Longitudinal Study of Acute Myocardial Infarction in the Southeast Osaka District From 1988 to 2002

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Background  Data on clinical characteristics, long-term mortality rates, and factors influencing outcome of acute myocardial infarction (AMI) based on an unselected cohort in the percutaneous coronary intervention (PCI) era are still limited in Japan.

Methods and Results  In the present study 415 consecutive patients with AMI who were admitted to hospital within 24 h of symptom onset between January 1988 and December 2002 were studied. There was a marked seasonal variation of AMI with a minimum in summer and a maximum in winter, as well as a marked circadian variation with a significant morning peak. Overall, 45.8% of patients were treated with primary PCI. Increased age and female sex were negatively associated with the probability of undergoing PCI. During the follow-up period (mean duration, 4.01±3.41 years), the unadjusted long-term all-cause mortality rate was 21.4%. Multivariate Cox regression analysis showed that age, prior cerebrovascular disease, renal failure, Killip≥2, and ventricular tachycardia/fibrillation were independent predictors of worse long-term mortality after AMI. Furthermore, the use of PCI was independently associated with favorable long-term survival after AMI.

Conclusions  Although PCI was associated with a favorable long-term mortality, it remains underused in subsets of patients and increased use may further reduce the long-term mortality rate in Japanese AMI patients.

Key Words: Long-term mortality; Myocardial infarction; Percutaneous coronary intervention

In the thrombolytic era the long-term mortality rates after acute myocardial infarction (AMI) in Japan are lower than those in Western countries.1,2 Rates of mortality from AMI have declined during the 1990s and this decline can be explained by greater use of percutaneous coronary intervention (PCI).3–8 However, data concerning clinical characteristics, long-term rates of mortality, and its predictors based on a large sample and unselected cohort in the PCI era are still limited in Japan. Cardiovascular disease is currently the second leading cause of death in Japan, so improved prognosis after AMI is important for public health as well as saving of national healthcare expenditure. The purposes of this study were to investigate the clinical characteristics, long-term prognosis, and the factors that influence the long-term mortality of unselected patients with AMI in the southeast Osaka district of Japan.

Methods

Patients  National Hospital Organization Osaka Minami Medical Center (former Osaka Minami National Hospital) is a general hospital located in the southeast Osaka district, which has a population of approximately 120,000. The hospital services Kawachinagano city and surrounding cities and towns and is a local cardiovascular center. The study population comprised 504 consecutive patients with AMI presenting within 15 days of onset who were admitted to the hospital between January 1988 and December 2002. Of those, 415 patients who were admitted within 24 h of symptom onset were studied after they had given informed consent.

Data Collection  A detailed standard case-report form was used by trained cardiologists to collect information on sociodemographic variables, medical history, clinical characteristics, therapeutic procedures, and clinical events during the patient’s admission. Information was obtained from the hospital medical records and by direct interview with the patient, family members, and the treating physician.

In patients who were discharged alive, we obtained fol-
low-up clinical data at 3, 6, and 12 months after the onset of AMI and annually thereafter. We obtained data concerning subsequent cardiac events by visits to the research outpatient clinic or, in a few instances, by verbal or written contact with the patient’s physician, the patient, or family members.

Obesity was defined as body mass index ≥25 kg/m², Diabetes mellitus was defined as a fasting plasma glucose concentration ≥126 mg/dl or the use of antidiabetic therapy. Hypertension was defined as a history of a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or the use of antihypertensive therapy. Hyperlipidemia was defined as a fasting total cholesterol concentration ≥220 mg/dl, a fasting triglyceride concentration ≥150 mg/dl, or the use of antihyperlipidemic therapy. Renal failure was defined as serum creatinine concentration ≥2.0 mg/dl. To determine the peak creatine kinase and glutamate oxaloacetate transaminase concentrations, blood samples were taken immediately after admission and at 6, 12, 18, 24, 36, 48 h later.

### Statistical Analysis

Time intervals are presented as median times and interquartile range. Other continuous variables are presented as mean ± standard deviation. Continuous variables between groups were compared by t-test. The monthly, weekly, and circadian distributions of the onset of AMI were first tested for homogeneity by chi-square goodness-of-fit test. When this test showed significant differences, a one-sided binominal test was performed to examine whether the frequency of AMI was higher than the expected rate. A multiple test was performed to examine the relative hazard of PCI. Cox regression analysis was used for assessing the relative hazard of events. Analyses of data were performed using SPSS statistical software (SPSS version 11.0, SPSS Japan Inc, Tokyo, Japan). For all analyses, significance was defined as p<0.05.

### Results

#### Baseline Characteristics

Overall, 18.1% of patients were obese, 24.8% had diabetes mellitus, 48.3% had hypertension and 29.3% had hyperlipidemia (Table 1). To clarify the frequency of a cluster of risk factors (i.e., obesity, hypertension, diabetes mellitus, and dyslipidemia), the number of risk factors, from 0 to 4, was investigated: approximately 70% of patients had at least 1 risk factor, and 2.1% had 4 risk factors.

#### Clinical Characteristics in Onset and on Admission

Significant monthly trends in the onset of AMI were seen in the total study population (chi-square test, p=0.003). Most patients were hospitalized in February (one-sided binomial test, p<0.001) and fewest in July and November (one-sided binomial test, p=0.049). There was also a significant seasonal variation (chi-square test, p=0.005) with a maximum incidence of AMI in winter (one-sided binomial test, p<0.001) and a minimum in summer (one-sided binomial test, p=0.033). The distribution of the day of onset of AMI showed no significant variation for all subjects (chi-square test, p=0.599), indicating that the distribution was fairly random in this community as a whole. Significant circadian distributions were seen in this study population (p=0.006), with 2 peaks around 10.00 and 21.00 h, respectively. When distribution of the onset of AMI was obtained for 4-h intervals, the morning peak between 8.00 and 11.59 h was statistically significant (p<0.001), but not the nighttime peak between 20.00 and 23.59 h (p=0.131).

The dominant presenting symptoms in the total study population were chest pain (92.8%), dyspnea (8.9%), vomiting (10.4%) and syncope (4.1%). In approximately 50%, the index AMI was preceded by chest pain episodes, 40% had an AMI after exertion and 59.6% of patients had an AMI at rest. The median delay between symptom onset and hospital arrival was 2.0 h (interquartile range 1.0–6.0 h): 78% of patients arrived within 6 h.

### In-Hospital Reperfusion Treatments and Outcomes

In the total study population, 68.7% of patients received reperfusion therapies: thrombolysis was used in 33.7%, PCI in 45.8%, and coronary artery bypass grafting in 3.1%. Table 2 shows factors independently associated with the use of PCI. Men and the registry year had a positive association with the use of primary PCI. The proportion of PCI cases was more frequent in men than in women (50.0% vs 32.7%, p=0.002) and significantly increased from 6.7% in 1989 to 72.2% in 2002 (p<0.001). Increased

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**Table 1** Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65±11.2</td>
</tr>
<tr>
<td>Age, range</td>
<td>35–91</td>
</tr>
<tr>
<td>Men, %</td>
<td>75.7</td>
</tr>
<tr>
<td>Obesity, %</td>
<td>18.1</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>24.8</td>
</tr>
<tr>
<td>Antidiabetic therapy, %</td>
<td>12.3</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>48.3</td>
</tr>
<tr>
<td>Antihypertensive therapy, %</td>
<td>32.3</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>29.3</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>197±43</td>
</tr>
<tr>
<td>No. of risk factors, %</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>29.8</td>
</tr>
<tr>
<td>1</td>
<td>36.1</td>
</tr>
<tr>
<td>2</td>
<td>21.6</td>
</tr>
<tr>
<td>3</td>
<td>10.3</td>
</tr>
<tr>
<td>4</td>
<td>2.1</td>
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<tr>
<td>Prior myocardial infarction, %</td>
<td>8.6</td>
</tr>
<tr>
<td>Prior cerebrovascular disease, %</td>
<td>10.4</td>
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<tr>
<td>Renal failure, %</td>
<td>9.2</td>
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<tr>
<td>Current smoker, %</td>
<td>53.2</td>
</tr>
<tr>
<td>Alcohol drinking, %</td>
<td>41.5</td>
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<tr>
<td>Infarct location, %</td>
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<tr>
<td>Anterior or lateral</td>
<td>63.1</td>
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<tr>
<td>Inferior or lateral</td>
<td>38.9</td>
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<tr>
<td>Right ventricular</td>
<td>2.9</td>
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</tbody>
</table>

**Table 2** Independent Predictors of the Use of Percutaneous Coronary Intervention

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds ratio (95% confidence interval)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.97 (0.94–0.99)</td>
<td>0.025</td>
</tr>
<tr>
<td>Men</td>
<td>2.47 (1.08–5.65)</td>
<td>0.032</td>
</tr>
<tr>
<td>Registry year</td>
<td>1.46 (1.34–1.59)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Variables incorporated into multivariate analysis included age, gender, obesity, diabetes mellitus, hypertension, hyperlipidemia, prior myocardial infarction, prior cerebrovascular disease, renal failure, smoker, alcohol drinker, anterior or lateral infarction, prodromal angina, time from onset to presentation, chest pain, dyspnea, vomiting, syncope, working, eating, sleeping, awakening, and registry year.
age was negatively associated with the probability of undergoing PCI: the proportion of PCI in patients ≥70 years tended to be lower than that in patients less than 70 (40.3% vs 48.9%, p=0.091).

Table 3 shows in-hospital outcomes: 9.7% of patients died before hospital discharge, and 3.2% had a nonfatal re-infarction. Congestive heart failure occurred in 16.9% of patients, mechanical complications in 1.5%, recurrent ischemia in 15.4%, and fatal arrhythmia in 23.3%.

Long-Term Mortality Rate

During the follow-up period (mean duration, 4.01±3.41 years), 89 patients died: 64 cardiovascular deaths. The unadjusted long-term all-cause mortality and cardiac mortality rates were 21.4% and 15.4%, respectively (Fig 1). Multivariate Cox regression analysis showed that age, prior cerebrovascular disease, renal failure, smoker, alcohol drinker, anterior or lateral infarction, prodromal angina, time from onset to presentation, chest pain, desipramine, vomiting, syncope, working, eating, sleeping, awakening, use of thrombolytic, PCI, and coronary artery bypass grafting, peak CK, peak GOT, re-infarction, congestive heart failure, mechanical complications, recurrent ischemia, second- or third-degree AV block, and ventricular fibrillation/flutter. PCI, percutaneous coronary intervention; CK, creatine kinase; GOT, glutamate oxaloacetate transaminase; AV indicates atrioventricular.

Discussion

The present study revealed the following 4 points: (1) a marked seasonal variation of the onset of AMI, as well as a marked circadian variation; (2) increased age and female sex were negatively associated with the probability of
undergoing PCI, even though PCI was the most common reperfusion therapy; (3) the unadjusted long-term all-cause mortality rate was 21.4% during the follow-up period; (4) multivariate Cox regression analysis showed that age, prior cerebrovascular disease, renal failure, Killip ≥2, and ventricular tachycardia/fibrillation are independent predictors of worse long-term mortality rates after AMI, whereas the use of PCI was independently associated with favorable long-term mortality rates.

Seasonal, Weekly, and Circadian Variation of AMI

The onset of AMI has a seasonal variation with a winter peak,10–12 and it is hypothesized that exposure to winter weather conditions may induce physiologic stresses, including sympathetic activation, hypercoagulability, and infection that increase the incidence of AMI.13 The present study showed a seasonal pattern in Japan, characterized by a marked peak of cases in the winter months, which suggests that exposure to cold temperature may trigger an AMI. Previous studies have shown that the time of onset of AMI has a circadian variation with a definite morning peak,14–17 associated with inherent biologic rhythms such as the morning surge of blood pressure,18–20 neurohumoral factors,21,22 and platelet aggregability;23–25 and a vague evening peak16,17 that is suggested to be associated with socioeconomic factors such as timing of the evening meal,26 mental stress,27–29 and overtime work.30 However, in the present study there was a morning peak but not an evening one. Because our study population had a high frequency of older patients, we speculate that there was a low frequency of workers. Although it is impossible from the present study to clearly identify the effect of employment on the nighttime work without investigating the work status of each patient, a low frequency of workers would seems to be associated with the lack of nighttime peak. Furthermore, other studies have found an increased risk for AMI on Monday, likely reflecting the increased physical and mental stress of returning to work after the weekend.31,32 However, in this study population there was not a weekly variation of the onset of AMI and although the precise reason for the lack of a Monday peak was not investigated, low frequency of worker may again be associated with this result.

Long-Term Mortality

The long-term mortality rates after AMI in Japan are lower than those in Western countries.1,2 In this study, during the follow-up period (mean duration, 4 years), the all-cause mortality rate was 21.4% and furthermore, the 1-year mortality rate after AMI in the total study population was 13.3% and that for in-hospital survivors was 4.3%. In contrast, previous studies of an unselected cohort of patients have shown that 1-year mortality rates after the onset of AMI were 15–30%.33–35 and approximately 10% after hospital discharge.36,37 Although it is difficult to make a simple comparison between present and previous studies, the 1-year mortality rate after AMI in this study seem to be lower than those in previous studies in Western countries.

Predictors of Long-Term Mortality

Predictors of long-term mortality after AMI have been reported from observational studies in Western countries,34,35,38–40 but because clinical management (the use of invasive procedures41 and length of admission42–47), as well as mortality rates in patients with AMI, differ between in Japan and Western countries,2 data from Western countries cannot be directly extrapolated to clinical practice in Japan. Therefore, it is important to accumulate clinical evidence from Japanese patients. There are some previous reports of predictors of long-term mortality in Japanese patients with AMI48–52 but they have several limitations: (1) no multivariate analysis, (2) selected patients, or (3) conducted before the PCI era. The present study of unselected AMI patients in the PCI era revealed predictors of long-term mortality by multivariate analysis. Although this study also has the limitation of being a single-center study, the data more accurately reflect real-world clinical practice in Japan. Previous studies have shown that age, prior myocardial infarction, renal failure, congestive heart failure, and arrhythmia are associated with increased risk of death after AMI48–53 and in the present study, age, prior cerebrovascular disease, renal failure, Killip ≥2, and ventricular tachycardia/fibrillation were independent predictors of worse long-term mortality after AMI, whereas the use of PCI was independently associated with favorable long-term mortality rates.

Conclusions

In this unselected series of AMI patients, the long-term mortality rate was lower than that in previous studies from Western countries. Although PCI is associated with a favorable long-term mortality, it remains underused in a subsets of Japanese patients (ie, elderly and women). Increased use of PCI may additionally reduce the long-term mortality in Japanese AMI patients, but further nation-wide surveys are needed to evaluate the general clinical data for
AMI in Japan.

Acknowledgments

We thank Naoko Mimura for her excellent assistance with data collection.

References


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Circulation Journal Vol.69, October 2005


Appendix 1

Participating Investigators