71/177 (40.1%)	0.18	274/512 (53.5%)	124/280 (44.3%)	0.013	66/120 (55.0%)	66/132 (50.0%)	0.43
Urgent PCI	901/960 (93.9%)	115/142 (81.0%)	<0.001	668/725 (92.1%)	160/178 (89.9%)	0.33	459/512 (89.7%)	250/282 (88.7%)	0.66	111/120 (92.5%)	124/132 (93.9%)	0.65
Time from door to balloon (min)	68 (49-105)	79 (56-111)	0.38	74 (52-113)	79 (54-130)	0.45	81 (55-145)	79 (56-127)	0.34	85 (55-133)	91 (67-186)	0.90
Time from onset to balloon (min)	219 (138-455)	240 (150-488)	0.22	251 (150-529)	263 (160-609)	0.29	293 (172-611)	306 (193-600)	0.94	354 (182-814)	353 (185-849)	0.76
Final TIMI 3 flow	830/898 (92.4%)	105/114 (92.1%)	0.90	607/663 (91.6%)	146/160 (91.3%)	0.90	424/457 (92.8%)	227/249 (91.2%)	0.45	96/110 (87.3%)	112/124 (90.3%)	0.46
Prescriptions at discharge												
Antiplatelet agent	733/917 (79.9%)	82/140 (58.6%)	<0.001	519/675 (76.9%)	124/166 (74.7%)	0.55	365/486 (75.1%)	190/265 (71.7%)	0.31	68/109 (62.4%)	95/127 (74.8%)	0.040
ACE inhibitor/ARB	726/914 (79.4%)	109/139 (78.4%)	0.78	544/669 (81.3%)	131/166 (78.9%)	0.48	375/483 (77.6%)	218/262 (83.2%)	0.072	82/110 (74.6%)	85/124 (68.6%)	0.31
β-blocker	639/915 (69.8%)	83/139 (59.7%)	0.017	482/671 (71.8%)	109/164 (66.5%)	0.18	326/481 (67.8%)	173/261 (66.3%)	0.68	69/110 (62.7%)	79/125 (63.2%)	0.94
Statin	835/914 (91.4%)	127/141 (90.1%)	0.62	583/674 (86.5%)	143/167 (85.6%)	0.77	412/486 (84.8%)	224/266 (84.2%)	0.84	87/110 (79.1%)	97/127 (76.4%)	0.62

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CAG = coronary angiography; PCI = percutaneous coronary intervention; TIMI = thrombolysis in myocardial infarction.

group stratified by age. In each group, baseline characteristics were generally comparable between men and women. Exceptions were higher incidence of current smoking in men, and in case of group 1 and 2, higher incidence of type 2 MI and lower max CK in women. There was no significant difference in the incidence of typical symptom between men and women patients in each group. Table 4 shows management in each group. Urgent CAG was performed with same frequency and angiographic findings were comparable between men and women in each group. Urgent PCI was performed and achieved final TIMI 3 flow to the same degree, except for more urgent PCI for men in group 1. The median time from symptom onset to balloon was comparable between men and women patients in each group. Prescriptions at discharge were almost comparable, but less antiplatelet agents and -blockers for women in group 1.

Kaplan-Meier curves for MACE in the entire study patients are shown in Figure 2. The crude incidence of 3-year MACE was significantly higher in women than men (36.4% vs 28.5%, p <0.001; Figure 2). Kaplan-Meier curve of each group stratified by age showed that the incidence of 3-year MACE increased consistently from group1 to group 4 (19.1% in group 1, 29.3% in group 2, 39.2% in group 3, and 55.9% in group 4, p <0.001; Figure 2).

Figure 3 shows Kaplan-Meier curves for all-cause death in each group stratified by age. In each group, the incidence of all-cause death was not significantly different between men and women patients (group1, 7.4% vs 9.5%, p = 0.34; group 2, 11.5% vs 11.0%, p = 0.63; group 3, 21.7% vs 22.2%, p = 0.73; and group 4, 34.4% vs 37.0%, p = 0.37). Figure 4 shows Kaplan-Meier curves for MACE in each group stratified by age. In each group, the incidence of 3-year MACE was not significantly different between men and women patients (group 1, 19.0% vs 19.6%, p = 0.74; group 2, 28.3% vs 33.1%, p = 0.25; group 3, 39.6% vs 38.9%, p = 0.54; and group 4, 56.8% vs 54.0%, p = 0.24, respectively). Same trends were observed when only patients with type 1 MI were analyzed.

Univariate analysis showed that gender was associated with worse 3-year MACE (HR 1.41, 95%CI 1.18 to 1.69, p <0.001). However, in multivariate analysis (Table 5), gender was not an independent predictor for 3-year MACE (HR 1.08, 95%CI 0.91 to 1.28, p = 0.40), but advanced age was (HR 1.02, 95%CI 1.02 to1.03, p <0.001).

Discussion

The major findings of this study were (1) women had higher crude incidence of 3-year MACE than men, (2) however, after stratification by age, the gender difference in 3-year MACE disappeared in each group and (3) gender was not an independent predictor for 3-year MACE.

Previous studies have demonstrated that women patients had worse outcomes than men after acute MI.[1-8] Women patients with MI generally have advanced age, more co-morbidities, more atypical symptom and less opportunity to receive optimal management.[13-19] Advanced age is one of the most important predictor for outcomes in patients with MI among these factors. However, there were few studies that compared long-term outcomes between men and women patients with acute MI in each group stratified by age.

Vaccarino et al. reported that mortality was higher in young women with acute MI than men of similar age, but the gender difference in mortality decreased with increasing age and reversed among older patients.[4] However, their patients left hospital from 1975 to 1995 and PCI was performed only less than 5% of the patients during hospitalization. Alter et al. reviewed long-term survival among 25,697

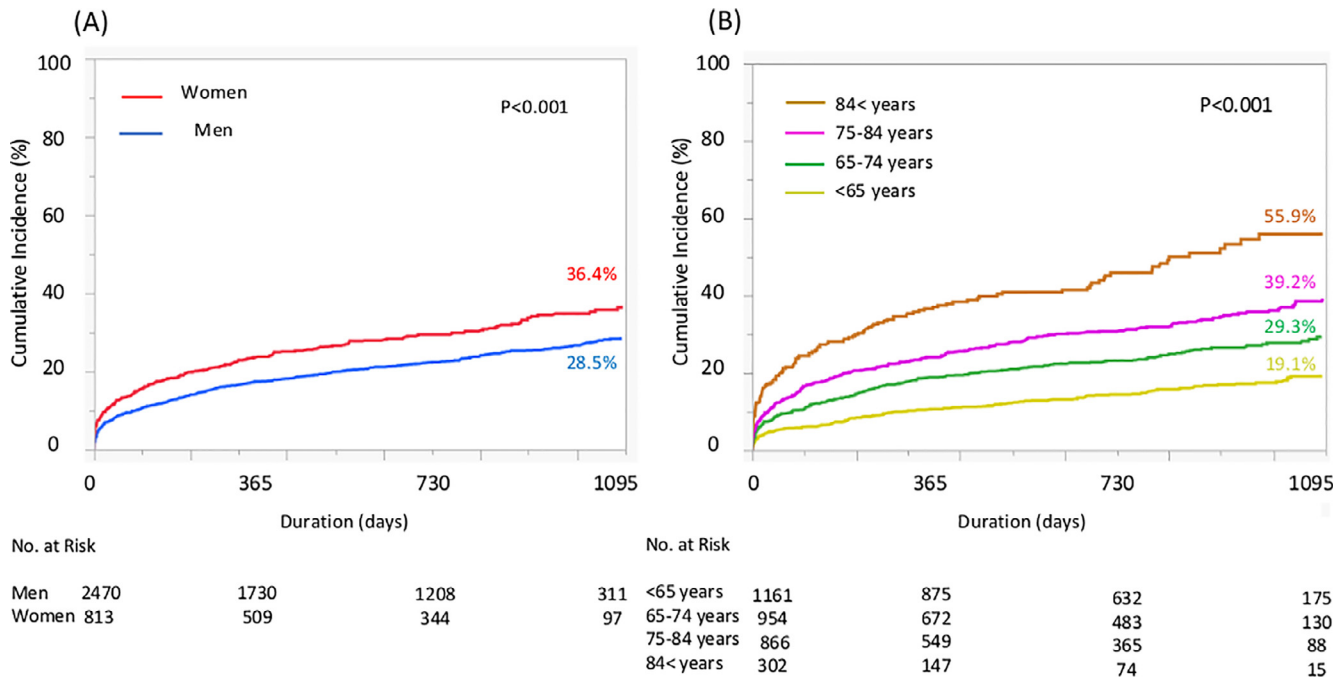

Figure 2. Kaplan-Meier curves for 3-year MACE in the entire study patients (A) between men and women and (B) each group stratified by age. MACE = major adverse cardiovascular event.

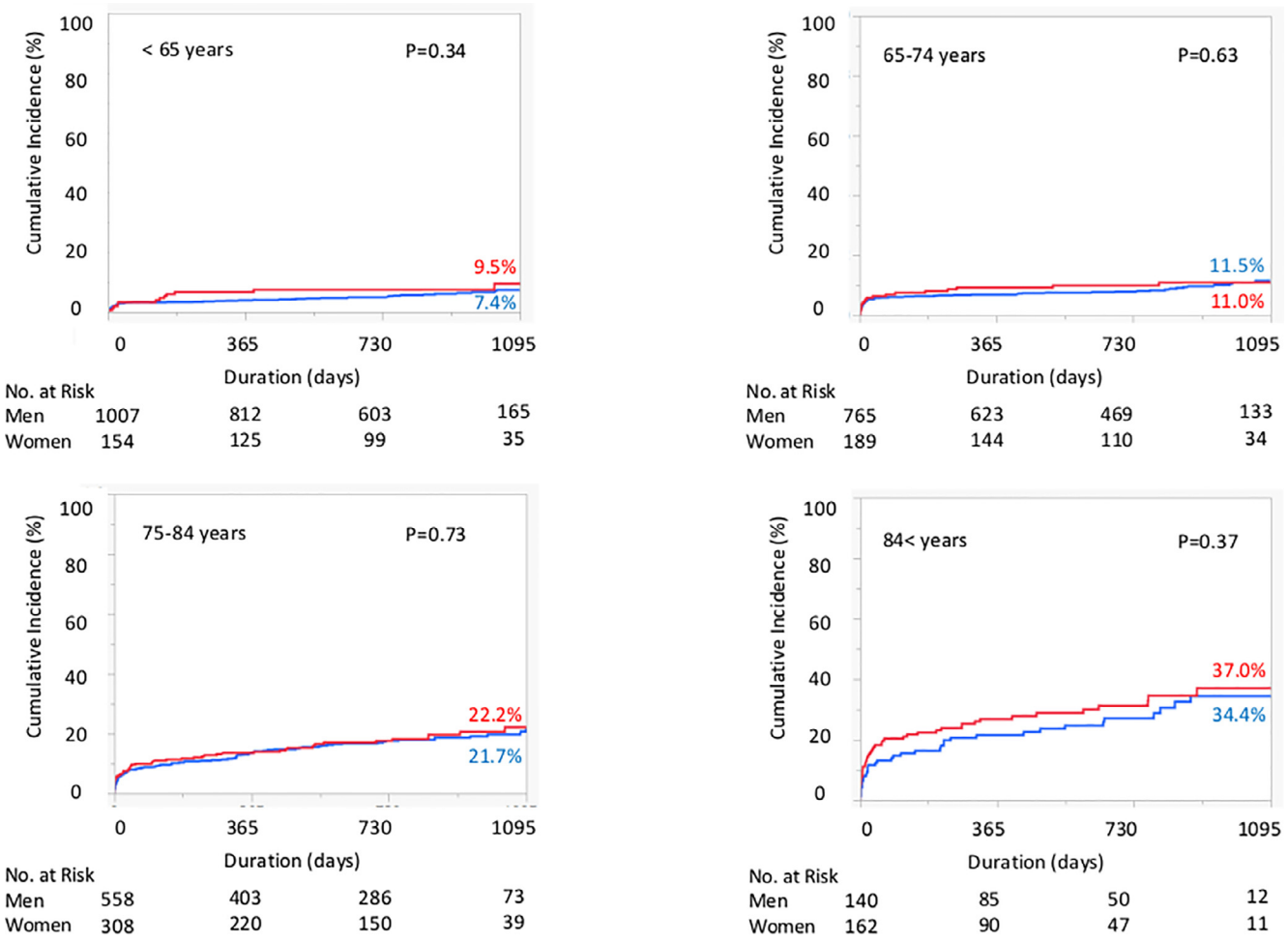

Figure 3. Kaplan-Meier curves for all-cause death between men and women in each group stratified by age.

patients hospitalized with acute MI between 1992 and 1993.[20] Although adjusted 5-year mortality rate was higher in women than men, the difference in 5-year mortality rate between men and women was lower in older group than younger group. Although growing evidence demonstrating gender differences in MI might have affected physicians' referrals for aggressive medical management for women, little is known about interaction between gender and age on management and outcomes in the contemporary PCI era. In the current study, there was no significant gender difference in the incidence of 3-year MACE in each group, even in the youngest group. Several factors might have affected for the difference in the results of the previous studies and the current study.

First, women had generally more atypical symptom than men. Failure to efficiently recognize acute MI from symptoms leads to delay in presentation, resulting in poor outcomes. We have previously reported that atypical symptoms of acute MI were associated with less invasive therapy and poor outcome.[21] Although women had more atypical symptom than men in the entire study patients, there was no significant gender difference in the incidence of atypical symptom in each group.

Second, women have had less opportunity to receive optimal management, including urgent CAG, PCI, and guideline-recommended drugs.[18,22,23] In line with results of previous studies, urgent CAG and PCI were performed less frequently in women than men. However, Urgent PCI was performed with the same frequency, except for group 1. Prescriptions at discharge were almost comparable between men and women, except for less antiplatelet agents and -blockers for women in group 1. Younger women (group 1) had higher incidence of spasm-related MI than men of similar age. Less urgent PCI, antiplatelet agents and -blockers in younger women (group 1) may be attributable to a higher incidence of spasm-related MI. The higher incidence of spasm-related MI in younger Japanese women may explain the relative favorable outcome compared with younger Caucasian women.

Finally, women have more co-morbidities including a higher incidence of hypertension, diabetes, dyslipidemia, atrial fibrillation and renal dysfunction than men.[13,14,19] In the current study, women had more incidence of chronic kidney disease, atrial fibrillation and Killip class ≥2 than men in entire study patients. However, the gender differences in these factors disappeared after stratification by age.

This study has several limitations. This study is based on a post hoc analysis and thus has potential influences which might have affected the results. This study lacked important data regarding spasm-related MI. There was no information regarding the definition of spasm among type 2 MI patients.

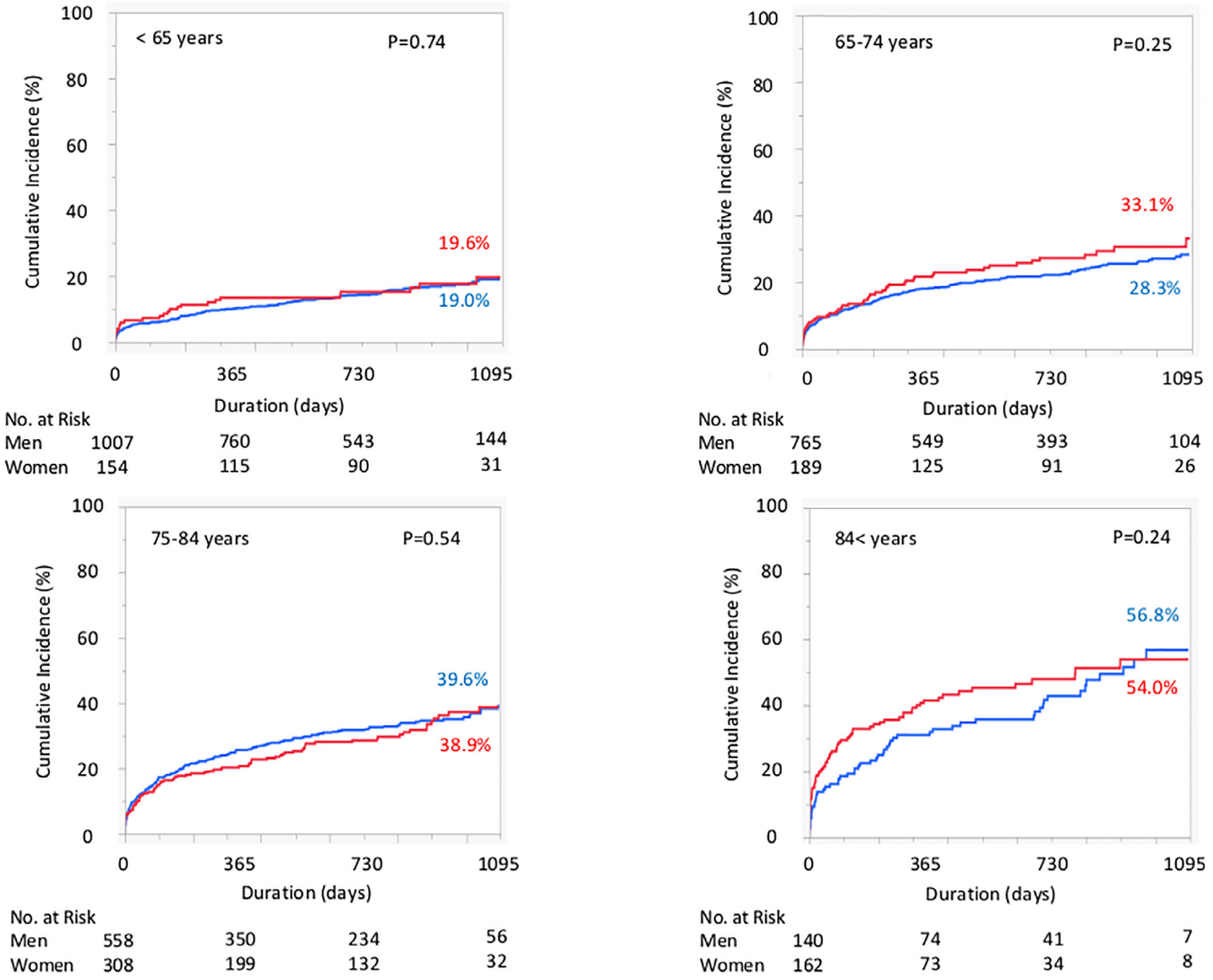

Figure 4. Kaplan-Meier curves for 3-year MACE between men and women in each group stratified by age. MACE, major adverse cardiovascular event.

Table 5
Cox regression models for 3-year MACE

	Univariate model		Multivariate model	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Gender (vs men)	1.41 (1.18-1.69)	<0.001	1.08 (0.91-1.28)	0.40
Age (each +1)	1.04 (1.03-1.05)	<0.001	1.02 (1.02-1.03)	<0.001
Hypertension	1.12 (0.94-1.32)	0.21		
Diabetes mellitus	1.24 (1.05-1.47)	0.01	1.08 (0.92-1.27)	0.32
Dyslipidemia	0.68 (0.57-0.79)	<0.001	0.73 (0.63-0.86)	<0.001
Chronic kidney disease	2.82 (2.39-3.33)	<0.001	1.63 (1.38-1.94)	<0.001
Stroke	2.26 (1.79-2.86)	<0.001	1.57 (1.29-1.92)	<0.001
PAD	2.47 (1.74-3.5)	<0.001	1.41 (1.06-1.88)	0.017
Previous MI	1.72 (1.37-2.15)	<0.001	1.24 (1.00-1.54)	0.049
Killip =>2	4.27 (3.59-5.09)	<0.001	2.85 (2.43-3.34)	<0.001
Urgent PCI	0.75 (0.60-0.93)	0.008	1.05 (0.86-1.30)	0.62
Time from onset to balloon	1.31 (0.81-2.13)	0.26		

MACE= major adverse cardiovascular event; MI= myocardial infarction; PAD= peripheral artery disease; PCI= percutaneous coronary intervention.

In conclusion, although women had higher crude incidence of 3-year MACE than men, the gender difference in long-term outcome disappeared after stratification by age. In the contemporary era, presentation, management, and outcome were comparable between men and women patients with MI of the same age range.

Authors Contribution

Toshio Kimura: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing-Original draft. Hirokuni Akahori: Software, Visualization, Writing review. Masanori Asakura: Writing-Review and Editing. Koichi Nakao: Resources, Writing-Review and Editing. Yukio Ozaki: Resources, Writing-Review and Editing. Kazuo Kimura: Resources, Writing-Review and Editing. Junya Ako: Resources, Writing-Review and Editing. Teruo Noguchi: Resources, Writing-Review and Editing. Satoru Suwa: Resources, Writing-Review and Editing. Kazuteru Fujimoto: Resources, Writing-Review and Editing. Yasuharu Nakama: Resources, Writing-Review and Editing. Takashi Morita: Resources, Writing-Review and Editing. Wataru Shimizu: Resources, Writing-Review and Editing. Yoshihiko Saito: Resources, Writing-Review and Editing. Atsushi Hirohata: Resources, Writing-Review and Editing. Yasuhiro Morita: Resources, Writing-Review and Editing. Teruo Inoue: Resources, Writing-Review and Editing. Atsunori Okamura: Resources, Writing-Review and Editing. Toshiaki Mano: Resources, Writing-Review and Editing. Minoru Wake: Resources, Writing-Review and Editing. Kengo Tanabe: Resources, Writing-Review and Editing. Yoshisato Shibata: Resources, Writing-Review and Editing. Mafumi Owa: Resources, Writing-Review and Editing. Kenichi Tsujita: Resources, Writing-Review and Editing. Hiroshi Funayama: Resources, Writing-Review and Editing. Nobuaki Kokubu: Resources, Writing-Review and Editing. Ken Kozuma: Resources, Writing-Review and Editing. Shiro Uemura: Resources, Writing-Review and Editing. Tetsuya Toubara: Resources, Writing-Review and Editing. Keijiro Saku: Resources, Writing-Review and Editing. Shigeru Oshima: Resources, Writing-Review and Editing. Kunihiro Nishimura: Resources, Writing-Review and Editing. Yoshihiro Miyamoto: Resources, Writing-Review and Editing. Hisao Ogawa: Resources, Writing-Review and Editing. Masaharu Ishihara: Conceptualization, Data curation, Funding acquisition, Methodology: Project administration, Resources, Supervision, Writing-Review and Editing.

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Appendix

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