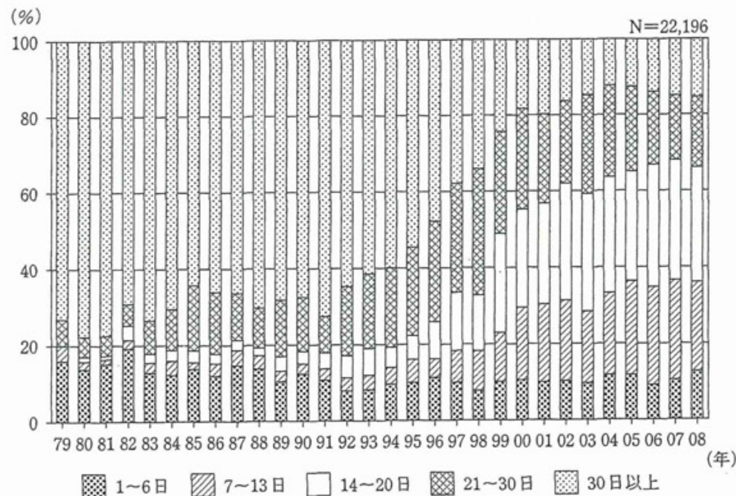


図 12　入院期間（文献1)から改変引用）

院は1979年当時20％にとどまっていたものの2008年には66％に増加していることがわかる。入院期間については2000年以降概ね20日以内が主体となっており，入院後診療についてはほぼ確立されてきているものと推測される。

## X．まとめ

1）過去30年間，心筋梗塞の発症数は明らかに増加傾向にあるものの，急性期死亡率は全体として劇的に改善してきている。

2）救急車利用率の増加，冠動脈インターベンションの普及が顕著な一方で，危険因子の管理は未だ十分ではない現状が明らかになった。

3）再灌流療法時代においても女性の死亡率は男性に比し依然として高率であり，その対策が重要であると考えられた。

## 結語

30年間に及ぶ宮城県心筋梗塞対策協議会の調査結果から，我が国の急性心筋梗塞診療の実態が明らかになった。設立当時の理念（＝急性心筋梗塞患者の救命率向上）を実践していくために，早期受診・治療を可能とする診療体制を構築していくことが今後ますます重要であると考えられる。また2010年3月11日に東日本大震災が宮城県を中心に発生した。未曾有の大災害が，心筋梗塞の発症にどのような影響を及ぼし得るのか，本協議会での30年データとの比較からその答えが得られるものと思われる。

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**ORIGINAL ARTICLE**
**Epidemiology**

# Urbanization, Life Style Changes and the Incidence/In-Hospital Mortality of Acute Myocardial Infarction in Japan

## – Report From the MIYAGI-AMI Registry Study –

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***Background:*** It remains to be examined whether urbanization and lifestyle changes are associated with the incidence and mortality from acute myocardial infarction (AMI) in Japan.

***Methods and Results:*** A total of 19,921 AMI patients (male/female 14,290/5,631) registered by the MIYAGI-AMI Registry Study from 1988 to 2009 were divided into 2 groups according to their residences; inside (urban area, n=7,316) and outside (rural area, n=11,402) of Sendai City. From 1988 to 2009, the incidence of AMI (/100,000 persons/year) increased more rapidly in the rural area (24.2 to 51.4) than in the urban area (31.3 to 40.8) ($P<0.001$), with rapid aging in both areas. Moreover, from 1998 to 2009, the age-adjusted incidence of AMI in young (<44 years) and middle-aged (45–64 years) male patients (both $P<0.05$) in the rural area increased significantly, along with a markedly increased prevalence of dyslipidemia ($P<0.001$). Although in-hospital mortality from AMI decreased in both areas over the last 20 years (both $P<0.001$), it remained relatively higher in female than in male patients and was associated with higher age of the onset, longer elapsing time for admission and lower prevalence of primary coronary intervention in female patients in both areas.

***Conclusions:*** These results demonstrate that urbanization and lifestyle changes have been associated with the incidence and mortality from AMI, although sex differences still remain to be improved. (*Circ J* 2012; **76:** 1136–1144)

**Key Words:** Acute myocardial infarction; Aging; Life-style; Risk factors; Sex

The incidence and mortality from coronary artery disease (CAD) has been declining in the United States and European countries.[1–4] These declines have been attributed to the control of risk factors (eg, hypertension, dyslipidemia and smoking) and the improvement in critical care (eg, coronary revascularization therapy).[5–7] In contrast to the Western countries, in Japan, a highly developed and racially homogeneous country that is rapidly aging, total cholesterol levels and the prevalence of obesity have been increasing as a result of lifestyle Westernization influence since the 1960s.[8,9] However, the mortality from CAD has been declining and has remained much lower compared with other Western countries from 1960 to 2000.[9–11] Importantly, there are some differences in lifestyle between people living in rural and urban areas in Japan. Indeed, it was reported that people in urban areas had greater intakes of fat and cholesterol than those in rural areas in Japan.[8] However, only a few studies have previously addressed the difference in the incidence and mortality from CAD between the rural and urban areas in Japan.[8,12]

In order to explore the annual trend for acute myocardial infarction (AMI) in Japan, we have been conducting the MIYAGI-AMI Registry Study for more than 30 years since 1979, where almost all AMI patients in the Miyagi prefecture have been prospectively registered.[10,13,14] The Miyagi prefecture, which is located in northeastern Japan, includes Sendai City, one of the 19 government-designed cites, and has a typical balance of urban and rural areas in Japan. Sendai City merged with neighboring municipalities in 1987–1988 and the population of Sendai City increased to 1,008,130 in 2000, which accounted for approximately 40% of the population of

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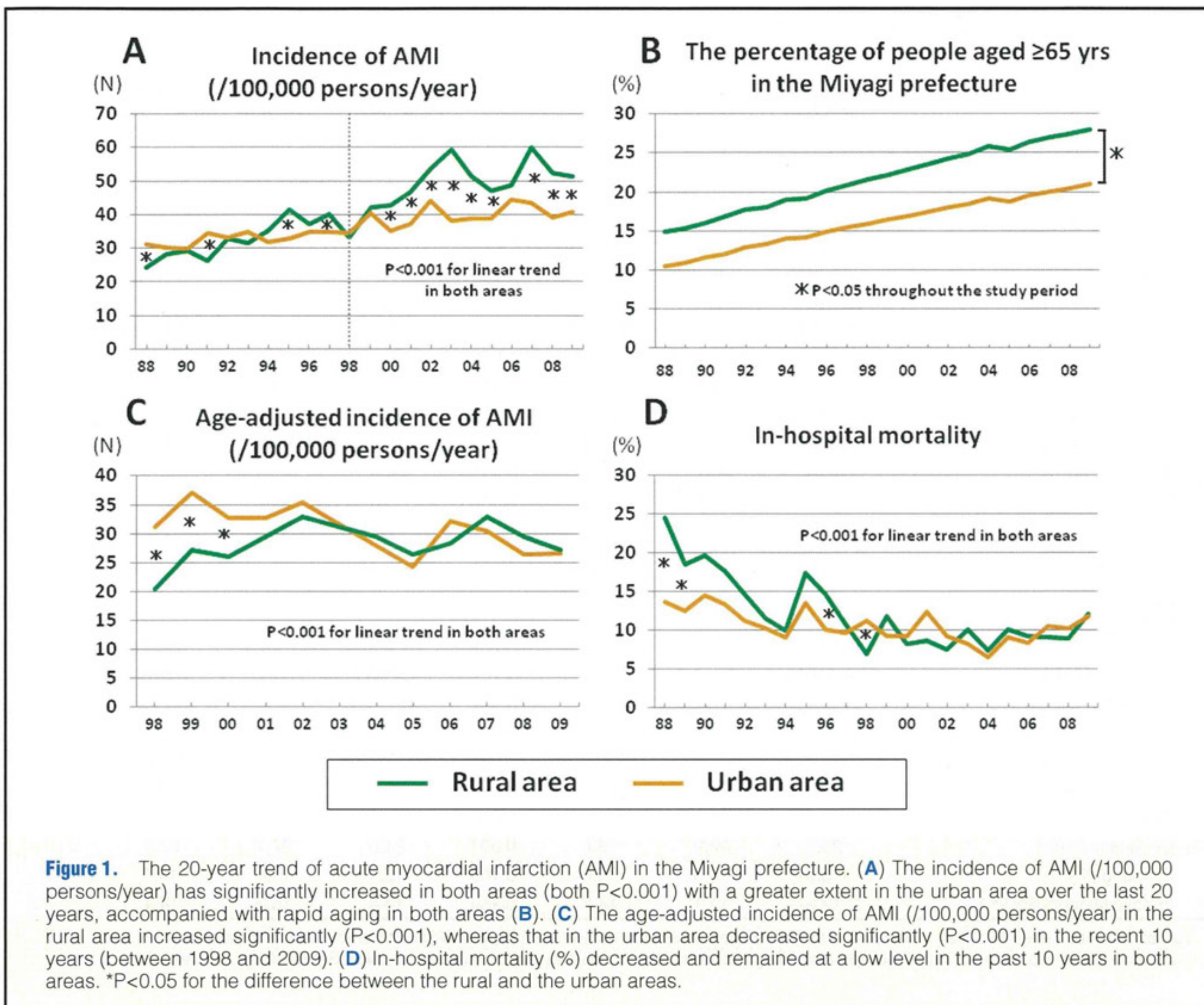


**Figure 1.** The 20-year trend of acute myocardial infarction (AMI) in the Miyagi prefecture. (**A**) The incidence of AMI (/100,000 persons/year) has significantly increased in both areas (both P<0.001) with a greater extent in the urban area over the last 20 years, accompanied with rapid aging in both areas (**B**). (**C**) The age-adjusted incidence of AMI (/100,000 persons/year) in the rural area increased significantly (P<0.001), whereas that in the urban area decreased significantly (P<0.001) in the recent 10 years (between 1998 and 2009). (**D**) In-hospital mortality (%) decreased and remained at a low level in the past 10 years in both areas. *P<0.05 for the difference between the rural and the urban areas.

the Miyagi prefecture, which was 2,365,320 in 2000. The population density of Sendai City (1,279/km² in 2000) has been much higher than that of any other parts of the Miyagi prefecture (209/km² in 2000).[15]

In the present study, we examined whether urbanization and lifestyle changes were associated with the incidence and mortality from AMI, with special reference to the difference between the urban and rural areas in our MIYAGI-AMI Registry Study.

## Methods

### The MIYAGI-AMI Registry Study

The MIYAGI-AMI Registry Study is a prospective, multicenter and observational study. As previously reported,[10,13,14] this registry was established in 1979 and all 43 hospitals with a coronary care unit and/or cardiac catheterization facility in the Miyagi prefecture have been participating (**Appendix 1**). In the Miyagi prefecture, almost all AMI patients are transferred to one of those participating hospitals via the emergency medical service. This study was approved by the Institutional Review Broad of Tohoku University Graduate School of Medicine under the condition that personal data are protected at all times.

In the MIYAGI-AMI Registry Study, the diagnosis of AMI and decision to use reperfusion therapy were made by individual cardiologists in charge. Diagnosis of AMI was made based on the WHO-MONICA criteria.[16] Briefly, it was based on the finding of typical severe chest pain accompanied by abnormal ECG changes and increased serum levels of cardiac enzymes (ie, creatine phosphokinase, aspartate amino transferase and lactate dehydrogenase). Coronary thrombolysis was performed with intravenous administration of urokinase (480–960×10³ IU for 30 min) or alteplase (290–435×10³ IU/kg for 60 min) or with intracoronary administration of urokinase (maximum 960×10³ IU) or alteplase (maximum 6.4×10⁶ IU). Rescue percutaneous coronary intervention (PCI) was performed when thrombolysis was unsuccessful. Primary PCI has been widely performed in the Miyagi prefecture since 1992, as reported previously.[10,13,14]

The registration form of the MIYAGI-AMI Registry includes the date and time of symptom onset, age, sex, pre-hospital management (eg, use of ambulance, time interval from the onset of symptoms to admission), infarction site, coronary risk factors (hypertension, diabetes mellitus, dyslipidemia and smoking), reperfusion therapies (eg, thrombolysis and/or PCI), and in-hospital outcome (eg, in-hospital mortality). In our MIYAGI-AMI Registry Study, we have revised the registra-

**Table.** Clinical Characteristics and Outcome of the Study Population

| | Rural area | | | P value for trend | Urban area | | | P value for trend |
|---|---|---|---|---|---|---|---|---|
| | 1998–2001 (n=2,145) | 2002–2005 (n=2,699) | 2006–2009 (n=2,807) | | 1998–2001 (n=1,529) | 2002–2005 (n=1,508) | 2006–2009 (n=1,682) | |
| **Male** | | | | | | | | |
| Age (years) | 66.2±12.4* | 67.0±12.9* | 66.7±12.7 | 0.373 | 65.0±12.7 | 65.2±12.9 | 65.9±12.9 | 0.046 |
| Age-adjusted incidence of AMI (/$10^5$ persons/year) | | | | | | | | |
| All | 42.3±3.8* | 47.2±3.2 | 47.3±2.5 | 0.274 | 55.1±4.7 | 49.3±10.9 | 47.9±4.1 | 0.163 |
| <45 years old | 4.9±0.9 | 5.8±0.7 | 6.9±1.2 | 0.018 | 5.1±0.7 | 5.7±0.5 | 6.0±2.7 | 0.460 |
| 45–64 years old | 66.6±6.3* | 83.2±5.5 | 88.9±14.9 | 0.016 | 91.2±4.9 | 85.9±21.0 | 83.7±8.2 | 0.402 |
| 65–74 years old | 170.2±32.9 | 186.3±39.2 | 179.3±17.8 | 0.679 | 228.2±18.1 | 208.1±56.3 | 180.1±15.6 | 0.065 |
| ≥75 years old | 253.5±47.0* | 261.1±62.9 | 250.8±33.4 | 0.937 | 355.0±48.0 | 277.8±73.4 | 308.0±19.7 | 0.207 |
| Hypertension (%) | 46.1 | 59.5* | 60.9 | <0.001 | 48.2 | 54.3 | 63.0 | <0.001 |
| Diabetes mellitus (%) | 27.5 | 32.9 | 29.5* | 0.265 | 30.6 | 31.6 | 34.1 | 0.070 |
| Dyslipidemia (%) | 22.4* | 34.1* | 41.4 | <0.001 | 32.2 | 39.0 | 42.0 | <0.001 |
| Smoking (%) | 40.6 | 42.1 | 40.6 | 0.956 | 44.0 | 41.8 | 38.6 | 0.008 |
| In-hospital mortality (%) | 7.6 | 6.8 | 7.8 | 0.832 | 8.8 | 5.7 | 8.7 | 0.997 |
| **Female** | | | | | | | | |
| Age (years) | 74.1±9.7 | 76.1±11.1 | 75.3±11.4 | 0.017 | 74.4±10.4 | 74.6±12.0 | 75.3±11.4 | 0.224 |
| Age-adjusted incidence of AMI (/$10^5$ persons/year) | | | | | | | | |
| All | 11.5±2.4* | 13.6±1.1 | 13.2±1.0 | 0.202 | 15.1±1.2 | 11.9±2.0 | 12.4±2.4 | 0.077 |
| <45 years old | 0.2±0.4 | 0.4±0.2 | 0.7±0.5 | 0.114 | 0.2±0.2 | 0.5±0.3 | 0.5±0.7 | 0.297 |
| 45–64 years old | 10.5±4.2 | 13.7±3.1 | 18.1±4.1 | 0.102 | 10.1±1.6 | 11.0±2.2 | 16.1±7.1 | 0.102 |
| 65–74 years old | 54.5±1.8* | 65.0±8.4 | 56.4±4.4 | 0.602 | 84.5±5.8 | 55.3±6.5 | 48.9±9.1 | <0.001 |
| ≥75 years old | 100.8±17.4* | 135.7±14.9 | 120.8±7.9 | 0.076 | 165.9±13.9 | 131.4±19.4 | 129.8±17.2 | 0.016 |
| Hypertension (%) | 55.8 | 69.3 | 67.5 | <0.001 | 60.2 | 63.5 | 65.0 | 0.137 |
| Diabetes mellitus (%) | 29.3 | 36.1 | 35.1 | 0.032 | 32.5 | 33.2 | 34.5 | 0.510 |
| Dyslipidemia (%) | 25.8 | 30.9 | 38.6 | <0.001 | 31.0 | 37.1 | 37.7 | 0.039 |
| Smoking (%) | 8.9 | 6.6* | 10.6 | 0.163 | 12.1 | 13.4 | 14.1 | 0.383 |
| In-hospital mortality (%) | 12.3 | 11.1 | 14.5 | 0.254 | 14.4 | 15.3 | 14.1 | 0.892 |

Values are mean ± SD or n (%). *P<0.05 for the difference between rural and urban areas. AMI, acute myocardial infarction.
Study population was divided into 2 groups according to the residence: inside (urban area) and outside Sendai City (rural area).

tion form gradually over the last 30 years. Thus, although the incidence of AMI and related data (time of onset, age and sex) are available for the last 30 years, the date on the pre-hospital management, infarction site, coronary risk factors, reperfusion therapies, duration of hospitalization and in-hospital outcome are only available for the last 10–20 years, which were analyzed in the present study.

### Data Analysis

In the present study, we have registered a total of 19,921 patients with AMI (male/female 14,290/5,631) over the last 20 years after the municipal merger in 1988. In particular, we have focused on the patients registered between 1998 and 2009 (total, 12,491; male/female, 8,969/3,522), who were divided into 2 groups according to their residences; inside (urban area, n=4,719) and outside Sendai City (rural area, n=7,651), after excluding the patients whose residences were unknown (n=159). We also divided the total observational period of 12 years into the 3 periods: 1998–2001, 2002–2005 and 2006–2009. To calculate the sex- and age-adjusted incidence of AMI (/100,000 person/years), we applied the direct standardization method using the age distribution of the Japanese population from the 2000 census,[5] as the standard population. In addition, in order to clarify the age-specific trend, we categorized the age at AMI onset into the 4 groups: ≤44 (young), 45–64 (middle-aged), 65–74 (old) and ≥75 years old (high-old).[15]

Results are expressed as mean±SD. Linear trends were examined for continuous variables by using analysis of variance (ANOVA) with repeated measures or the Jonckheere-Terpstra trend test as appropriate, and for categorical variables by using the chi-square test for trend. Differences in mean values were examined with a t-test, Mann-Whitney test or chi-square test as appropriate. Multiple logistic regression analysis was used to examine determinants of risk factor prevalence in AMI patients. Variables used for analysis included: sex, age at onset of AMI (per 10 years), study periods (1998–2001, 2002–2005 and 2006–2009), residence (rural vs. urban), and other risk factors. The odds ratios (ORs) and 95% confidence intervals (95%CI) were calculated. A P-value less than 0.05 were considered to be statistically significant. All statistical analyses were performed using the statistical software SPSS version 18 for Windows.

## Results

Over the last 20 years, the incidence of AMI (/100,000 persons/year) significantly increased in both the rural and the urban areas in the Miyagi prefecture (2.1- and 1.3-fold, respectively, both P<0.001) (**Figure 1A**). Furthermore, the extent of the increase in AMI incidence was greater in the rural area than in the urban area, finally exceeding that in the urban area after 2000. These changes were accompanied with rapid aging

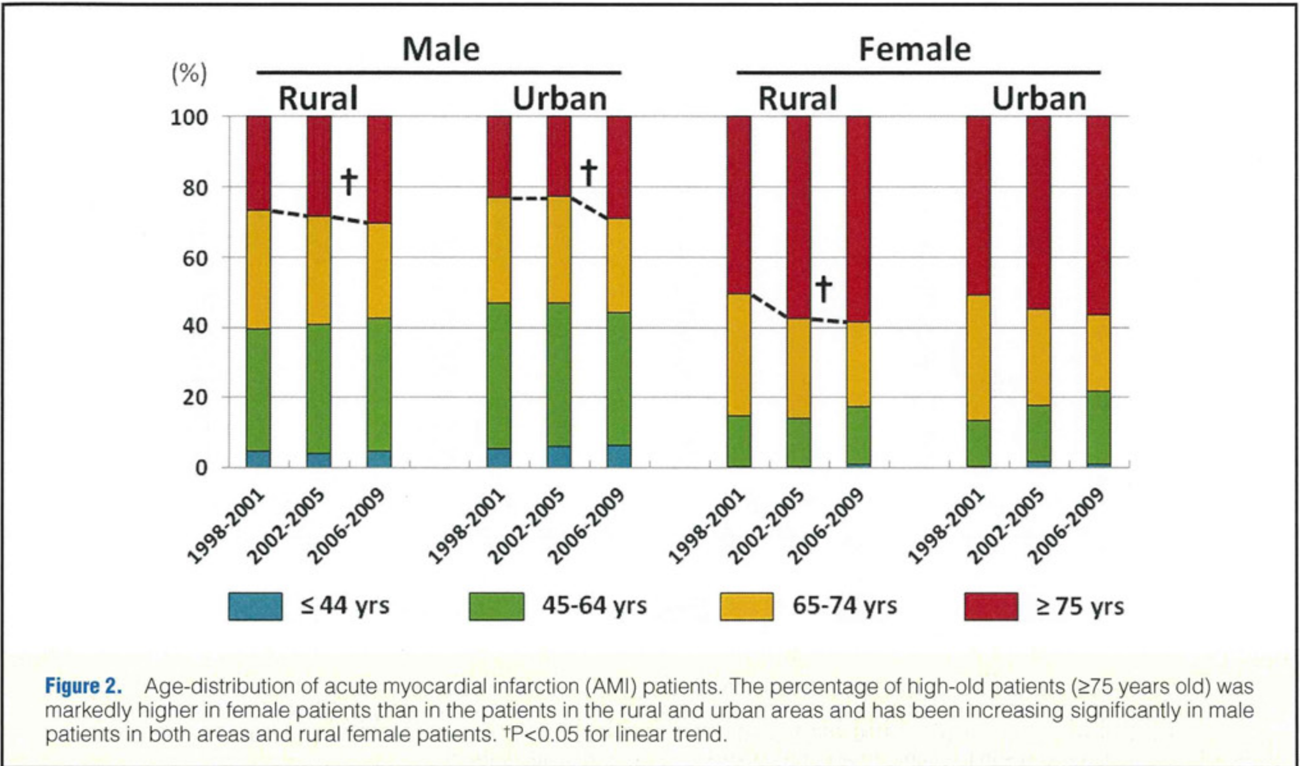


**Figure 2.** Age-distribution of acute myocardial infarction (AMI) patients. The percentage of high-old patients (≥75 years old) was markedly higher in female patients than in the patients in the rural and urban areas and has been increasing significantly in male patients in both areas and rural female patients. †P<0.05 for linear trend.

**Figure 3.** Age-specific incidence of acute myocardial infarction (AMI) (/100,000 persons/year). The significant increase in the age-adjusted incidence of AMI was noted in <44 and 45–64 year old rural male patients, and the significant decrease was noted in 65–74 and >75 year old urban female patients. Values are presented as mean±SE. *P<0.05 for the difference between rural and urban areas. †P<0.05 for linear trend.

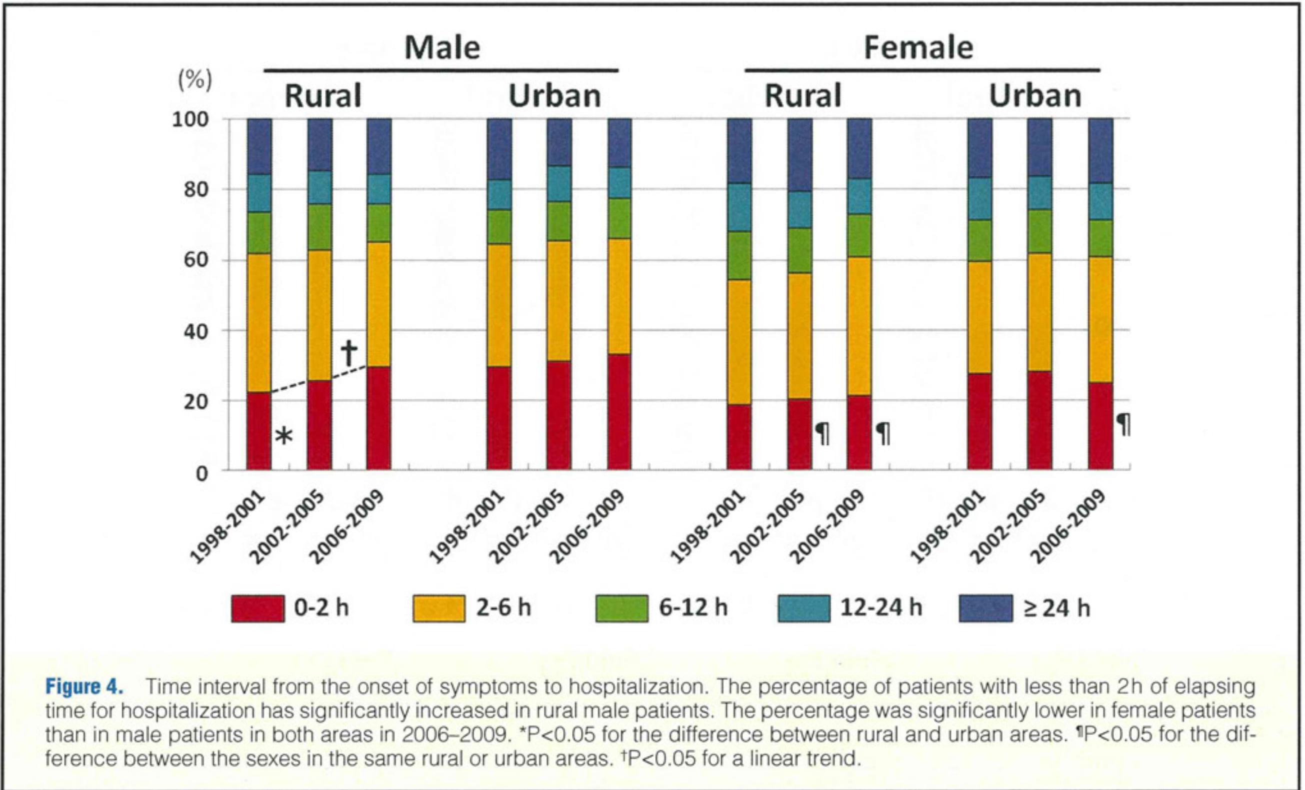


**Figure 4.** Time interval from the onset of symptoms to hospitalization. The percentage of patients with less than 2h of elapsing time for hospitalization has significantly increased in rural male patients. The percentage was significantly lower in female patients than in male patients in both areas in 2006–2009. *P<0.05 for the difference between rural and urban areas. ¶P<0.05 for the difference between the sexes in the same rural or urban areas. †P<0.05 for a linear trend.

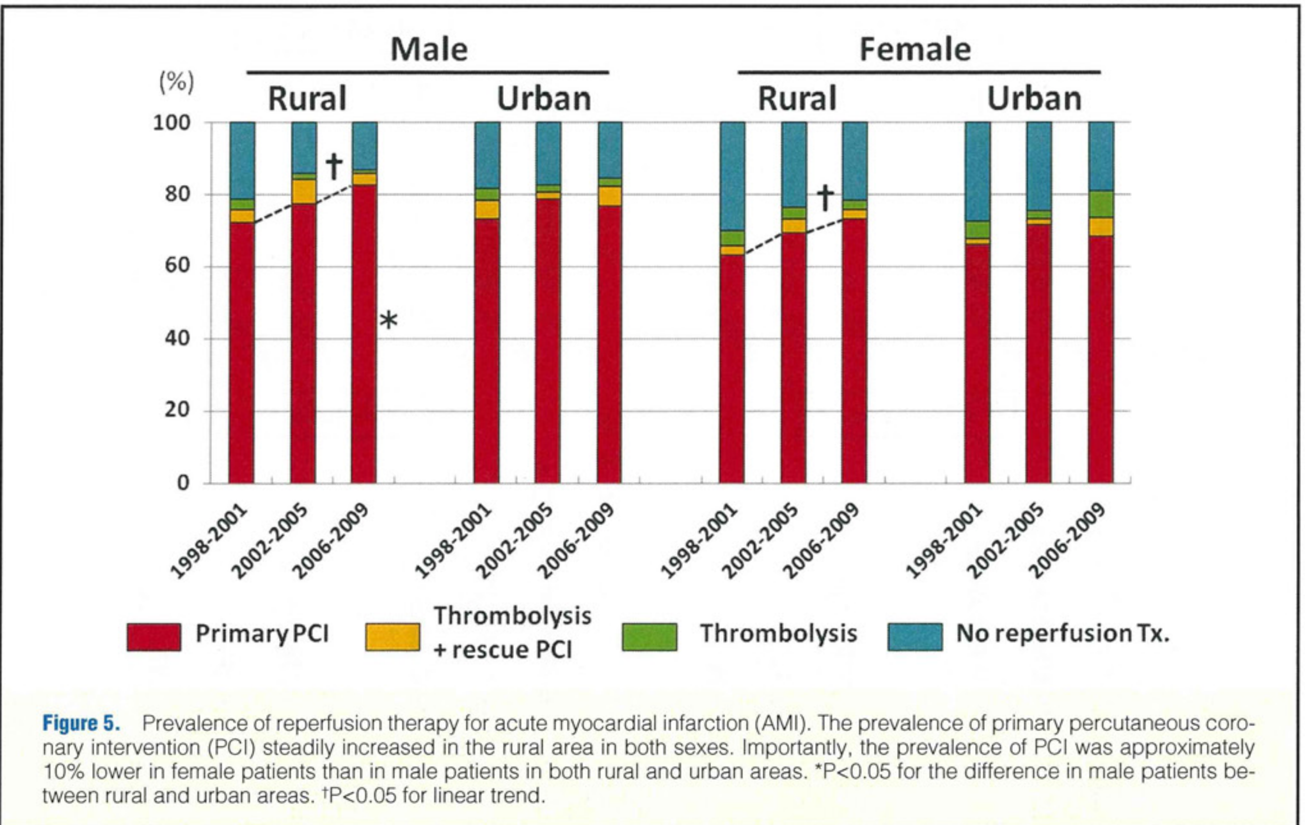


**Figure 5.** Prevalence of reperfusion therapy for acute myocardial infarction (AMI). The prevalence of primary percutaneous coronary intervention (PCI) steadily increased in the rural area in both sexes. Importantly, the prevalence of PCI was approximately 10% lower in female patients than in male patients in both rural and urban areas. *P<0.05 for the difference in male patients between rural and urban areas. †P<0.05 for linear trend.

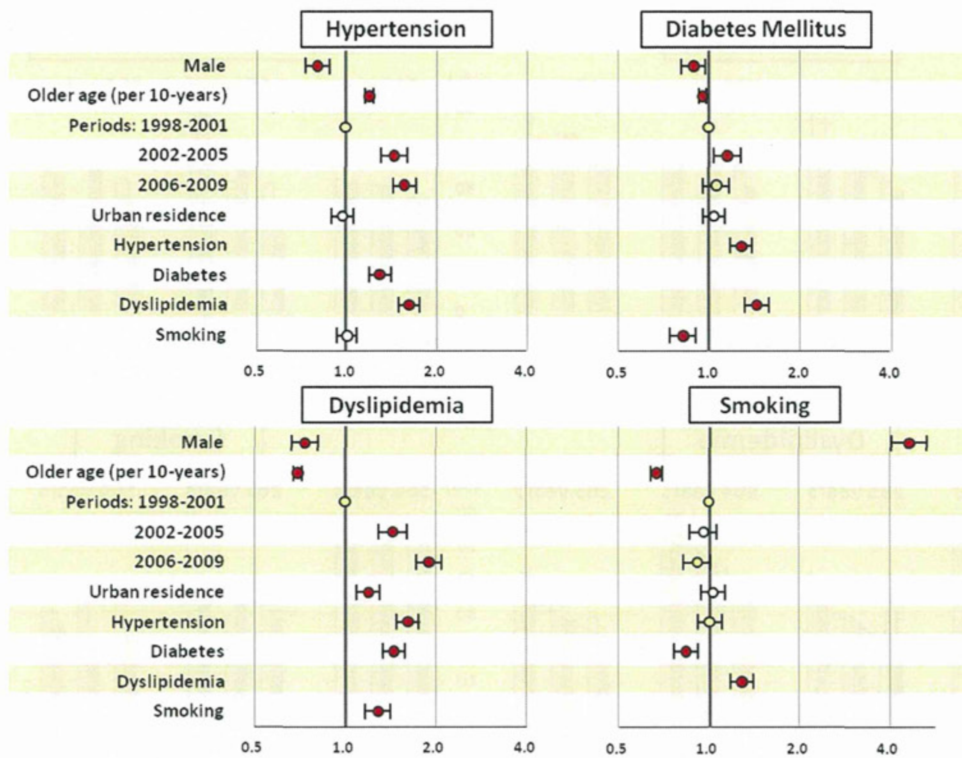


**Figure 6.** Multivariate analysis of coronary risk factors in acute myocardial infarction (AMI) patients. During the study periods, the prevalence of hypertension and dyslipidemia significantly increased in AMI patients. Hypertension was associated with older age but not with residence, whereas dyslipidemia was associated with younger age and urban residence. Smoking was associated with male sex and younger age. The odds ratios and 95% confidence intervals for factors are shown with red circles for P<0.05.

in both areas in the Miyagi prefecture (**Figure 1B**). Following age adjustment (**Figure 1C**), the incidence of AMI in the rural area increased significantly (P<0.001), whereas that in the urban area decreased significantly (P<0.001) in the recent 10-year period (between 1998 and 2009). In contrast, in-hospital mortality significantly decreased in both areas (both P<0.001), but to a greater extent in the rural area (0.5-fold in the rural area and 0.9-fold in the urban area) (**Figure 1D**). In 1998–2001, there was no significant difference in in-hospital mortality between the rural and urban male patients (P=0.263), and in-hospital mortality remained low (~8%) from 1998–2001 to 2006–2009 in both the rural and urban male patients (rural: P=0.832; urban: P=0.997) (**Table**). Importantly, in-hospital mortality of the female patients in both the rural and the urban areas remained doubled compared with the male patients during the study period (**Table**).

The clinical characteristics of the AMI patients in the present study are shown in **Table**. The female patients were approximately 10 years older than the male patients and approximately a half of them were ≥75 years-old in 1998–2001 in both areas, with a significant further increase in the rural area (male, P<0.001; female, P<0.001) and such a trend in the urban area (male, P=0.054; female, P=0.176) (**Figure 2**). In 1998–2001, the age-adjusted incidence of AMI was significantly lower in the rural area than in the urban area for both sexes (male, P=0.019; female, P=0.035) (**Table**). However, the difference between the 2 areas became insignificant in 2006–2009 for both sexes (male, P=0.824; female, P=0.530). When investigating the age-specific trend, the significant increase in the age-adjusted incidence of AMI was noted in the young (<44 years-old) and middle age (45–64 years-old) male patients only in the rural area (young, P=0.018; middle age, P=0.016), and the significant decrease was noted in the old (65–74 years-old) and high-old (>75 years-old) female patients in the urban area (old, P<0.001; high-old, P=0.016) (**Table**, **Figure 3**).

Regarding the time from the onset of AMI to admission, the percentage of the patients with less than 2h of elapsing time at admission was significantly lower in the rural area than in the urban area for the male patients in 1998–2001 (P<0.001) (**Figure 4**). However, the difference became insignificant in 2006–2009 (P=0.051), accompanied with the significant increase in the percentage in the rural area (rural, P<0.001; urban, P=0.082). Importantly, in the rural female patients, the percentage of patients with less than 2h of elapsing time at admission remained at a low level (~20%), and the difference between the sexes in the rural area became greater from 1998–2001 (P=0.086) to 2006–2009 (P<0.001). In contrast, the difference between the sexes in the urban area was significant in 2006–2009 (P=0.04). Moreover, the prevalence of primary PCI in the female patients was lower by ~10% compared with the male patients in both areas (**Figure 5**). In the male patients, the prevalence of primary PCI significantly increased only in the rural area from 1998–2001 to 2006–2009 (rural, P<0.001; urban, P=0.054), and a similar trend was also noted in the female patients (rural, P<0.001; urban, P=0.176).

Multivariate analysis of the coronary risk factors in AMI patients showed that the prevalence of hypertension and dys-

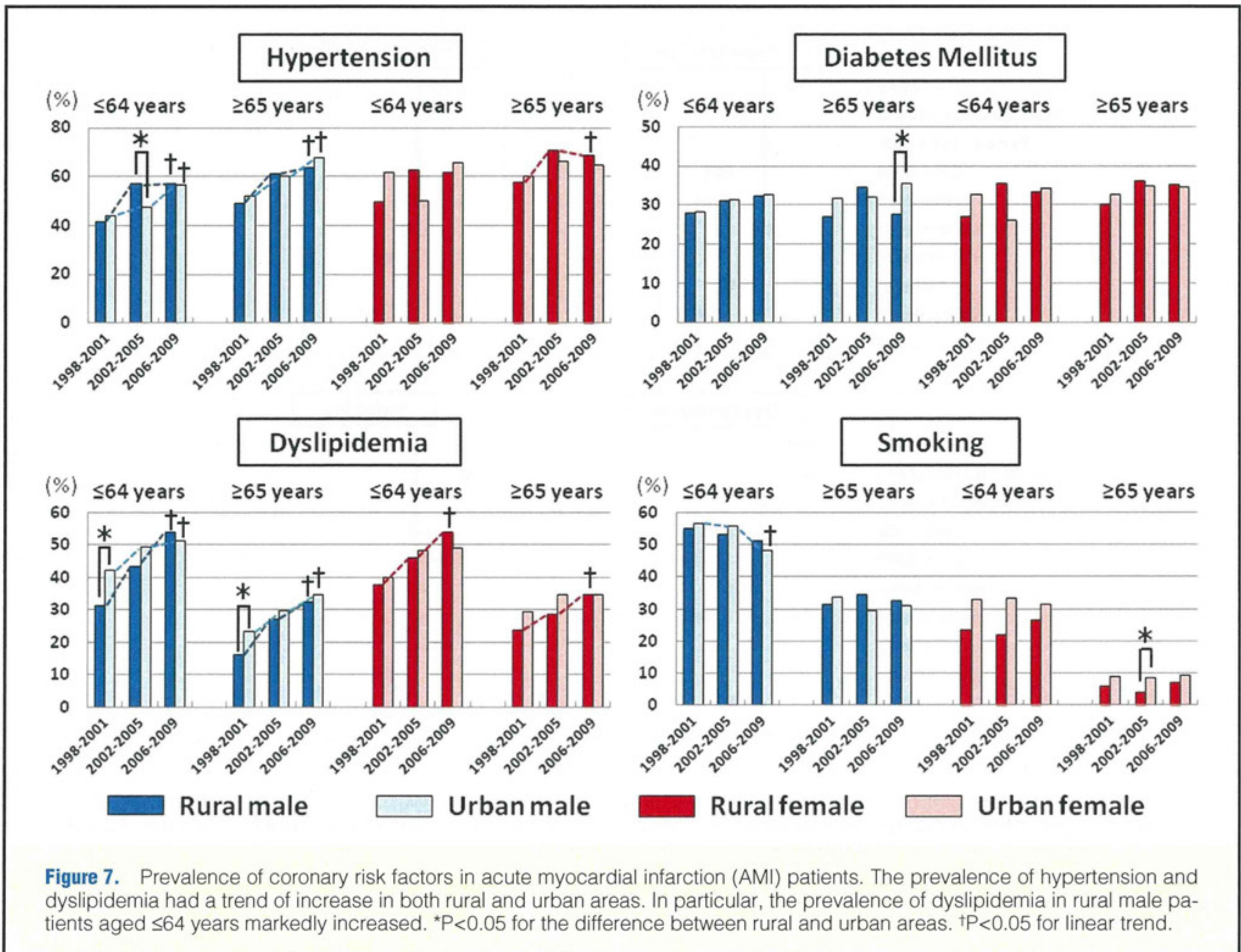


**Figure 7.** Prevalence of coronary risk factors in acute myocardial infarction (AMI) patients. The prevalence of hypertension and dyslipidemia had a trend of increase in both rural and urban areas. In particular, the prevalence of dyslipidemia in rural male patients aged ≤64 years markedly increased. *P<0.05 for the difference between rural and urban areas. †P<0.05 for linear trend.

lipidemia significantly increased and that of diabetes tended to increase (Figure 6). Hypertension was associated with older age but not with residence, whereas dyslipidemia was associated with younger age and urban residence. Although the prevalence of dyslipidemia in the male patients was significantly lower in the rural area than in the urban area in 1998–2001, it significantly increased in the rural area and the difference between the 2 areas became insignificant in 2006–2009 (Table). Moreover, the progressive increase in the prevalence of dyslipidemia was noted in both areas for both sexes with a more sharp increase in the rural area (Figure 7). Smoking was associated with male sex and younger age, but not with residence (Figure 6), and the prevalence of smoking largely remained unchanged in both areas for both sexes (Figure 7).

## Discussion

The novel findings of the present study were that the incidence of AMI increased more rapidly in the rural area than in the urban area, with rapid aging in both areas. Moreover, the incidence of AMI in the rural male patients ≤64 years-old was increased along with the marked increase in the prevalence of dyslipidemia in Japan. Although in-hospital mortality from AMI markedly decreased in both areas over the last 20 years, it remained relatively high in female patients than in male patients in both areas. To the best of our knowledge, this is the first study that demonstrates the association between urbanization, life-style changes and the incidence and mortality of AMI in the largest number of patients in Japan.

### Comparison of the Incidence of AMI Between Rural and Urban Areas

Although in the United States and European countries, the incidence of CAD has been declining in the last decades,[1,2,4] the present study demonstrates that the incidence of AMI has been rapidly increasing in both the rural and urban areas over the last 20 years, with a more noted increase in the former than in the latter. However, this tendency has disappeared following age adjustment in recent years only in the urban area, which implied that the increased tendency in the incidence of AMI in the rural area might be not be associated with rapid aging alone in recent years.

There were few studies that addressed the difference in the incidence of CAD between rural and urban areas in Japan. The Akita-Osaka study is the community-based survey, where the residents of the Yao City, Osaka prefecture (an urban community with a total census population of 23,552 in 2000) and those of Ikawa Town, Akita prefecture (a rural community with a total census population of 6,116 in 2000) were compared during the period of 1964–2003.[12] In this study, significant increases in the age-adjusted incidence of AMI and sudden cardiac death were noted in Yao City (in male patients from 1980 to 2003) but not in Ikawa City in both sexes.[12] The present study confirmed the results of the Akita-Osaka study

in the rural and urban areas of the same Miyagi prefecture. The Yamagata AMI Registry study provided more recent data and an age-specific trend in the period of 1993–2007.[17] The population density of the Yamagata prefecture was 133/km$^2$ in 2000, which was comparable with that of the rural area in the present study.[15] In this study, the age-adjusted incidence of AMI in the male but not that in the female patients significantly increased. In particular, the male population who were younger than 65 years old showed a marked increase in AMI, a consistent finding with the present results for the rural area. These results indicate that the incidence of AMI has been increasing in the younger male population in the rural areas of Japan. Taken together, unlike the trend in Western countries, it appears that the incidence of AMI has been increasing in Japan to a greater extent in the rural area than in the urban area over the last 20 years and has been associated with rapid aging.

### Decreasing In-Hospital Mortality and Improvement in Critical Care

In the present study, the in-hospital mortality from AMI significantly decreased in both the urban and the rural areas over the last 20 years. The present study also demonstrates that primary PCI was performed more frequently in the rural area than in the urban area, along with the shortening in the elapsing time from the onset to hospitalization. The recent progress in critical care might have beneficial effects, overcoming the rapid aging in AMI patients.

In the most recent 10 year period, the in-hospital mortality remained at a low level in male patients, whereas in female patients, the mortality remained doubled compared with the male patients in both the rural and the urban areas. It was previously reported that the poorer outcome of the female AMI patients could be caused by multiple factors, including higher age, higher risk profiles, longer elapsing time from the onset to hospitalization, higher incidence of Killip class ≥2, and less frequent use of primary PCI.[18–20] Indeed, in the present study, the female patients were approximately 10 years older than the male patients and half of them were older than 75 years and needed a longer time from the onset of AMI to hospitalization in the both areas in 2006–2009. These points might have limited the use of primary PCI with a resultant poor outcome for the female AMI patients in the present study.

### Changes in the Prevalence of Coronary Risk Factors in AMI Patients

The WHO-MONICA studies, as well as several Japanese cohort studies, demonstrated that the incidence of cardiovascular diseases increased and were associated with the clustering of risk factors.[21–23] In the present study, the prevalence of hypertension and dyslipidemia in AMI patients significantly increased in both the rural and urban areas. Importantly, there was a significant difference in the prevalence of dyslipidemia between the rural and urban areas with a marked increase noted in the rural area, especially in those male patients aged ≤64 years. Indeed, previous studies demonstrated that dyslipidemia is an independent risk factor in male but not in female patients,[17,24] and in the Yamagata-AMI Registry study, the increased prevalence of dyslipidemia in the younger male patients with AMI was also associated with an increased incidence of AMI.[17] In the Miyagi prefecture, the intake of animal fat was significantly higher in the rural than in the urban area in 2000 (rural 20.7 g/day vs. urban 23.4 g/day, $P<0.05$).[25] Moreover, in Japan, fat intake and serum levels of total cholesterol were higher in the urban than in the rural areas in 1966; however, the difference in cholesterol levels between the 2 areas became smaller in 1966–1985 along with the influence of Westernization of food habits in the rural area.[8] Taken together, it might indicate that the increase in the incidence of AMI in younger male patients in the rural area was likely to be associated with the marked increase in the prevalence of dyslipidemia.

The present study also demonstrates the increase in the prevalence of hypertension in AMI patients. In the Tohoku district, including the Miyagi prefecture, the prevalence of hypertension was relatively higher compared with other parts of Japan,[12,26] and thus more careful and strict control of risk factors is needed.

The prevalence of smoking remained high not only in the urban areas but also in the rural areas. In particular, in the younger male patients, the prevalence of smoking (~50%) was higher compared with the general Japanese population (36.8% in males and 9.1% in females in 2008).[27] Importantly, in the younger urban female patients, it remained more than 30%; 3 times higher than in the general Japanese population.

### Study Limitations

Several limitations should be mentioned for the present study. First, although in the Miyagi prefecture, almost all AMI patients are transferred to our participating hospitals via the established emergency medical system, we cannot completely confirm that all patients have been registered in our registry. Second, while the MIYAGI-AMI Registry Study has been conducted over 20 years, the diagnosis of AMI has been changing.[28] In the present study, the diagnosis was made on the basis of the WHO-MONICA criteria with creatine kinase (CK).[16] Indeed, troponins are widely used in recent clinical practice and are more sensitive and specific biomarkers of myocyte necrosis than CK,[29] which might affect the results. Third, this study is an observational study and cannot reach the cause-effect relationship. Moreover, we did not examine the prevalence of risk factors in control subjects and did not collect the data of medical treatment for prevention, thus we were unable to precisely estimate the influence of risk factors on the incidence of AMI. Finally, in the present study, we did not examine the long-term mortality but only examined in-hospital mortality. The increasing incidence of decreasing in-hospital mortality from AMI in the Japanese population has apparently resulted in the recent increase in the number of patients with ischemic heart failure, as recently demonstrated in our heart failure cohort study, the CHART-1 and the CHART-2 studies.[30,31] Thus, a more effective strategy to improve the management of post-infarction heart failure needs to be developed.

## Conclusions

Our MIYAGI-AMI Registry Study demonstrates that urbanization and life-style changes have been associated with the incidence and mortality of AMI in Japan, although sex differences still remain to be improved.

### Acknowledgments

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Miyagi Cardiovascular and Respiratory Center, Osawa N, MD.
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ORIGINAL ARTICLE
Epidemiology

# Trends in Acute Myocardial Infarction Incidence and Mortality Over 30 Years in Japan:
## Report From the MIYAGI-AMI Registry Study

Toru Takii, MD; Satoshi Yasuda, MD; Jun Takahashi, MD; Kenta Ito, MD;
Nobuyuki Shiba, MD; Kunio Shirato, MD; Hiroaki Shimokawa, MD;
on behalf of the MIYAGI-AMI Study Investigators

***Background:*** Worldwide, the rate of aging is highest in Japan, especially the female population. To explore the trends for acute myocardial infarction (AMI) in Japan, the MIYAGI-AMI Registry Study has been conducted for 30 years since 1979, whereby all AMI patients in the Miyagi prefecture are prospectively registered.

***Methods and Results:*** In 1979–2008, 22,551 AMI patients (male/female 16,238/6,313) were registered from 43 hospitals. The age-adjusted incidence of AMI (/100,000 persons/year) increased from 7.4 in 1979 to 27.0 in 2008 (P<0.001). Although control of coronary risk factors remained insufficient, the rates of ambulance use and primary percutaneous coronary intervention (PCI) have increased, and the overall in-hospital mortality (age-adjusted) has decreased from 20.0% in 1979 to 7.8% in 2008 (P<0.0001). However, the in-hospital mortality remains relatively higher in female than in male patients (12.2% vs 6.3% in 2008). Female patients were characterized by higher age and lower PCI rate.

***Conclusions:*** The MIYAGI-AMI Registry Study demonstrates the steady trend of an increasing incidence, but decreasing mortality, for AMI in Japan over the past 30 years, although the female population still remains at higher risk for in-hospital death, despite improvements in the use of ambulances and primary PCI. (*Circ J* 2010; **74:** 93–100)

**Key Words:** Acute myocardial infarction; Aging; Gender; Risk factors

Acute myocardial infarction (AMI) is a major cause of morbidity and mortality worldwide. In the United States, nearly 1 million patients suffer from AMI each year.[1] In the past decades, industrialization, urbanization, and associated life-style changes have taken place worldwide as the population grows older in association with the epidemics of obesity and metabolic syndrome. Especially in Japan, these changes have become more evident because the rate of aging is the highest in the world and the westernization of lifestyle has progressed rapidly.[2] In order to estimate the trends in the burden of disease, particularly that of AMI, it is important to monitor and track the incidence and mortality of AMI in the same community for a long time. Indeed, the World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease (WHO-MONICA) project reported the prevalence and case-fatality rate in 21 countries,[3] but Japan was not included. Moreover, in Japan, there have been few studies specifically for AMI and most of them have included a small number of annual events with a relatively short monitoring period.[4–7]

**Editorial p 43**

To explore the actual trend for AMI reflecting "real-world" practice in Japan, we have been conducting the MIYAGI-AMI Registry Study for 30 years since 1979, whereby all AMI patients in the Miyagi prefecture have been prospectively registered and there has been a relatively stable population over those years.[8,9]

## Methods

### The MIYAGI-AMI Registry Study

The Miyagi prefecture is located in northeastern Japan and has had a relatively stable population of approximately 2 million over the last 30 years (2,054,000 in 1979 and

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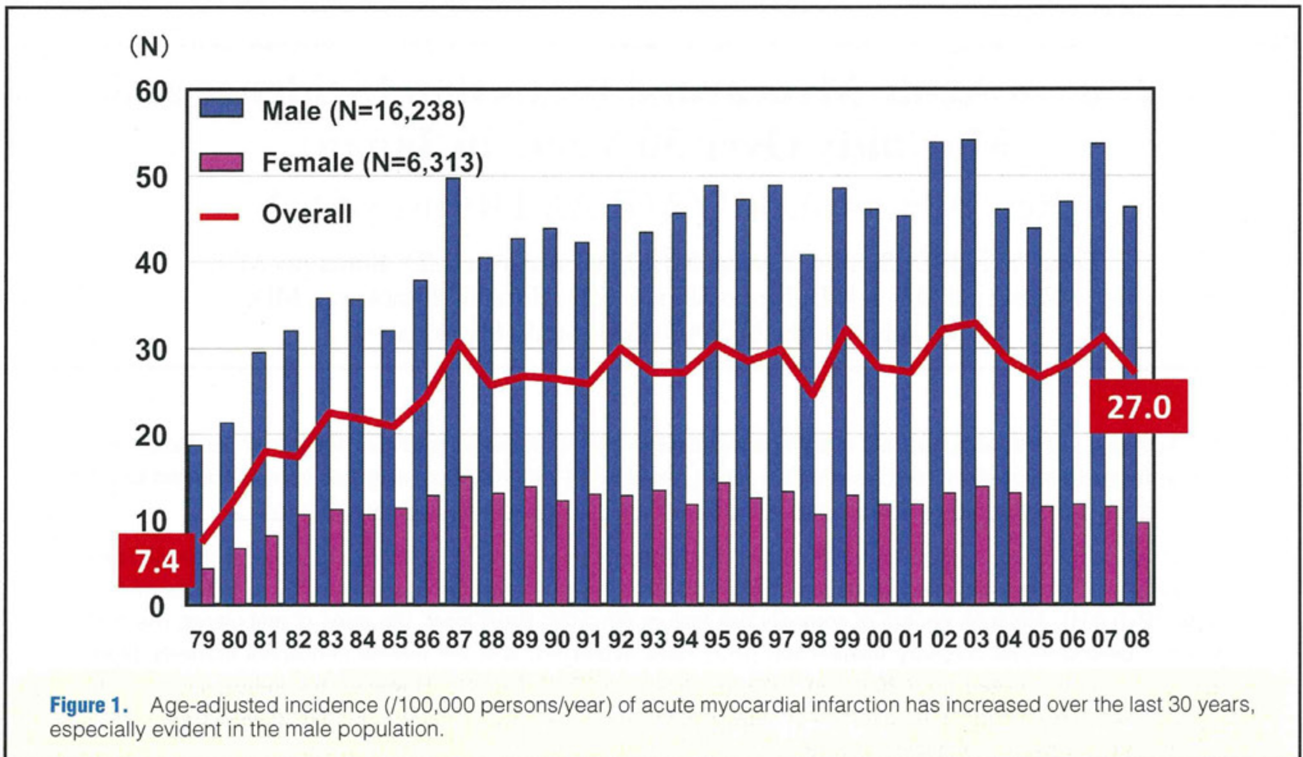


**Figure 1.** Age-adjusted incidence (/100,000 persons/year) of acute myocardial infarction has increased over the last 30 years, especially evident in the male population.

2,340,000 in 2008). The MIYAGI-AMI Registry Study is a prospective, multicenter, observational study. Details of data collection have been published previously.[8,9] Briefly, this registry was established in 1978 and the 43 major hospitals with a coronary care unit and/or cardiac catheterization facilities in the Miyagi prefecture have been participating (Appendix 1). In our study, almost all the patients with AMI were finally admitted to 1 of the 43 participating hospitals in the Miyagi prefecture, enabling us to precisely examine the practice for AMI. This study was approved by the Institutional Review Board of Tohoku University Graduate School of Medicine, under the condition that personal data are protected at all times.

Diagnosis of AMI was made by the individual cardiologists in charge, based on the WHO-MONICA criteria.[3] Generally, it was based on the findings of typical chest pain symptoms, ECG changes and increased serum levels of cardiac enzymes (ie, creatine phosphokinase, aspartate aminotransferase and lactate dehydrogenase).

The registration form included the date and time of symptom onset, age, sex, pre-hospital management (eg, use of ambulance, time interval from the onset of symptoms to admission), infarction site, coronary risk factors (hypertension, diabetes mellitus, dyslipidemia, and smoking), reperfusion therapies (eg, thrombolysis or percutaneous coronary intervention (PCI)), duration of hospitalization and in-hospital outcome (eg, in-hospital mortality). In the Miyagi-AMI Registry Study, we have revised the registration form step by step over the past 30 years. Thus, although the incidence of AMI and related data (time of onset, age and sex) are available for those 30 years, the date of pre-hospital management, infarction site, coronary risk factors, reperfusion therapies, duration of hospitalization, and in-hospital outcome are available for the past 10–20 years.

In the Miyagi-AMI Registry Study, the decision of reperfusion was made by the individual cardiologists in charge. Primary PCI has been commonly performed since 1992, according to the protocol of each hospital. Thrombolysis was performed with intravenous administration of urokinase (480–960×10³ IU for 30 min) or alteplase (290–435×10³ IU/kg for 60 min) or with intracoronary administration of alteplase (maximum 6.4×10⁶ IU) or urokinase (maximum 960×10³ IU).[2,3] Rescue PCI was performed when thromolysis was unsuccessful in terms of symptoms, ECG changes and/or coronary blood flow.

### Data Analysis

In the present study, we registered a total of 22,551 patients with AMI (males/females 16,238/6,313) who were hospitalized between 1979 and 2008. Sex- and age-adjusted incidence rates of AMI per 100,000 person-years were calculated. To adjust the age distribution differences among the periods, we applied the direct method using the Japanese population from the 2000 census,[10] as the standard population.

Results are expressed as mean ± SD. Trend in age-adjusted incidence, age-adjusted in-hospital mortality, and use of ambulance were assessed using the Cochran-Armitage trend test.[11,12] Age and therapy differences were estimated by the $\chi^2$-test. These analyses were carried out with SAS software version 9.1 (SAS Institute, Inc, Cary, NC, USA). P-values <0.05 were considered to be statistically significant.

## Results

The overall age-adjusted incidence of AMI (/100,000 persons/year) markedly increased by 3.6-fold, from 7.4 in 1979 to 27.0 in 2008 (P<0.001) (**Figure 1**). The average age of the male and female AMI patients in the whole period was 65±13 and 75±11 years, respectively. In males, the age-adjusted incidence of AMI (/100,000 persons/year) significantly increased by 2.5-fold, from 18.7 in 1979 to 46.4 in 2008 (P<0.0001), whereas in females, it tended to be increased by

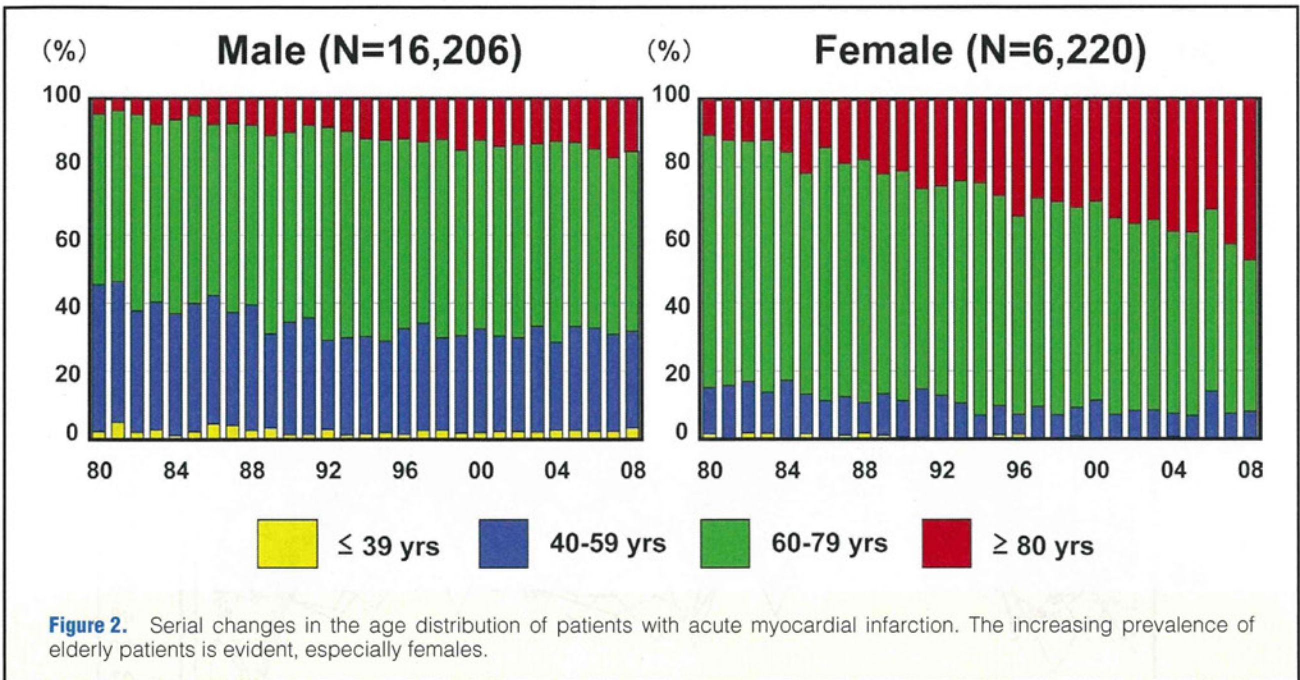


**Figure 2.** Serial changes in the age distribution of patients with acute myocardial infarction. The increasing prevalence of elderly patients is evident, especially females.

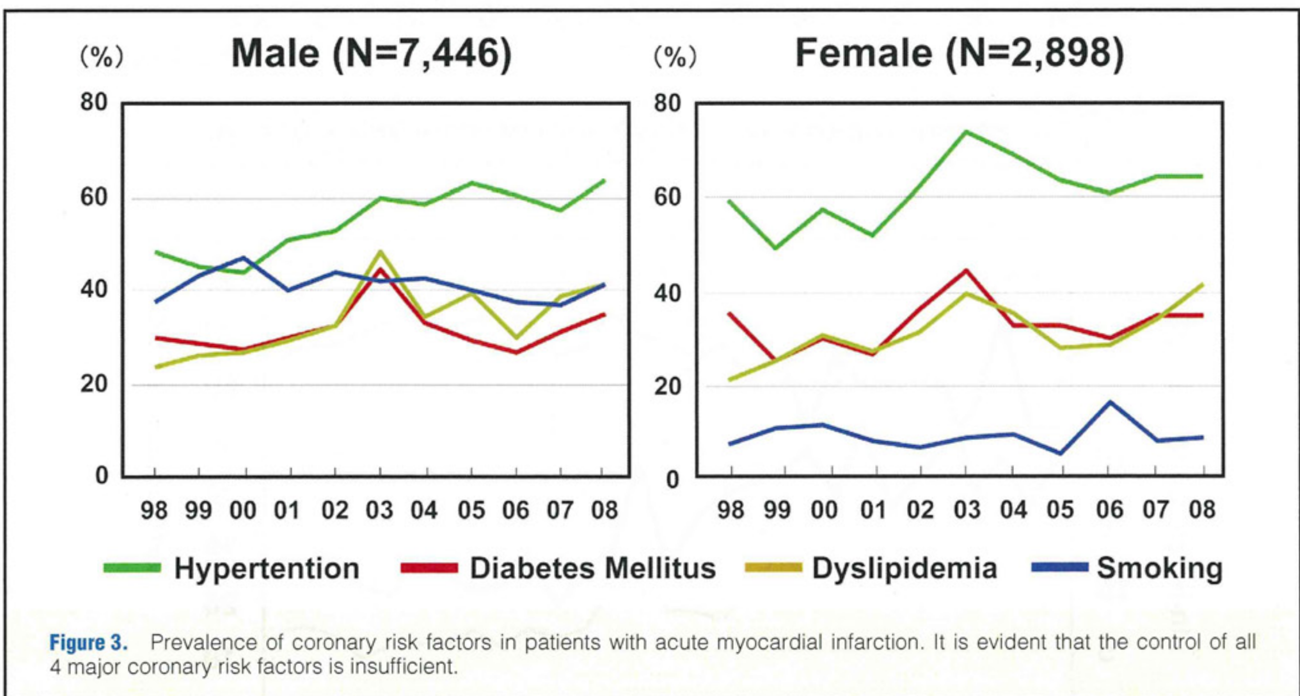


**Figure 3.** Prevalence of coronary risk factors in patients with acute myocardial infarction. It is evident that the control of all 4 major coronary risk factors is insufficient.

2.3-fold, from 4.2 in 1979 to 9.6 in 2008, but did not reach a statistically significant level (P=0.15).

The distribution of age significantly changed with the increased population of elderly patients, especially that of ≥80-year-old patients, in both sexes (both P<0.001) (**Figure 2**). Moreover, the prevalence of hypertension, diabetes mellitus, and dyslipidemia also significantly increased over time in both sexes (all P<0.01) (**Figure 3**). Smoking habit also remained at ~40% in male and ~10% in female patients (**Figure 3**). The peak time of onset of AMI remained in the early morning (**Figure 4**), and the distribution of the infarct site was the anterior wall in 45%, inferior/posterior wall in 43%, and other in 12%.

Over the past 30 years, the use of ambulances significantly increased from 47% in 1980 to 64% in 2008 (P<0.0001) (**Figure 5**). Along with this increased use, the overall in-hospital mortality has markedly decreased from 20% in 1979 to 8% in 2008 (P<0.0001) (**Figure 5**). However, the in-hospital mortality of female patients remained relatively higher than for male patients over the past 30 years (6.3% in males and 12.2% in females in 2008) (**Figure 5**).

Use of primary PCI has dramatically increased from 20% in

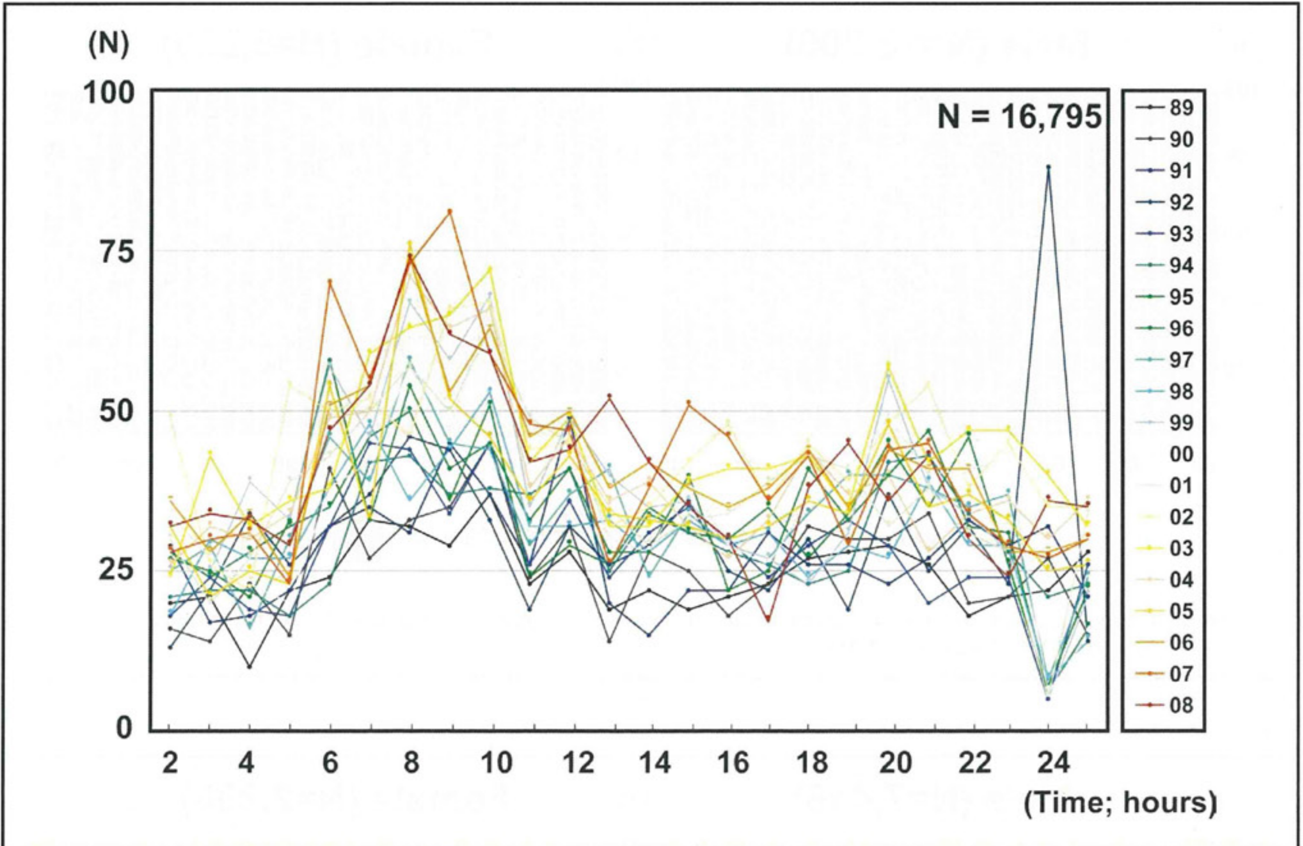


**Figure 4.** Peak time of onset of acute myocardial infarction has remained in the early morning.

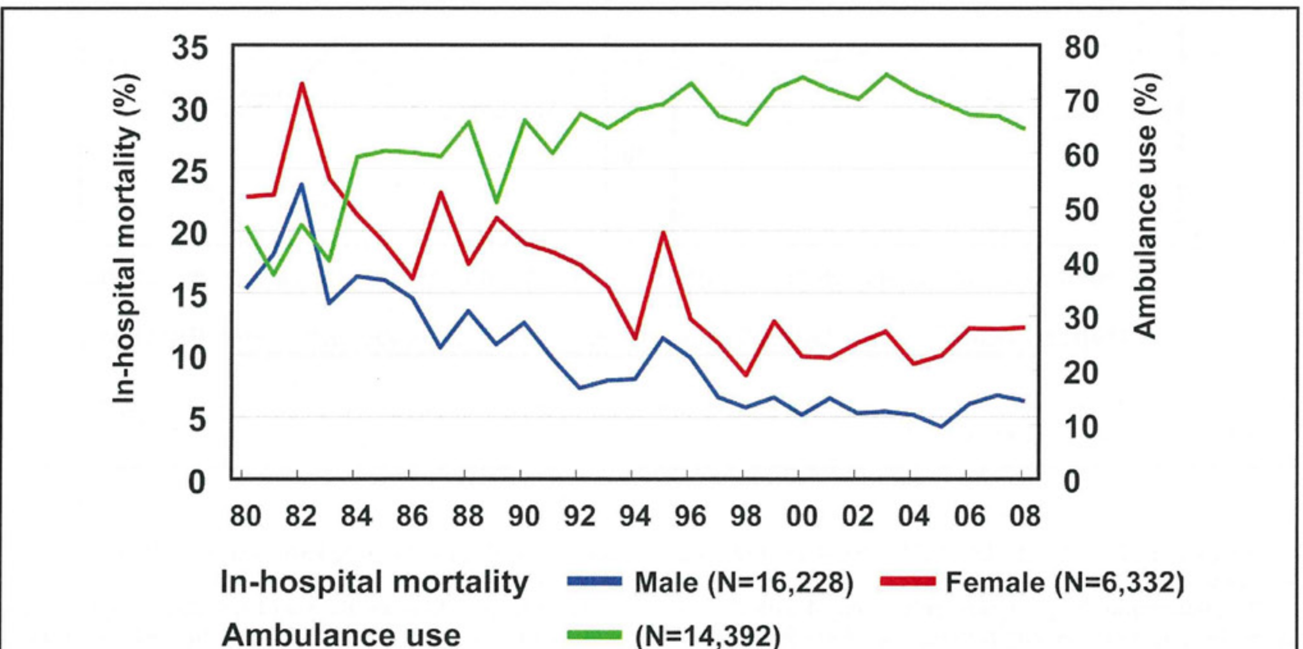


**Figure 5.** Age-adjusted in-hospital mortality (/100,000 persons/year) and ambulance use. Together, with the increased use of ambulances, in-hospital mortality has dramatically decreased; however, female patients still are at higher risk than male patients.

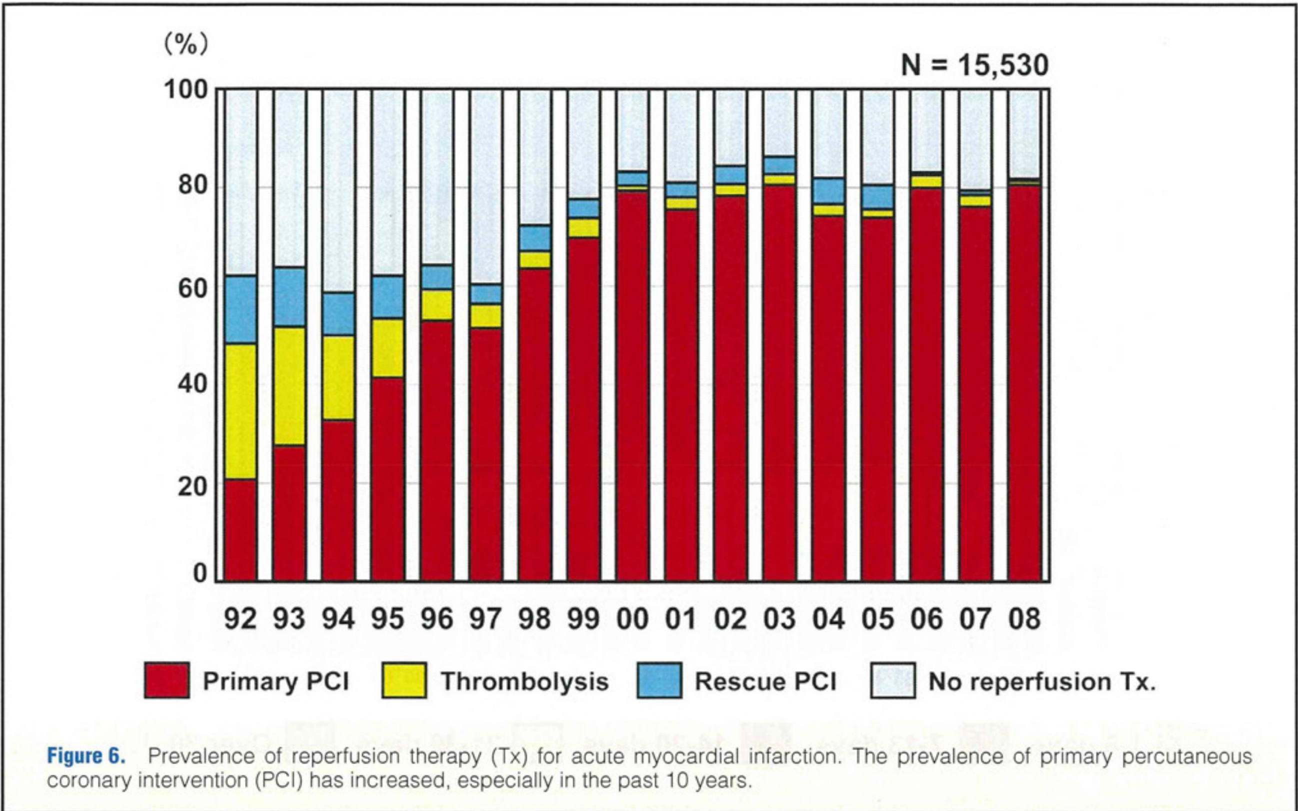


**Figure 6.** Prevalence of reperfusion therapy (Tx) for acute myocardial infarction. The prevalence of primary percutaneous coronary intervention (PCI) has increased, especially in the past 10 years.

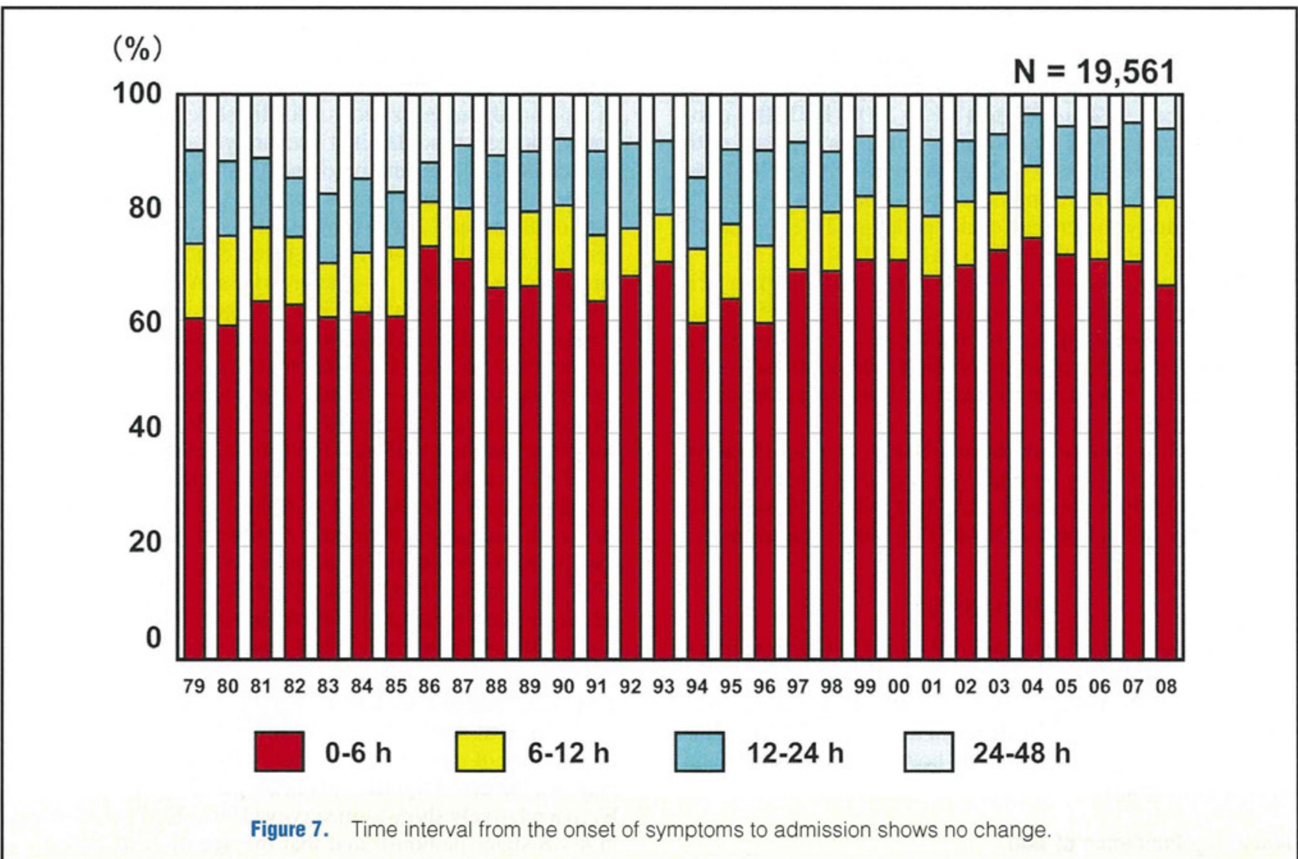


**Figure 7.** Time interval from the onset of symptoms to admission shows no change.

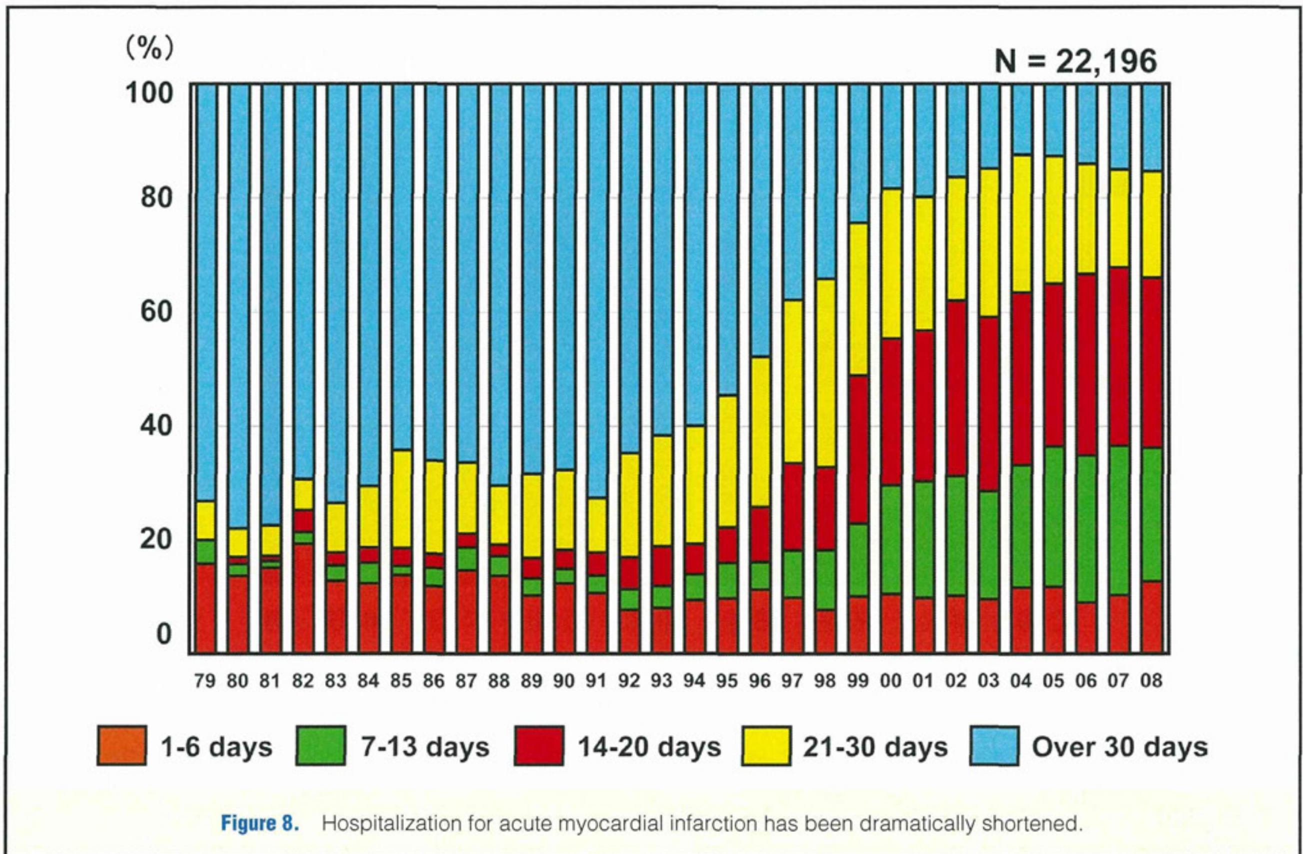


**Figure 8.** Hospitalization for acute myocardial infarction has been dramatically shortened.

1992 to 80% in 2008 (P<0.0001) (**Figure 6**). In contrast, the prevalence of patients without reperfusion therapy significantly decreased from 38% in 1992 to 18% in 2008 (P<0.0001). In-hospital mortality was significantly lower for patients with primary PCI (5%, n=8,693) than for those without it (17%, n=254) (P<0.01). Importantly, the prevalence of primary PCI was significantly lower for female patients (71%, n=2,412) than for male patients (80%, n=6,061) (P<0.01).

In 1979, approximately 30% of patients had more than 12h from the onset of AMI to hospitalization, while 60% of patients were hospitalized within 6h after the onset (**Figure 7**). This tendency for the majority of AMI patients to be hospitalized within 6h was fairly consistent throughout the study period (**Figure 7**).

Finally, the duration of hospital stay has significantly shortened over the past 30 years; the prevalence of discharge within 20 days after the onset of AMI significantly increased from 20% in 1979 to 66% in 2008 (P<0.0001) (**Figure 8**).

## Discussion

The data from the 30-year MIYAGI-AMI Registry Study demonstrates that there is the steady trend of increasing incidence, but decreasing mortality, for AMI in Japan and that the female population still remains at higher risk for in-hospital mortality, despite progress in both patient transfer and reperfusion therapy.

### Increasing Incidence of AMI

There have been few studies regarding the incidence of AMI in Japan and most were performed between the 1960s and 1980s.[4,13,14] Their results were conflicting as they reported either a declining or flattened[4,13,14] trend in the incidence of AMI. After the 1990s, the rate of aging has been the highest in Japan and westernization of the lifestyle has rapidly accelerated; however, no detailed data are yet available regarding the actual incidence and outcome of AMI.

The Miyagi prefecture is located on the Pacific Ocean side of Japan and has a typical balance of urban and rural districts. Our MIYAGI-AMI Registry Study provides important insights into the 30-year trend for AMI in Japan from 1979 to 2008. As shown in **Figure 1**, the overall age-adjusted incidence of AMI (/100,000 persons/year) increased from 7.4 in 1979 to 27.0 in 2008, indicating a steady trend of increasing incidence of AMI. The incidence of AMI was male-predominant (males 46.4 vs females 9.6 in 2008), a consistent finding with the Takashima AMI registry (males 100.7 vs females 35.7 in 1999–2001)[5] and the Niigata and Nagaoka study (males 41.9 vs females 5.3 in 1994–1996).[6] However, the current incidence of AMI in Japan is still lower than that in North America and Europe; the incidence of AMI for males (/100,000 persons/year) is 824 in Finland, 823 in United Kingdom, 605 in Canada, 508 in the United States, 314 in France, and 270 in Italy.[15]

Age is a most important risk factor for the development of cardiovascular diseases and accompanying clinical events. In the present study, the aging of the population is evident; the number of aged patients, especially that of ≥80-year-old patients, increased significantly in the past 30 years (**Figure 2**). Even a relatively short-term survey (1992–2001) of Medicare in 4 US states demonstrated that the age of AMI patients is older and that the proportion of the population >85 years old has increased.[16] These findings indicate the urgent need for evidence-based management strategies applicable to increas-

ingly elderly AMI patients.[17]

### Insufficient Control of Coronary Risk Factors

The WHO-MONICA studies, as well as the Japanese epidemiological studies, have previously shown that the risk of cardiovascular diseases increases with clustering of risk factors, such as hypertension, hyperlipidemia and diabetes mellitus.[18–20] The present study demonstrates that the control of major coronary risk factors is still insufficient in Japan (**Figure 3**), which could largely account for the increasing incidence of AMI. The westernization of lifestyle and the high rate of aging in Japan are apparent causative factors for the trend. Furthermore, the prevalence of smoking still remains high at ~40% in male patients with AMI, although it has been reported that the smoking rate has declined by 20% in the general Japanese population.[21,22]

### Higher Risk for Females for In-Hospital Mortality of AMI

One of the important findings in the present study is that the in-hospital mortality still remains relatively higher for female patients than for male patients (**Figure 5**). A similar trend has been reported from the American Heart Association Heart Disease and Stroke Statistics.[23] Several factors could be involved in the sex difference in in-hospital mortality, including higher age, longer time elapsed from onset to hospitalization, and low prevalence of PCI in female AMI patients. Indeed, in the present study, the average age of the female patients was 10 years older than that of the male patients. The older age of female patients at the time of admission may further limit the use of several therapies,[24] which could have been the case in the present study. In addition, the incidence of death from procedural complications, such as vascular and hemorrhagic complications, is greater in females.[25] Thus, more attention should be paid to these factors when treating female AMI patients.

### Unchanged Time of Onset and Infarct Site

It has been repeatedly demonstrated that the onset of AMI peaks early in the morning in both Japan[26] and Western countries.[27,28] The present study not only confirmed this point but also demonstrated that such a tendency has remained unchanged for the past 30 years in Japan (**Figure 4**). These results suggest that the triggering mechanism(s) for AMI has remained unchanged despite the increasing incidence of the disease.

The present study also demonstrated that the AMI site has unchanged in the last 30 years. Although anterior AMI is associated with worse outcome, as compared with inferior AMI,[29] the present result indicates that the improvement of morality is likely to be related to factors other than the AMI site.

### Improvement of Critical Care and In-Hospital Care for AMI

The present study demonstrated the overall in-hospital mortality (age-adjusted) has significantly reduced from ~20% in 1979 to 12.2% in 2008. The duration of hospital stay was also significantly shortened over the past 30 years (**Figure 8**), during which the paradigm of AMI management has shifted from a conservative strategy to an interventional strategy.[30] In fact, in the present study, use of primary PCI has been increasing from 20% in 1992 to ~80% in 2008 (**Figure 6**), and in-hospital mortality was lower in patients who underwent primary PCI than in those who did not. The progress in reperfusion therapy, especially that of primary PCI, appears to have contributed to the reduction in in-hospital mortality and hospital stay, as previously reported from this registry.[8,9]

Currently, approximately half of AMI patients in the Western countries are transported to hospital by ambulance.[31,32] The present study demonstrated the ambulance use in Japan has increased to ~70% in the past 10 years (**Figure 5**). Because the majority of AMI patients in the past 30 years were hospitalized within 6h (**Figure 7**), the increased use of ambulances may not have directly contributed to the shortened interval from onset of symptoms to hospitalization. However, the increased use of ambulances should have resulted in increased use of primary PCI with a resultant improvement in the in-hospital mortality.

The increasing incidence of, but decreasing in-hospital mortality from, AMI in Japan may have resulted from the recent increase in the number of patients with ischemic heart failure, as reported in the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART) registry study.[33] For surviving AMI patients, it is important to understand the underlying risk factors that lead to secondary cardiac events.[34] Indeed, a more effective strategy to improve the management of post-infarction heart failure needs to be developed.[33,34]

## Conclusions

Our MIYAGI-AMI Registry Study demonstrates that over the past 30 years in Japan, there has been a steady trend of increasing incidence, but decreasing mortality, for AMI in the Japanese population, although female patients are still at higher risk for in-hospital mortality than male patients, a result in which both positive (eg, increased use of ambulance and primary PCI) and negative factors (eg, insufficient control of coronary risk factors and aging of the whole society) may be involved.

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## Appendix 1

**List of Participating Hospitals**

Fukaya Hospital, Hiroshi Akiho, MD; Hikarigaoka Spellman Hospital, Tomofumi Mimata, MD; Ishinomaki Municipal Hospital, Kenjirou Akai, MD; Ishinomaki Red-Cross Hospital, Hiroyasu Sukegawa, MD; JR Sendai Hospital, Masao Kuroha, MD; Katta General Hospital, Hiroyuki Kanno, MD; Kesen-numa Hospital, Kazunori Ogata, MD; Kurihara Central Hospital, Seiji Komatsu, MD; Tohoku Rosai Hospital, Tatsuya Komaru, MD; Marumori National Health Insurance Hospital, Masataka Otomo, MD; Miyagi Eastern Cardiovascular Institute, Toru Naganuma, MD; Miyagi Cancer Center, Nobuo Tomisawa, MD; Miyagi Cardiovascular and Respiratory Center, Noboru Osawa, MD; Mori Hospital, Akio Mori, MD; Nagamachi Hospital, Hidetoshi Mitobe, MD; Nishitaga National Hospital, Shigenori Kitaoka, MD; NTT EAST Tohoku Hospital, Aki Yamada, MD; Oizumi Memorial Hospital, Yoshirou Koiwa, MD; Osaki Citizen Hospital, Tetsuya Hiramoto, MD; Saito Hospital, Keiji Otsuka, MD; Saka General Hospital, Atsushi Obata, MD; Sanuma Municipal General Hospital, Hiroshi Ishii, MD; Sendai Cardiovascular Center, Shin-ya Fujii, MD; Sendai City Hospital, Tetsuo Yagi, MD; Sendai Kosei Hospital, Taiichirou Meguro, MD; Sendai Medical Center, Tsuyoshi Shinozaki, MD; Sendai Open Hospital, Masaharu Kanazawa, MD; Sendai Public Health Insurance Hospital, Yoshichika Oikawa, MD; Sendai Red-Cross Hospital, Yuji Konno, MD; Sendai Tokushukai Hospital, Kimihiko Ogata, MD; Sen-en General Hospital, Ryouichi Hashiguchi, MD; Shichigashuku National Health Insurance Clinic, Takahiro Nagashima, MD; Shiogama City Hospital, Jun Goto, MD; South Miyagi Medical Center, Kan-ichi Inoue, MD; Tohoku Kosai Hospital, Mitsumasa Fukuchi, MD; Tohoku University Hospital, Department of Cardiovascular Medicine, Hiroaki Shimokawa, MD; Department of Cardiovascular Surgery, Kouichi Tabayashi, MD; Department of Gastroenterology, Toru Shimosegawa, MD; Tohoku Welfare and Pension Hospital, Yoshiaki Katahira, MD; Tome Public Hospital, Munehiko Ishii, MD.