Increased Cardiac Mortality in Women Compared with Men in Patients with Acute Myocardial Infarction

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Abstract

Objective It has been reported that women with acute myocardial infarction (AMI) have a higher short-term mortality rate than men, but the reason is not known. The profile in relation to age, gender and risk factors was evaluated to compare AMI and unstable angina pectoris (UAP).

Methods Findings from 984 patients including 580 patients with AMI (129 women, 451 men) and 404 patients with UAP (131 women, 273 men) were analyzed by the South Osaka Acute Coronary Syndrome Study Group (SACS). The primary endpoint of the study was in-hospital death. The primary endpoints of interest (cardiac death) were fatal recurrent myocardial infarction, death from congestive heart failure, and sudden death.

Results Cardiac death during hospitalization within 30 days in AMI was higher in women than in men (12.4% vs 6.7%, $p < 0.05$). On the other hand, in UAP there was no significant difference between women and men (1.5% vs 0.7%, NS). The incidence of cardiac death in AMI was significantly higher for patients 75 years old and older (19.0%) than for patients less than 55 years old (4.2%), 55–64 years old (3.5%) and 65–74 years old (4.7%) ($p < 0.001$, respectively).

Conclusions Cardiac death was higher for women compared with men in patients with AMI. The worse prognosis for the AMI women patients was likely to be derived from less performance of percutaneous coronary intervention, and a high incidence of severe myocardial infarction. Further research should be focused on the analysis of various clinical backgrounds. (Internal Medicine 43: 911–918, 2004)

Key words: acute myocardial infarction, unstable angina pectoris, gender

Introduction

In-hospital and long-term prognosis have been reported to be worse for women with acute myocardial infarction (AMI) than for men (1, 2). However, other studies have reported that there is no significant difference in the mortality rate between men and women (3–5). The profile in relation to age and gender to discriminate AMI and unstable angina pectoris (UAP) is unclear. Although there are many reports on AMI, the characteristics and outcome of women and men with UAP have been rarely investigated (3, 6, 7). Hochman et al (6) reported that among patients with UAP women were associated with an independent protective effect. Thus, the effect of gender may be different between AMI and UAP. However, there are several differences between the Japanese and Western populations with regard to treatment. In Japan, thrombolysis is used less frequently, and balloon angioplasty and stenting are more common therapeutic strategies for acute coronary syndromes (ACS), which may lead to different outcomes in Japanese patients. Therefore, we investigated the clinical outcome for Japanese patients among patients with ACS.

Methods

Subjects

One thousand and twenty patients were prospectively enrolled in this study. Thirty-six patients were excluded because of insufficient medical records. Finally, we analyzed

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data from 984 patients: 580 patients with first AMI (129 women, 451 men) and 404 patients with UAP (131 women, 273 men) between February 2001 and January 2002. This study included 23 different hospitals in South Osaka area (South Osaka Acute Coronary Syndrome Study Group; SACS). The electrocardiographic criteria included ST elevation or depression of more than 0.5 mm in 2 or more contiguous leads. Patients with AMI within 7 days after onset were included in this study. AMI was considered to have occurred if the level of creatine kinase MB isoenzyme was above normal. When the creatine kinase MB level had not been measured, then the total creatine kinase level needed to be more than twice the upper limit of the normal range. Diagnosis of UAP depended on the presence of one or more of the following three historical features: 1) new angina of effort of less than 1 month's duration, 2) a changing pattern, 3) new angina at rest (8).

Data collection

Data were collected at the time of admission and during the hospital period through direct patient interviews and medical record reviews. Prior to cardiac catheterization, coronary thrombolysis, percutaneous coronary intervention, and coronary artery bypass grafting (CABG), the purpose, methods, and risk were explained. Written informed consent for the procedures was obtained from the patients. All in-hospital data without the patient's full name and hospital ID number were transmitted to the SACS office located at the Department of Cardiology, Kinki University. Therefore, analysis at the SACS office could not specify the patients. Final diagnoses were assigned after review of the patients' medical records and data collection forms by participating physician investigators at each study site. Outcome of patients at 30 days of onset was analyzed at the hospital participating in this study. The primary end-point of the study was in-hospital death. The primary end points of interest (cardiac death) were fatal recurrent myocardial infarction, death from congestive heart failure and sudden death. Recurrent myocardial infarction had to fulfill the same criteria as the qualifying myocardial infarction for patient enrollment. Diagnosis of congestive heart failure was made from characteristic signs and symptoms compatible with congestive heart failure with or without echocardiographic, roentgenographic, and hemodynamic evidence of heart failure. Diagnosis of death from congestive heart failure was established when cause of death was directly attributed to congestive heart failure. Sudden death, in accordance with Braunwald's definition (9) was defined as death occurring unexpectedly with no premonitory symptoms or with symptoms lasting no longer than one hour. Non-cardiac death was defined as death by cerebrovascular injury, cancer, pneumonia, or other various extracardiac disorders. Diagnosis of death from non-cardiac death was established by clinical features, X-ray findings and other various clinical diagnostic findings.

The clinical characteristics of the population in each period were assessed for prevalence of gender, age, hyper-

lipidemia, hypertension, smoking, diabetes mellitus, obesity. ST elevation of electrocardiogram, Killip class, procedure of coronary angiography, coronary thrombolysis, percutaneous coronary intervention and CABG. Risk factors determined included the following: current smoking, hypertension (treatment with antihypertensive medication or documented blood pressure ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic before admission), diabetes mellitus (treatment with antidiabetic drugs or diagnosis of diabetes during hospital stay), history of myocardial infarction or angina pectoris. Obesity was defined as body mass index ≥ 25 kg/m². Hyperlipidemia was defined as fasting total cholesterol ≥ 220 mg/dl, fasting triglycerides ≥ 150 mg/dl, or antilipidemic therapy.

Statistical analysis

Results are expressed as mean $\pm$ standard deviation. We compared the baseline characteristics and clinical outcomes between women and men. Subjects were grouped on the basis of sex and age. We report here the results based on an analysis that included all patients. Statistical testing was performed using the chi-square test for categorical variables and unpaired t test or one-way ANOVA for continuous variables. For each relative risk, we calculated the odds ratio and 95% confidence interval (10).

To assess the possible modifying effects of patients characteristics, subgroup analyses were performed within a strata of all 14 variables. Multivariate analysis was performed by Cox hazard models. P values were two sided. A p value less than 0.05 was considered statistically significant.

Results

Baseline characteristics at onset

The women were older than the men in AMI (72 ± 11 years vs 65 ± 11 years, $p < 0.001$) and in UAP (68 ± 11 years vs 65 ± 11 years, $p < 0.01$) (Table 1). The women had a lower rate of smoking in both AMI and UAP (AMI: 25.4% vs 64.0%, $p < 0.001$, UAP: 33.3% vs 64.2%, $p < 0.001$), and a higher rate of obesity in both AMI and UAP (AMI: 29.1% vs 18.7%, $p < 0.01$, UAP: 33.3% vs 24.0%, $p < 0.05$). The women had a lower rate of history of angina pectoris in AMI (23.9% vs 34.3%, $p < 0.05$), and a lower rate of Killip class than the men in AMI (64.3% vs 76.9%, $p < 0.01$). Percutaneous coronary intervention was performed less frequently in the women than in the men in AMI (61.9% vs 70.9%, $p < 0.05$), but not in UAP (43.2% vs 48.0%, NS). CABG was performed less frequently in the women than in the men in AMI (6.0% vs 7.6%, $p < 0.05$), but not in UAP (12.9% vs 13.3%, NS). Two hundred twenty-one patients (52.9%) were admitted to the hospital within 3 hours after onset of AMI.

Profile of onset of AMI and UAP patients

The gender ratio used to evaluate the incidence of AMI and UAP was expressed as the number of the men divided by the total number of the men and the women (Fig. 1). The gender ratio was higher in AMI than UAP in those less than

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Table 1. Clinical Characteristics

	AMI Men	AMI Women	UAP Men	UAP Women
n	451	129	273	131
Age (years)	65±11	72±11 ***	65±11 †††	68±11 ***†§§
Infarct site (anterior)	47.8%	47.2%		
Time from onset to admission	10.6±29.0	10.6±29.4		
Risk factors				
Hyperlipidemia	40.1%	50.0% *	40.9%	48.5%
Hypertension	52.9%	60.4%	57.7%	62.9% *
Smoking	64.0%	25.4% ***	64.2% †††	33.3% ***†§§§
Diabetes mellitus	32.3%	28.4%	29.7%	37.1%
Obesity	18.7%	29.1% **	24.0%	33.3% ***§
History of MI	11.9%	6.7%	14.7% †	12.9%
History of AP	34.3%	23.9% *	40.1% ††	47.7% ***†††
ST elevation	78.7%	78.4%	9.7% ***†††	9.8% ***†††
Killip (I)	76.9%	64.3% **	99.6% ***†††	99.1% ***†††
CAG (+)	82.4%	78.4%	78.1%	75.8%
CT (+)	18.4%	17.2%	1.4% ***†††	0.8% ***†††
PCI (+)	70.9%	61.9% *	48.0% ***††	43.2% ***††
CABG (+)	7.6%	6.0% *	13.3% †	12.9%
MI onset during hospitalization	4.8%	5.2%	0.4% ***†††	0.8% *†

AMI: Acute myocardial infarction, UAP: Unstable angina pectoris, CAG: Coronary angiography, CT: Coronary thrombolysis, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass grafting.

*p<0.05, **p<0.01, ***p<0.001, vs AMI Men

†p<0.05, ††p<0.01, †††p<0.001, vs AMI Women

§p<0.05, §§p<0.01, §§§p<0.001, vs UAP Men

m±SD.

Figure 1. Gender ratio between AMI and UAP. Gender ratio was expressed as the number of the men divided by the total number of the men and the women. The gender ratio was used to evaluate the incidence of AMI and UAP.

Table 2. In Hospital Prognosis (Death during Hospitalization within 30 Days)

	AMI Men	AMI Women	UAP Men	UAP Women
Cardiac death	30 (6.7%)	16 (12.4%)	2 (0.7%)	2 (1.5%)
Non-cardiac death	10 (2.2%)	3 (2.3%)	1 (0.4%)	0 (0.0%)

AMI: Acute myocardial infarction, UAP: Unstable angina pectoris, * $p < 0.05$.

Figure 2. In hospital prognosis in relation to age between AMI and UAP.

75 years old. When age was less than 55 years old, the incidence of the men with AMI was higher than that with UAP (91% vs 77%, $p < 0.05$); with 55–64 years old, (88% vs 74%, $p < 0.01$); with 65–74 years old, (75% vs 65%, $p < 0.05$), however, with 75 years old and over, there was no significant difference between AMI and UAP (63% vs 58%, NS).

In-hospital outcome

The cardiac death during hospitalization within 30 days in AMI was higher in women than in men (12.4% vs 6.7%, $p < 0.05$), on the other hand, in UAP there was no significant difference between women and men (1.5% vs 0.7%, NS) (Table 2). In the non-cardiac death during hospitalization within 30 days in both AMI and UAP, there was no significant difference between women and men (AMI: 2.3% vs 2.2%, NS, UAP: 0.0% vs 0.4%, NS). Outcome by age of

AMI and UAP during hospitalization within 30 days is shown in Fig. 2. The incidence of cardiac death in AMI was significantly higher in patients 75 years old and over (19.0%) than in patients less than 55 years old (4.2%), 55–64 years old (3.5%) and 65–74 years old (4.7%) ($p < 0.001$, respectively). There were no significant differences in non-cardiac death among the groups. Percentage of cardiac death and non-cardiac death is shown in Table 3. When age was 75 years old and over, the incidence of cardiac death in women was 1.5 times higher than men (24.1% vs 16.1%). The proportional hazard approach is a multivariate analysis and uses information from all patients with AMI in the trial. The analysis confirmed that the AMI patients with diabetes mellitus were worse (odds ratio 2.06, 95% confidence interval 1.01–4.19, $p < 0.05$), and AMI patients with severe myocardial infarction (Killip class II–IV) were worse (odds ratio

Table 3. Percentage of Cardiac and Non-cardiac Death in AMI

Age		-54 (n=96)	55-64 (n=144)	65-74 (n=193)	75- (n=147)
Cardiac death	Men	4/87 (4.6%)	4/126 (3.2%)	7/145 (4.8%)	15/93 (16.1%)
	Women	0/9 (0.0%)	1/18 (5.6%)	2/48 (4.2%)	13/54 (24.1%)
Non-cardiac death	Men	0/87 (0.0%)	3/126 (2.4%)	3/145 (2.1%)	4/93 (4.3%)
	Women	0/9 (0.0%)	0/18 (0.0%)	1/48 (2.1%)	2/54 (3.7%)

PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass grafting, CAG: Coronary angiography, CT: Coronary thrombolysis, AP: Angina pectoris, MI: Myocardial infarction.

Figure 3. Results of multivariate analysis for predictors of cardiac death during hospitalization within 30 days in patients with AMI.

9.63, 95% confidence interval 4.60–20.15, $p<0.001$). The analysis also confirmed that AMI women patients were not independent predictors (odds ratio 1.32, 95% confidence interval 0.60–2.91, NS) (Fig. 3).

Subgroup analysis

The characteristics of the patients in AMI men and women patient groups are shown in Table 4. Patients were divided into subgroups based on the occurrence of cardiac death. The incidence of cardiac death was compared in relation to age, risk factors, history of myocardial infarction or

angina pectoris, ST elevation, Killip class, coronary angiography at acute phase and treatment. The AMI women patients had a higher cardiac death rate than AMI men patients among patients without obesity (13.3% vs 6.5%, $p<0.05$). The AMI women patients had a higher cardiac death rate than AMI men patients with Killip class I (7.6% vs 1.5%, $p<0.01$). In addition, AMI women patients had a higher cardiac death rate than AMI men patients without CABG (12.4% vs 6.6%, $p<0.05$).

Table 4. Subgroup Analysis among Various Backgrounds in Patients with Acute Myocardial Infarction

		AMI Men			AMI Women			P value
		N	Cardiac death		N	Cardiac death		
			n	%		n	%	
Age years old	<65	213	8	3.8	27	1	3.7	p<0.05
	65	238	22	9.2	102	15	14.7	
Hyperlipidemia	Yes	184	14	7.6	64	5	7.8	
	No	248	14	5.6	51	6	11.8	
Hypertension	Yes	238	18	7.6	78	9	11.5	
	No	194	11	5.7	39	4	10.3	
Smoking	Yes	288	12	4.2	34	2	5.9	
	No	123	11	8.9	82	10	12.2	
Diabetes Mellitus	Yes	147	15	10.2	37	5	13.5	
	No	289	13	4.5	81	8	9.9	
Obesity	Yes	83	5	6.0	35	2	5.7	
	No	352	23	6.5	83	11	13.3	
History of MI	Yes	54	7	13.0	9	3	33.3	
	No	376	19	5.1	109	8	7.3	
History of AP	Yes	255	12	4.7	77	7	9.1	
	No	156	11	7.1	32	4	12.5	
ST elevation	Yes	93	7	7.5	22	4	18.2	
	No	354	22	6.2	102	12	11.8	
Killip class	I	338	5	1.5	79	6	7.6	
	II-IV	103	24	23.3	44	9	20.5	
CAG at acute phase	Yes	372	22	5.9	103	8	7.8	
	No	75	8	10.7	25	8	32.0	
CT	Yes	85	5	5.9	22	3	13.6	
	No	360	24	6.7	105	13	12.4	
PCI	Yes	342	17	5.0	89	7	7.9	
	No	105	12	11.4	38	9	23.7	
CABG	Yes	34	1	2.9	7	1	14.3	
	No	410	27	6.6	121	15	12.4	

MI: Myocardial infarction, AP: Angina pectoris, CAG: Coronary angiography, CT: Coronary thrombolysis, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass grafting.

Discussion

Coronary risk factors with AMI and UAP

The reasons given for the worse prognosis of women have been older age (2–6, 11) more disorders such as diabetes and hypertension (1–6, 11), worse hemodynamics (2–6), differences in the time of presentation (1, 12), the rates of aspirin and beta-blocker usage (1, 11) mechanical complications (4, 11), electrical complications (1, 4), thrombotic and fibrinolytic activity (13–15), and reduced collateral flow (16). In the present study, the women were older and had a higher rate of obesity, severe grade of Killip class and a lower rate of PCI than the men, but the prevalence of diabetes and hypertension were not different between the two genders.

Panagiotakos et al (17) reported that exposure to cigarette smoke is associated with a significant increase in coronary risk. Yamagishi et al (18) showed that the risk of coronary heart disease was four times higher in current smokers than in never-smokers. Smoking causes direct injury of endothe-

lial cells (19), atheroma formation through low high-density lipoprotein (HDL)-cholesterol levels (20), and acceleration of thrombus formation through increased plasma fibrinogen (21), increased platelet aggregability (22), and decreased fibrinolytic activity (23).

In-hospital outcomes with AMI and UAP

Japanese women with ACS had a higher in-hospital mortality rate than men, and older age is a potential explanation for the higher in-hospital mortality among the women with AMI (24). Several studies have reported that there is no significant difference in the mortality rates between men and women for ACS after adjusting for differences in age and other prognostic factors (3–5). However, several studies have reported that the gender difference in outcome varies among the types of ACS (6, 7). Hochman et al (6) reported that among patients with UAP, the women were associated with an independent protective effect. In addition, they reported that the women were older than the men. In Hochman et al

(6), the women with UAP had a lower rate of 3-vessel disease than the men, which may explain the better outcome for the women in their study. The reason why being a women by itself is an independent predictor of in-hospital mortality in the patients with UAP is unclear, but may relate to poorer myocardial reserve in the women suggested by diastolic dysfunction (7), and reduced collateral blood flow (16). Moreover, the number of leads with ST depression during an anginal attack (25), absence of persistent ischemic chest pain (26), and lack of microvascular reperfusion following revascularization (27) were independent risk predictors of clinical outcome. Japanese women with ACS present with similar angiographic findings and hemodynamics, but have a higher in-hospital mortality rate than male patients. The present results suggest that older age may be a potential explanation for the higher in-hospital mortality in women with AMI, but female gender itself may be an important predictor for it among those with UAP (28).

Multivariate analysis showed that cardiac death was increased in patients with diabetes mellitus and severe grade of Killip class in the patients with AMI. Subgroup analysis showed that AMI women patients had a higher cardiac death rate than AMI men patients in the patients without obesity and without severe grade of Killip class. These data suggest that AMI women patients had a risk for the occurrence of AMI.

In the present study, the cardiac death rate during hospitalization within 30 days in AMI was higher in the women than in the men. When age was with 75 years old and over, the incidence of cardiac death in the women was 1.5 times higher than the men. The incidence of events was higher in AMI than UAP in the patients less than 75 years old between AMI and UAP, however, there was no significant difference in the patients 75 years old and over between AMI and UAP. Epidemiologic data have indicated that the women are relatively spared from coronary heart disease up to the age of 75 (29). Although the reasons for this protection are not entirely clear, estrogen is thought to play a part (30). The pathophysiology of coronary heart disease in premenopausal or middle-aged women may differ from the patients with older women and from men. Plaque erosions are the predominant abnormality in premenopausal women who die suddenly, whereas rupture of plaques is more common in older women and in men (31).

Limitations of the study

In Japan, the decline in the incidence of cardiac events among post-myocardial infarction patients reflects implementation of new therapeutic modalities (32). Accumulating evidence is clarifying which drugs are effective for secondary prevention for myocardial infarction and which are not (33). We only investigated the profile of AMI and UAP, and outcome during hospitalizations within 30 days. However, these results will contribute to solving the problems of ACS, and also clarify the profile of occurrence in the patients with AMI and UAP in the Japanese population.

In conclusion, the cardiac death rate was higher in women compared with men in patients with AMI. The worse prognosis for the AMI women patients was likely to be derived from less performance of percutaneous coronary intervention, and a high incidence of severe myocardial infarction. Further research should be focused on the analysis of various clinical backgrounds.

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