Early Mortality After Acute Myocardial Infarction

— Observational Study in Yamagata, 1993–1995 —

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Although considerable information is available regarding the prognosis after acute myocardial infarction (AMI) in Western populations, little is known about the fate of Japanese subjects after AMI. The purpose of this study was to assess short-term mortality and factors influencing it after AMI in Japan. From April 1993 to December 1995, 1,014 patients with AMI from 41 hospitals in Yamagata Prefecture were registered by cardiologists for the prospective survey. Among patients who died within 28 days after the onset of AMI, immediate causes of death were examined and the clinical profiles of these subjects were compared with those of patients that survived. Early death occurred in 184 patients (short-term mortality 18%). Patients who died were significantly older than survivors (76.1 ± 9.4 vs 67.6 ± 11.8 years, $p < 0.01$). They were also more likely to be women (50% vs 31%, $p < 0.01$), to have had hypertension (64% vs 54%, $p < 0.05$), diabetes mellitus (29% vs 20%, $p < 0.02$), prior MI (17% vs 12%, $p < 0.05$), or Killip class III or IV disease (63% vs 15%, $p < 0.01$), and were significantly less likely to be current smokers (26% vs 45%, $p < 0.01$) or to have been treated with reperfusion therapy (27% vs 63%, $p < 0.01$). Multivariate logistic analysis demonstrated that independent predictors of early death were Killip class III or IV and advanced age. Reperfusion therapy was a negative predictor of death. Patients who died had arrived at hospital earlier than patients who survived. Mortality as a result of heart failure, cardiac rupture, or arrhythmia fell exponentially after the onset of AMI. Thus, the predictors of short-term mortality were similar to those reported in Western populations. More deaths occurred just after the onset of disease, suggesting that early therapy is important in reducing short-term mortality. (*Jpn Circ J* 1998; 62: 414–418)

Key Words: Mortality; Acute myocardial infarction; Epidemiologic methods

Since World War II, the life expectancy of the Japanese has progressively increased and is now the highest in the world for both men and women (76.6 and 83.0 years respectively in 1994)! Although the number of patients receiving medical and/or surgical treatment for ischemic heart disease increases year by year, mortality remains low (46.7/100,000 people; one-fourth of the rate in the USA)! Unlike in Western populations, little information is available on the prognosis of Japanese subjects after acute myocardial infarction (AMI)? Thus, we conducted a district-based survey to assess short-term mortality and the factors influencing it in patients with AMI in Yamagata Prefecture, Japan.

Methods

Study Population

In April 1993, we began a prospective survey of AMI in Yamagata Prefecture, which is located in the northern part of the Main Island. In the 1995 census, the population was recorded as 1,257,000 and the ratio of people ≥ 65 years was high (20.5%) — in fact, the third highest

of 42 prefectures in Japan (14.8% on average). The study population comprised 1,014 patients (451 women and 663 men, aged 69.1 ± 11.9 years) admitted with confirmed AMI to 41 hospitals in the Yamagata Prefecture from April 1, 1993 to December 31, 1995 (Table 1). Nineteen of 41 hospitals have facilities for cardiac catheterization. The diagnosis of AMI required the “definite criteria of AMI” as described in the WHO MONICA Project³. Briefly, the criteria for a diagnosis of AMI were: (1) a definite ECG; (2) a probable ECG and abnormal enzyme levels; (3) typical symptoms and abnormal enzyme levels; or (4) death that appeared to the naked eye to be due to fresh myocardial infarction (MI) and/or recent coronary occlusion found at necropsy.

Data Collection and Analysis

A standard data set was collected prospectively and entered on a computer database. It included details of clinical presentation (age, sex, admission Killip classification), medical history (time and date of onset and arrival at hospital), coronary risk factors (hypertension, diabetes mellitus), hyperlipidemia (serum cholesterol ≥ 220 mg/dl), cigarette smoking status, prior MI, anterior MI or inferior MI, treatment [whether or not reperfusion therapy (iv or ic thrombolysis and/or primary angioplasty) was performed], and acute outcome. Hypertension was diagnosed when the average of 2 or more diastolic blood pressure measurements was ≥ 90 mmHg or when the average of multiple systolic blood pressure readings was consistently above 140 mmHg (WHO criteria, 1978) and diabetes mellitus was diagnosed when glucose equaled or

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exceeded 140 mg/dl (WHO criteria, 1985), respectively. Early death was defined as death occurring within 28 days of the onset of AMI. Causes of death were classified into pump failure, cardiac rupture of free wall, or ventricular septal perforation (rupture), arrhythmia and others.

Categorical variables were compared by chi-square analysis. Continuous variables were presented as means $\pm$ SD and were compared using a Student *t* test. After patients with unknown data had been excluded from the analysis, out of 1014 patients studied, the numbers of patients

analyzed were 520, 890, and 626 for early death, Killip classes, and treatment with reperfusion therapy, respectively. Multivariate stepwise logistic regression analysis was performed, incorporating variables with a bivariate *p* value <0.05 , to determine independent predictors of early death, Killip class, or treatment with reperfusion therapy. For bivariate and multivariate analyses, patients' age was divided into 4 categories; ≤ 60 years, $>60-70$, $>70-80$, and >80 years. All analyses were performed using SPSS 6.1 for the Power Macintosh.

Table 1 Clinical Characteristics of Patients

Age (years)	69.1 $\pm$ 11.9*
Onset to arrival (h)	18 $\pm$ 54*, median 3
Sex (women)	45%
Hypertension	56%
Diabetes mellitus	22%
Hyperlipidemia	34%
Smoking	42%
Prior MI	13%
Anterior MI	51%
Inferior MI	42%
Killip class III or IV	25%
Reperfusion therapy	56%

*Mean $\pm$ SD.

Results

Early Mortality

The clinical characteristics of patients enrolled are summarized in Table 1. Of 1,014 patients studied, 184 patients (18%) died within 28 days after the onset of AMI (early death). The number of patients who died of pump failure, rupture, and arrhythmia was 109 (11%), 28 (3%), and 28 (3%), respectively.

Predictors of Early Death

The variables associated with early death by bivariate analysis are shown in Table 2. Compared with survivors, patients who died were significantly older (76.1 $\pm$ 9.4 vs

Table 2 Factors Influencing Early Death

Variables	Died (n=184)	Survived (n=830)	Bivariate analysis		Multivariate analysis	
			Odds ratio (95% CI)	<i>p</i> value	Odds ratio (95% CI)	<i>p</i> value
Age (vs ≤ 60 years)	5%	25%		<0.01		<0.01
>60 to ≤ 70	20%	31%	3.22 (1.52–6.84)		1.58 (1.14–2.18)	
>70 to ≤ 80	42%	31%	6.95 (3.41–14.20)		2.49 (1.81–3.44)	
>80	33%	13%	13.1 (6.27–27.42)		3.94 (2.85–5.44)	
Sex (women)	50%	31%	2.20 (1.59–3.05)	<0.01		NS
Hypertension	64%	54%	1.46 (1.03–2.07)	<0.05		NS
Diabetes mellitus	29%	20%	1.60 (1.08–2.37)	<0.02		NS
Hyperlipidemia	31%	35%	0.86 (0.57–1.32)	NS		
Smoking	26%	45%	0.43 (0.29–0.64)	<0.01		NS
Prior MI	17%	12%	1.61 (1.04–2.49)	<0.05		NS
Anterior MI	56%	49%	1.32 (0.96–1.83)	NS		
Inferior MI	40%	43%	0.88 (0.63–1.22)	NS		
Killip class III or IV	63%	15%	9.60 (6.72–13.71)	<0.01	7.02 (3.90–12.63)	<0.01
Reperfusion therapy	27%	63%	0.23 (0.14–0.35)	<0.01	0.32 (0.17–0.60)	<0.01

CI, confidence interval; NS, not significant; MI, myocardial infarction.

Table 3 Factors Influencing Killip Class and Reperfusion Therapy

Variables	Killip class III or IV Odds ratio (95% CI)		Reperfusion therapy Odds ratio (95% CI)	
	Bivariate analysis	Multivariate analysis	Bivariate analysis	Multivariate analysis
Age (vs ≤ 60 years)				
>60 to ≤ 70	1.46 (0.89–2.41)	1.98 (1.65–2.38)**	0.68 (0.42–1.09)	0.61 (0.51–0.74)**
>70 to ≤ 80	3.12 (1.96–4.96)**	3.92 (3.28–4.71)**	0.38 (0.24–0.60)**	0.38 (0.31–0.46)**
>80	5.03 (3.05–8.30)**	7.79 (6.49–9.33)**	0.15 (0.09–0.26)**	0.23 (0.19–0.28)**
Sex (women)	1.49 (1.11–2.01)**	NS	0.42 (0.30–0.59)**	0.61 (0.42–0.89)**
Hypertension	1.21 (0.89–1.65)		NI	
Diabetes mellitus	1.40 (0.98–1.99)		NI	
Hyperlipidemia	1.08 (0.76–1.53)		NI	
Smoking	0.46 (0.32–0.64)**	NS	NI	
Prior MI	2.21 (1.49–3.27)**	1.92 (1.21–3.04)**	0.62 (0.38–1.01)	NS
Anterior MI	1.42 (1.06–1.91)*	1.40 (1.00–1.96)*	1.11 (0.81–1.52)	NS
Inferior MI	0.89 (0.66–1.20)		1.12 (0.82–1.54)	NS
Killip class III or IV			0.41 (0.28–0.59)**	0.57 (0.38–0.85)**

* $p < 0.05$, ** $p < 0.01$, NI, variable not included in the analysis; other abbreviations as in Table 1.

Fig 1. Comparison of time from onset to hospital arrival between patients who died and patients who survived. There was a significant difference in the ratio of patients who arrived within 2 h after onset ($p < 0.05$).

67.6±11.8 years, $p < 0.01$), were more likely to be women, hypertensive, diabetic, or to have a history of prior MI or Killip class III or IV, and had a lower incidence of current smoking and reperfusion therapy. When factors influencing early death were considered together in multivariate analysis, independent predictors were Killip class III or IV, treatment with reperfusion therapy (negative predictor), and advanced age (Table 2). Among these predictors, Killip class III or IV and treatment with reperfusion therapy but not advanced age were probably influenced by other factors. Thus, we investigated further the factors influencing Killip class III or IV and treatment with reperfusion therapy (Table 3). Multivariate analysis demonstrated that independent predictors of Killip class III or IV were advanced age, prior MI, and anterior MI, and those of reperfusion therapy (negative predictors) were advanced age, Killip class III or IV, and female gender.

Time to Admission

In Fig 1 cumulative rates of arrival times after the onset of AMI in patients who experienced early death and those who survived are compared. Patients who died were significantly more likely to have been admitted within 2 h after disease onset than were survivors ($\chi^2 = 5.1$, $p < 0.05$); this difference declined at later admission times. Fifty-seven percent of patients who died and 52% who survived were admitted within 3 h ($p > 0.25$).

Time to Early Death

Fig 2 shows the duration from the onset of disease to death in patients who died of pump failure (top), rupture (middle), or arrhythmia (bottom). The cumulative curves are similar, and in each group the largest number of deaths occurred within 24 h. The death rates within 3 days due to pump failure, rupture, and arrhythmia were 60%, 54%, and 50%, respectively.

Discussion

Mortality Rate and Causes of Death

The 28-day mortality rate in the present study was 18%, which is higher than the in-hospital mortality rate of less than 10% reported in most Western studies^{4,5}. It is possible that this higher mortality rate is in part due to our study protocol. We attempted to determine the general situation among AMI patients in Yamagata

Fig 2. Cumulative death curves among patients who died of pump failure (top), rupture (middle), or arrhythmia (bottom). A small circle indicates 1 death per day.

Prefecture and thus conducted a prospective survey of almost all hospitals in Yamagata Prefecture, only half of which had facilities for cardiac catheterization. The cause of death in the majority of patients was pump failure, which is compatible with recent Western reports^{4,6}.

Predictors of Early Death

In general, the predictors of short-term mortality were quite similar to those reported in Western populations, although the prevalence of AMI is much lower in Japan. The poorer prognosis among the elderly^{4,7,8} women^{4,9-11} and patients with hypertension^{4,12} diabetes mellitus^{4,6,13-15} prior MI^{4,12,16} or Killip class III or IV (pulmonary edema/shock)^{12,16} has been confirmed repeatedly in Western populations.

It is to be expected that patients receiving reperfusion therapy would have a better prognosis, but the lower mortality rate among current smokers is apparently paradoxical. According to the multivariate analysis, however, current smoking was not an independent predictor of early death. Thus, it is concluded that this group had a lower incidence of positive predictors for early death. For example, the mean age of current smokers was 63.0±11.9 years, which is significantly lower than the mean age (73.3±9.7 years) of non-current smokers ($p < 0.01$). Reduced short-term mortality from AMI in smokers and the lower risk profile of this patient group have also been observed in Western populations^{12,17,18}.

We found that hyperlipidemia was not correlated with early mortality in AMI patients. Hyperlipidemia has been clearly shown to increase the risk for AMI in young and middle-aged persons in Western countries^{19,20} but the importance of hyperlipidemia as a risk factor for AMI in persons older than 70 years remains unclear^{21,22}. As cholesterol levels are lower in Japan than in Western

countries²³ the significance of hyperlipidemia in predicting short-term mortality after AMI may differ between Japanese and Westerners. However, hyperlipidemia has not been identified as a predictor of short-term mortality after AMI even in Western populations^{16,24}

Advanced age was not only an independent predictor of short-term mortality but also a significant determinant of other independent predictors, namely Killip class III or IV and reduced likelihood of receiving reperfusion therapy. Thus, more aggressive treatment with reperfusion therapy may improve the prognosis in the elderly in our prefecture. The higher short-term mortality in women has been accounted for by other risk factors, primarily by age^{9,10} and we also reached the same conclusion that female gender is not itself an independent predictor of early death; the mean ages of men and women in the present study were 66.5 ± 12.2 and 74.1 ± 9.5 years, respectively ($p < 0.01$). The reason that women were less likely to receive reperfusion therapy remains to be clarified. However, the lower use of thrombolysis in women and the elderly has also been found in a European population-based study²⁵

AMI is a major cause of morbidity and mortality in diabetic patients. However, the importance of diabetes as an independent predictor for short-term mortality after AMI remains controversial¹³⁻¹⁵ and the high mortality during the early phase of AMI is often attributed to a higher incidence of severe heart failure¹³. The prevalence of diabetes mellitus was significantly higher in the group of patients that experienced early death than in patients who survived in the present bivariate analysis. However, the multivariate analysis showed that diabetes mellitus itself was not an independent predictor of severe heart failure (Killip class III or IV) or of early death.

Delay in Arriving at Hospital

With respect to the time delay itself, the median time (< 3 h) in the present study was similar to those experienced in Western countries²⁶. If the baseline characteristics of patients are similar, one would expect the risk of death to reduce as the time between disease onset and hospital arrival becomes shorter. However, we found that patients who died arrived earlier than patients who survived. A similar phenomenon was noted in patients within the first 4 h after the onset of symptoms of AMI: patient delay was positively correlated with the level of left ventricular function assessed on admission²⁷. Thus, patients who arrived at hospital later were biased in favor of a good prognosis.

Time From Onset to Early Death

In a community study it was found that about two-thirds of deaths occurred before hospital arrival and that most deaths occurred within 24 h among those who reached the hospital²⁸. We have clearly shown that the number of deaths falls exponentially after the onset of AMI, independent of the cause of death. This finding suggests that early treatment is critical in reducing short-term mortality not only after but also before reaching hospital.

Conclusions

We have found no previous reports of district-based surveys of early mortality after AMI in Japan. Although

the prevalence of AMI is lower among Japanese, the predictors of short-term mortality were quite similar to those in Western populations. Therefore, the therapeutic strategy for patients with AMI designed in Western countries might be directly applicable to Japanese patients in order to reduce short-term mortality.

Appendix

In the period from April, 1993, until December, 1995, the following institutions and chief investigators participated in the prospective survey of AMI in Yamagata Prefecture, Japan: Yamagata Prefectural Central Hospital (K. Takahashi, T. Araki, K. Yokoyama); Yamagata Prefectural Nihonkai Hospital (M. Oguma); Yamagata Prefectural Kahoku Hospital (I. Ohta); Yamagata Prefectural Shinjo Hospital (K. Hanashima); Yonezawa City Hospital (K. Ashikawa); Sakata City Hospital (T. Shibata); Kitamurayama Public Hospital (O. Kim); Nagai City General Hospital (K. Nakamura); Yamagata City Hospital Saiseikan (K. Saito); Shonai Amarume Hospital (S. Takizawa); Tohoku Central Hospital (T. Kanaya); Yamagata Saisei Hospital (K. Ikeda); Shinoda General Hospital (N. Kato); Sanyudo Hospital (T. Komatsu); Tendo Shinoda Hospital (T. Shinoda); Kojirakawa Shiseido Hospital (M. Ohe); Sagae City Hospital (T. Misawa); Nanyo City General Hospital (M. Yamaki); Tendo City Hospital (T. Endo); Tsuruoka Shonai Hospital (K. Kojima); National Yamagata Hospital (M. Suzuki); Honma Hospital (T. Sugawara); Shirataka Town Hospital (H. Takahashi); Oguni Town Hospital (K. Abe); Takahata Public Hospital (T. Kanno); Yabuki Hospital (S. Yabuki); Mamurogawa Town Hospital (T. Itoh); Nishikawa Town Hospital (M. Suzuki); Asahi Town Hospital (T. Kobayashi); Mogami Town Hospital (T. Akiba); Kawanishi Town Hospital (Y. Sugawara); Yahata Town Hospital (T. Okada); Kanayama Town Hospital (A. Kinebuchi); Yamada-Kikuchi Hospital (S. Yamada); Iide Clinic (S. Ohkawara); Zao-Miyuki Hospital (J. Harada); Yoshioka Hospital (N. Yoshioka); Tsuruoka Kyoritsu Hospital (A. Inomata); Funayama Hospital (S. Funayama); Oda Clinic (J. Oda); Yamagata University Hospital (H. Ito, I. Kubota and H. Tomoike).

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