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Age-Specific Trends in the Incidence and In-Hospital Mortality of Acute Myocardial Infarction Over 30 Years in Japan

— Report From the Miyagi AMI Registry Study —

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Background: We are now facing rapid population aging in Japan, which will affect the actual situation of cardiovascular diseases. However, age-specific trends in the incidence and mortality of acute myocardial infarction (AMI) in Japan remain to be elucidated.

Methods and Results: We enrolled a total of 27,220 AMI patients (male/female 19,818/7,402) in our Miyagi AMI Registry during the past 30 years. We divided them into 4 age groups (≤59, 60–69, 70–79 and ≥80 years) and examined the temporal trends in the incidence and in-hospital mortality of AMI during 3 decades (1985–1994, 1995–2004 and 2005–2014). Throughout the entire period, the incidence of AMI steadily increased in the younger group (≤59 years in both sexes), while in the elderly groups (≥70 years in both sexes), the incidence significantly decreased during the last decade (all P<0.01). In-hospital cardiac mortality significantly decreased during the first 2 decades in elderly groups of both sexes (all P<0.01), whereas no further improvement was noted in the last decade irrespective of age or sex, despite improved critical care of AMI.

Conclusions: These results provide the novel findings that the incidence of AMI has been increasing in younger populations and decreasing in the elderly, and that improvement in the in-hospital mortality of AMI may have reached a plateau in all age groups in Japan.

Key Words: Acute myocardial infarction; Aging; Epidemiology; Sex

Acute myocardial infarction (AMI) is a leading cause of death and a serious public health problem worldwide, especially in developed countries.[1–3] In Western countries, decreasing trends in the incidence and mortality of AMI have been reported since the 1980 s,[4–8] in association with public efforts to reduce coronary risk factors and improved critical care for AMI (e.g., reperfusion therapies).[9–11] In contrast, in Asian countries, including Japan, Taiwan and Korea, AMI has become more common because of prolonged life expectancy, rapid socioeconomic advances, and westernization of life style and diet.[12,13]

In Japan, there have been a few registry studies of AMI and most of them included a relatively small number of patients and/or a relatively short study period.[14–17] In order to elucidate the accurate trend of AMI in Japan, we have been conducting the Miyagi AMI Registry Study for 37 years since 1979, where almost all AMI patients in the Miyagi Prefecture have been prospectively registered.[18–20] In a previous report, we demonstrated the trend for increasing incidence and decreasing in-hospital mortality of AMI from 1979 to 2008 in Japan.[19] Since then, we have been facing rapid social aging in Japan, where such aging should affect the actual situation of cardiovascular diseases, including AMI. Thus, in the present study, we examined the temporal age-specific trends in the incidence and in-hospital mortality of AMI during the past 30 years (from 1985 to 2014) in our Miyagi AMI Registry.

Methods

The present study was approved by the Institutional Review Board of Tohoku University Graduate School of Medicine

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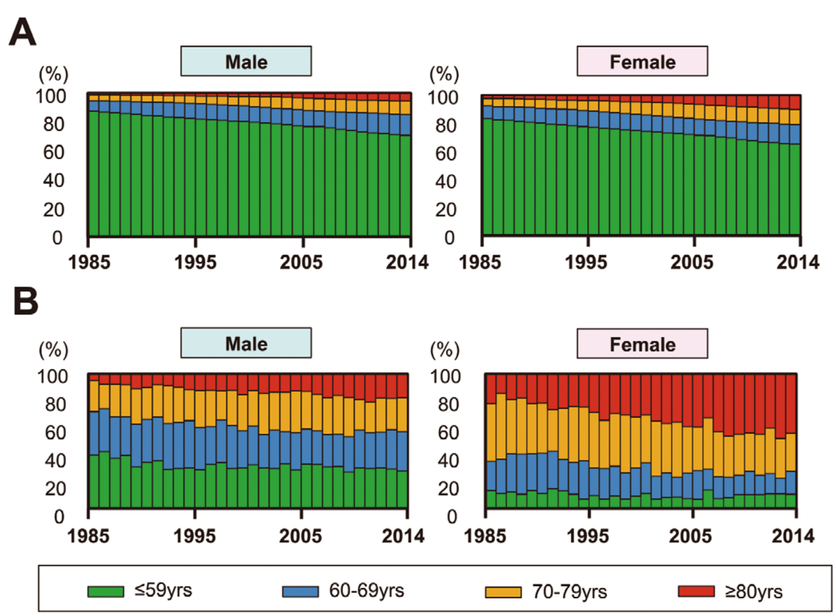

Figure 1. Aging of the general population (**A**) and patients with acute myocardial infarction (**B**) in Miyagi Prefecture over the 30 years from 1985 to 2014.

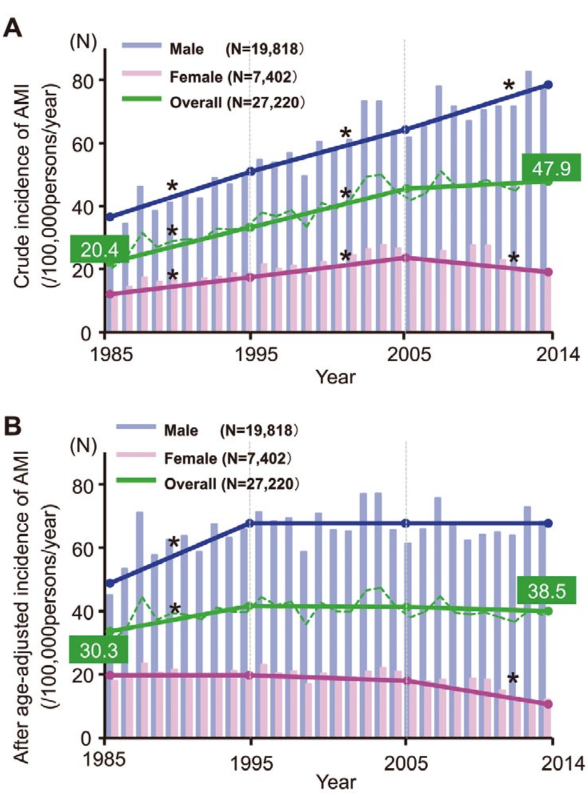

Figure 2. Crude (**A**) and age-adjusted (**B**) incidence of acute myocardial infarction (/100,000 persons/year) over the 30 years from 1985 to 2014 in Miyagi Prefecture. *P<0.05 for Piecewise linear trend.

under the condition that all personal data were protected at all times.

The Miyagi AMI Registry Study

The Miyagi AMI Registry is a prospective, multicenter and observational study that was established in 1979 and has been conducted for 37 years.[18–20] Miyagi Prefecture is located in northeastern Japan, with a population of approximately 2.35 million and an area of 7,282 km^2,[21] and all 45 hospitals with a cardiac care unit and/or cardiac catheterization facilities in the Prefecture have been participating in the Miyagi AMI Registry Study (**Appendix**).[22,23] Thus, almost all AMI patients in Miyagi Prefecture are transferred to one of the participating hospitals via the emergency medical service and have been prospectively registered in the Registry. The diagnosis of AMI was based on the WHO-MONICA criteria, including typical and severe chest pain accompanied by abnormal ECG changes and increased serum levels of cardiac enzymes [e.g., creatinine phosphokinase (CPK), aspartate aminotransferase, and lactate dehydrogenase].[24] Treatments including reperfusion therapies were left to the discretion of individual cardiologists in charge.

The registration form of the Miyagi AMI Registry Study includes age, sex, the date and time of symptom onset, prehospital management (e.g., 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 (e.g., thrombolysis and/or PCI), and in-hospital outcomes.[18–20] We revised the registration form occasionally during the 37 years as required. Thus, although the number of incidents of AMI and the basic demographic data (age, sex and time of onset) are available for all patients over the entire period of 37 years, the data regarding prehospital managements, infarction site, coronary risk factors, reperfusion therapies, or in-hospital outcomes were only available for patients registered during the last 10–20 years.[18–20] Additionally, information on the type of AMI [ST-segment elevation MI (STEMI) vs. non-STEMI] was unavailable for most of the study period. Basically, the Miyagi AMI Registry Study has not included AMI patients with out-of-hospital cardiac

Table 1. Trend Analysis of AMI in Japan by Piecewise Linear Regression Models

	Slope (1985–1994)	P value	Slope (1995–2004)	P value	Slope (2005–2014)	P value
Crude incidence of AMI						
Male	1.964	<0.001	1.328	<0.001	1.328	<0.001
Female	0.607	<0.001	0.607	<0.001	−0.624	<0.001
Overall	1.116	<0.001	1.116	<0.001	0.154	0.503
Age-adjusted incidence of AMI						
Male	1.432	0.001	−0.096	0.614	−0.096	0.614
Female	−0.03255	0.556	−0.03255	0.556	−0.85023	<0.001
Overall	0.736	0.003	−0.188	0.074	−0.188	0.074
Age-adjusted in-hospital mortality						
Male	−0.770	<0.001	−0.370	0.001	0.214	0.158
Female	−0.619	<0.001	−0.619	<0.001	0.275	0.187
Overall	−0.784	<0.001	−0.414	<0.001	0.178	0.178

AMI, acute myocardial infarction.

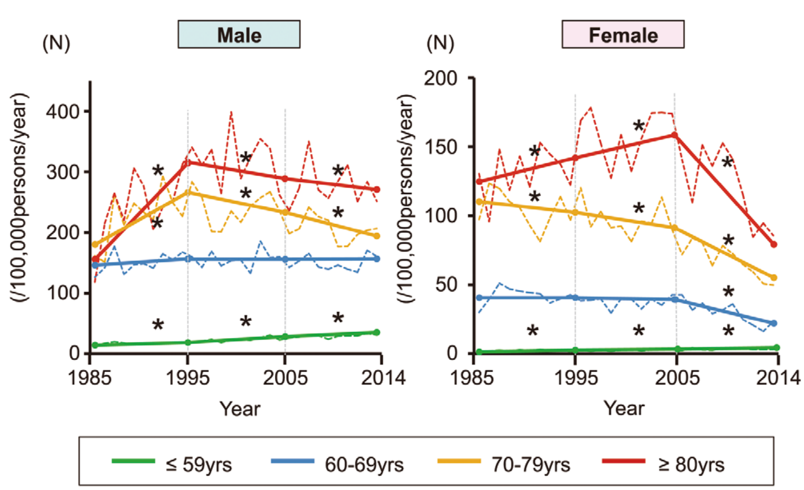

Figure 3. Temporal trends in the age-specific incidence of acute myocardial infarction over the 30 years from 1985 to 2014 in Miyagi Prefecture. Younger patients of both sexes aged ≤59 years had consistent increasing trends throughout the study period, whereas male patients aged ≥70 years and female patients aged ≥60 years showed decreasing trends in the last decade. *P<0.05 for Piecewise linear trend.

arrest who were not hospitalized. Furthermore, in the database of the Miyagi AMI Registry Study, we were able to divide the mode of in-hospital death into only 2 types: cardiac and non-cardiac in origin. Thus, detailed information of cardiac death (e.g., sudden cardiac death, heart failure death, or others) was not available.

Statistical Analysis

The present study population comprised a total of 27,220 patients with AMI (male/female 16,228/6,332) enrolled in the Miyagi AMI Registry Study between 1985 and 2014. In order to examine the temporal trends in the incidence and in-hospital mortality of AMI during the past 30 years, we applied Piecewise linear regression models[25] with the change points in 1995 and 2005, which were selected by stepwise backward elimination. We then calculated the Piecewise linear trend according to 3 decades (1985–1994, 1995–2004, and 2005–2014). To adjust for age distribution differences among the study periods, we used a direct method using the 2000 census Japanese population as the standard population.[26] Furthermore, to examine the age-specific trends, we divided the patients into 4 age groups (≤59, 60–69, 70–79, and ≥80 years). As mentioned before, several data items regarding prehospital management, coronary risk factors, presence or absence of heart failure on admission, and reperfusion therapies were available only for patients registered in the last 15 years. Thus, we examined the temporal trends in those factors for the last three 5-year periods and analyzed the trend with the Cochran-Armitage trend test or the Jonckheere-Terpstra test.[11,19,23] The confidence intervals for the proportions were obtained by Clopper-Pearson exact confidence interval. The confidence intervals for the medians were obtained by the bootstrap procedure. A P-value <0.05 was considered to be statistically significant for all tests. These analyses were carried out with R software version 3.2.2 (http://www.r-project.org).

Results

Temporal Trends in the Incidence of AMI and the Prevalence of Comorbidities

Compared with the aging of the general population in Miyagi Prefecture during the past 30 years (**Figure 1A**), the aging of AMI patients was more evident, especially in female patients older than 80 years, which accounted for

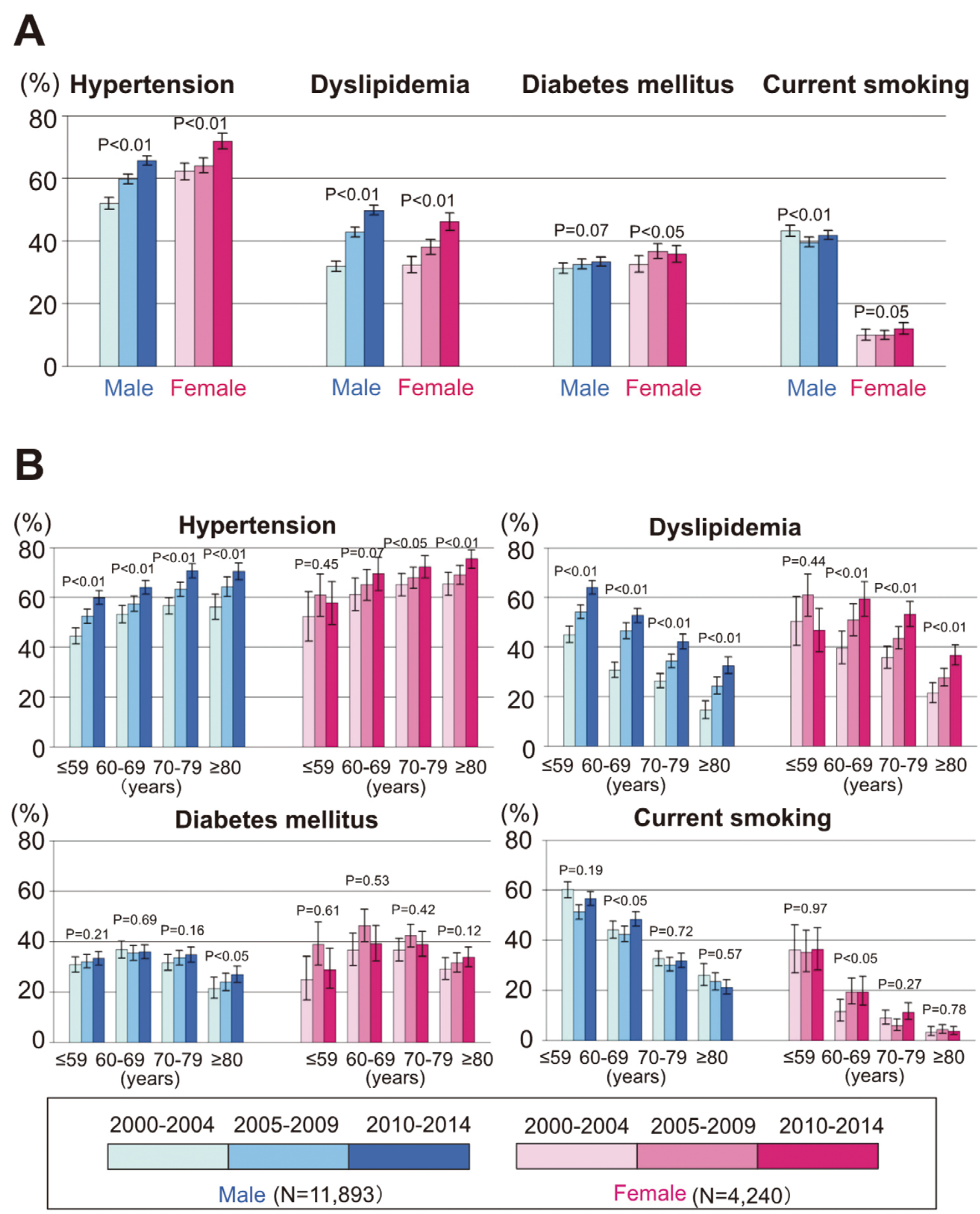

Figure 4. Temporal trends in the prevalence of the 4 major coronary risk factors (hypertension, dyslipidemia, diabetes mellitus, and current smoking) in patients by sex (**A**) and age (**B**) with acute myocardial infarction during the 15 years from 2000 to 2014 in Miyagi Prefecture. P for linear trend.

more than 40% in recent years (**Figure 1B**). The crude incidence of AMI (/100,000 persons/year) increased during the 1st and 2nd decades (1985–1994 and 1995–2004) (both P<0.001), but remained unchanged in the last decade (2005–2014) (**Figure 2A**, **Table 1**). Intriguingly, when analyzed by sex, crude AMI incidence increased in males, but decreased in females, during the last decade (both P<0.001) (**Figure 2A**). After age-adjustment, the increasing trend in the overall incidence of AMI was noted only in the 1st decade, and remained unchanged in the following 2 decades (**Figure 2B**, **Table 1**). The same trend was noted for male patients, whereas age-adjusted AMI incidence significantly decreased in female patients in the last decade (P<0.001) (**Figure 2B**). When analyzed by age, the age-specific incidence of AMI consistently increased in younger patients aged ≤59 years of both sexes throughout the entire period (P<0.01 in both sexes), while it remained unchanged in male patients aged 60–69 years (**Figure 3**). In contrast, in the remaining groups, including males aged ≥70 years and females aged ≥60 years, the age-specific incidence of AMI significantly decreased in the last 2 decades (P<0.01 in both sexes) (**Figure 3**).

Regarding the prevalence of coronary risk factors in AMI patients, the prevalence of hypertension and dyslipidemia continued to increase steadily regardless of age or sex (all P<0.05) and that of diabetes mellitus also tended to increase (P=0.07 in males, P<0.05 in females) (**Figure 4A**). In contrast, the prevalence of current smoking significantly decreased in male patients, whereas it tended to increase in female patients (**Figure 4A**). When analyzed by age groups, the prevalences of hypertension and dyslipidemia were significantly increased among almost all age groups of both sexes except the youngest females aged ≤59 years (**Figure 4B**). Furthermore, it is interesting to note that the prevalence of diabetes mellitus has increased in the most elderly group aged ≥80 years (P<0.05 in males, P=0.12 in females) (**Figure 4B**).

Temporal Trends in In-Hospital Mortality

The overall age-adjusted in-hospital cardiac mortality significantly decreased during the first 2 decades (1985–1994, 1995–2004) (P<0.001), whereas it rather tended to increase in the last decade (2005–2014) (P=0.071) (**Figure 5A**, **Table 1**). Furthermore, when analyzed by age, in-hospital cardiac mortality decreased in all age groups of both sexes during the 1st decade, while in the 2nd decade, mortality decreased in patients older than 70 years and remained unchanged in younger patients (**Figure 5B**). Furthermore, in-hospital cardiac mortality tended to increase during the last decade in both sexes, especially in patients older than 80 years (**Figure 5B**).

Regarding the critical care of AMI patients between 2000 and 2014, the time from symptom onset to admission became shorter, whereas the prevalence of heart failure with Killip class ≥2 on admission increased in both sexes

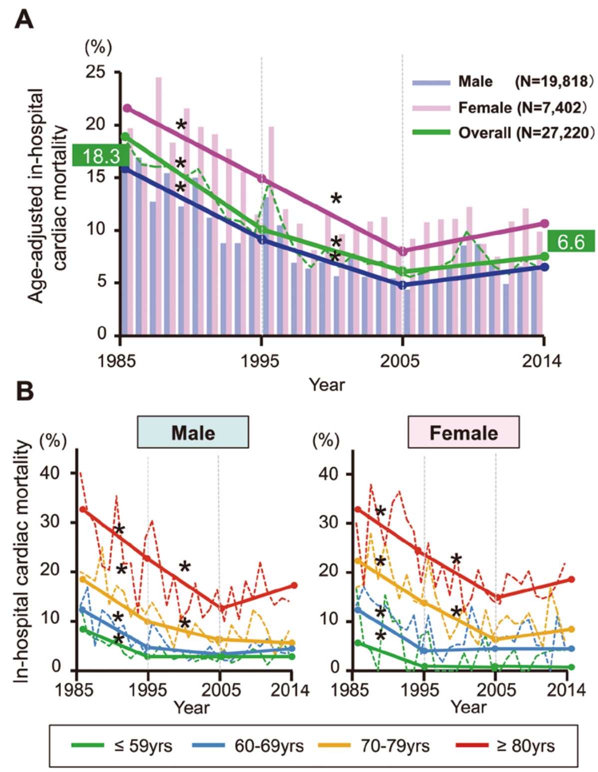

Figure 5. Temporal trends in age-adjusted in-hospital cardiac mortality in patients with acute myocardial infarction (**A**) and age-specific in-hospital mortality (**B**) over the 30 years from 1985 to 2005 in Miyagi Prefecture. *P<0.05 for Piecewise trend.

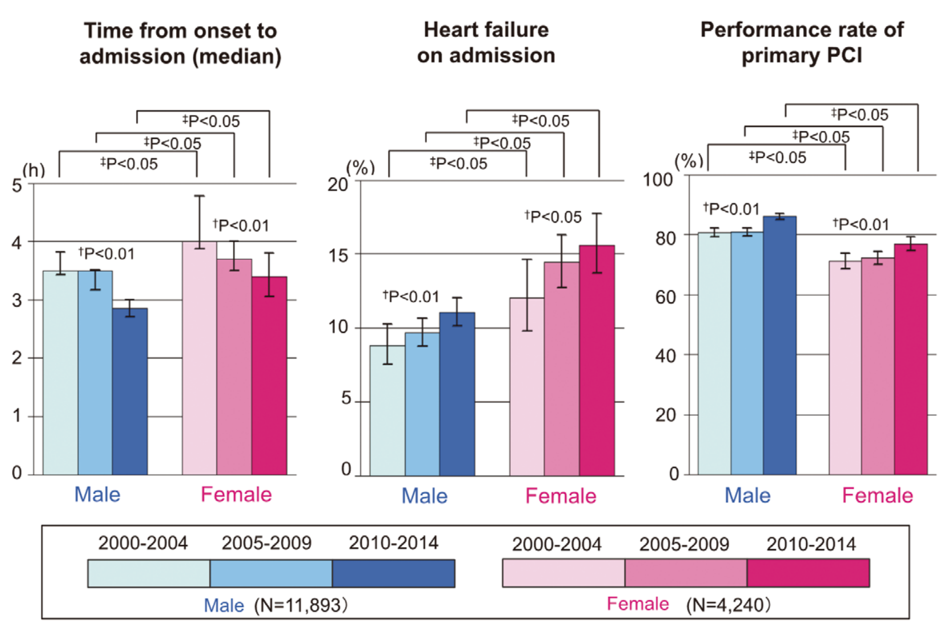

Figure 6. Temporal trends in the critical care of acute myocardial infarction from 2000 to 2014. Time from symptom onset to admission became shorter, whereas the prevalence of heart failure with Killip class ≥2 on admission increased in both sexes. Moreover, the performance rate of primary PCI was further improved in both sexes. †P<0.05 for linear trend, ‡P<0.05 for sex difference.

Table 2. Temporal Trends in the Incidence and In-Hospital Mortality of AMI in Western and Asian Countries

Country	Period	Sex	Incidence	In-hospital mortality
USA[8]	1987–2008	Male (White)	–4.3%/year	–3.5%/year
		Female (White)	–3.8%/year	–3.0%/year
USA[8]	1987–2008	Male (Black)	–3.4%/year	–3.6%/year
		Female (Black)	–1.5%/year	–2.6%/year
USA[7]	1999–2008	Overall	274 → 208*	10.5% → 7.8%
Denmark[5]	1984–2008	Male	410 → 213*	31.4% → 14.8%
		Female	209 → 131*	
Six European countries[6]	1985–2010	Male	–4.0%/year	–6.0%/year
		Female	–4.2%/year	–6.3%/year
Taiwan[12]	1999–2008	Male	41.8 → 62.5*	20% → 8%
		Female	13.5 → 26.0*	
Korea[13]	1997–2007	Male	60.4 → 92.2*	13.4% → 9.7%
		Female	40.7 → 63.7*	15.2% → 12.4%
Korea[27]	2006–2010	Male	60.1 → 40.9*	–
		Female	31.6 → 17.6*	–
Japan[19]	1979–2008	Male	18.7 → 46.4*	21.4% → 6.3%
		Female	4.2 → 9.6*	19.4% → 12.2%
Japan (Present study)	2005–2014	Male	61.3 → 68.1*	4.4% → 6.1%
		Female	17.7 → 12.2*	9.2% → 9.9%

Superscript numbers denote reference number. *Age-adjusted incidence per 100,000 person-years. AMI, acute myocardial infarction.

(both P<0.05) (**Figure 6**). Importantly, the performance rate of primary PCI still continued to increase slightly but significantly, even in recent years, in both sexes (both P<0.05) (**Figure 6**). However, female patients were inferior to male patients in those 3 factors for the critical care of AMI in any of the 3 periods (all P<0.05) (**Figure 6**).

Discussion

The novelty of this study was that we aimed to elucidate the temporal trends in AMI practice in Japan among different age groups (≤59, 60–69, 70–79, and ≥80 years) and 3 decennial periods (1985–1994, 1995–2004, and 2005–2014), including the most recent 6 years since our previous study.[19] The novel findings of the present study are as follows. (1) During the recent 30 years in Japan, the age-adjusted incidence of AMI increased significantly in the first decade (1985–1994), but has remained unchanged or slightly but significantly decreased in females in the last 2 decades (1995–2004, 2005–2014). (2) When analyzed by age, the age-adjusted incidence of AMI has continued to increase in younger patients (≤59 years) and decrease in elderly patients (≥70 years) in both sexes during the last decade. (3) Among the coronary risk factors, the prevalence of both hypertension and dyslipidemia continued to increase during the 3 decades. (4) Although in-hospital cardiac mortality of AMI progressively decreased during the 1st and 2nd decades (1985–1994, 1995–2004), particularly in elderly patients, no further improvement was noted in the last decade (2005–2014) irrespective of age or sex. (5) Significant progress has been made in the critical care of AMI in Japan, but the severity of AMI on admission may have worsened. These trends may result from the balance between the factors improving the mortality rate (improved time elapsed from onset to admission and increasing performance rate of primary PCI) and those that worsen it (patient aging and increasing prevalence of hypertension, dyslipidemia, and heart failure on admission). Thus, the present study clearly demonstrated the recent trend in the incidence and in-hospital mortality of AMI patients in Japan.

Comparison With Trends of AMI in Other Countries

The previous reports on the trends in the incidence and mortality of AMI patients in Western and Asian countries are summarized in **Table 2**. In Western countries, it was previously reported that the age-adjusted incidence of AMI decreased in the USA (from the late 1980s to 2000s),[7,8] Sweden (from1985 to 2004),[4] Denmark (from 1984 to 2008),[5] and 6 other European countries (from 1985 to 2010)[6] (**Table 2**). These declines in the incidence of AMI are considered to be attributed to the reduction in the prevalence of coronary risk factors such as hypertension, dyslipidemia, and smoking.[9,10] In contrast, in Asian countries, together with westernization of diet and lifestyle and societal aging, increasing trends in the age-adjusted incidence of AMI have been reported in Taiwan (from 1999 to 2008)[12] and Korea (from 1997 to 2007).[13] However, the latest study in Korea found that the age-adjusted incidence of AMI turned to decline between 2006 and 2010,[27] which could be caused, at least in part, by preventive care programs and projects for chronic illnesses and cardio-cerebrovascular diseases towards the 2000s in Korea.[28]

We previously reported that the age-adjusted incidence of AMI increased approximately 4-fold between 1979 and 2008 in Japan.[19] In the present study of the past 3 decades, we demonstrated that the initial increasing trend in AMI has stopped and appears to decline in females in the last decade. Furthermore, when analyzed by age, it also declined significantly in the elderly of both sexes (≥70 years in males and ≥60 years in females), as in Western countries[4–8] and Korea.[13,27] Among elderly patients, it is noteworthy that

AMI incidence continued to decline despite increased prevalences of hypertension and dyslipidemia (**Figure 4B**).[20] Increased use of antihypertensive agents and statins in the elderly may explain, at least in part, the decline in AMI incidence in this population.[29] In contrast, AMI incidence continues to increase in younger patients aged ≤59 years of both sexes in the past 3 decades. Indeed, we and others previously reported that the increased prevalence of dyslipidemia in younger patients with AMI was responsible, at least in part, for the increased incidence of AMI in this population.[17,20] Additionally, the temporal trend in the prevalence of smoking hovered at a high of approximately 40% in male patients and tended to increase in female patients. These results suggest that more strict control of coronary risk factors is needed in young populations to reduce the occurrence of AMI.

The present results are in agreement with other Japanese cohort studies. According to the Hisayama Study, a prospective cohort study of cardiovascular disease in Japan, the incidence of ischemic stroke decreased as a result of improved management of hypertension and reduced smoking rates during the 50-year period from 1961 to 2009.[30] However, in the meantime, there was no clear change in the incidence of AMI, probably because of the increasing metabolic risk factors including diabetes mellitus, dyslipidemia, and obesity.[30] Those results are in agreement with the present study that suggests intensive management of coronary risk factors is needed for further prevention of AMI in Japan.

Regional Differences in the Incidence of AMI in Japan

It has been recently reported that the incidence of AMI was steadily decreasing in Kumamoto Prefecture in both sexes between 2004 and 2011 (n=8,131).[31] In the present study, we found such a trend only in females but not in males. This discrepancy may be explained by the difference in the age of the study population in the 2 studies: average age in the Miyagi and Kumamoto Prefectures in 2010 was 43.1 vs. 44.2 years in males and 46.1 vs. 48.1 years in females, respectively,[26] suggesting that the increase in AMI incidence in younger patients influenced the overall trend more in Miyagi Prefecture than in Kumamoto Prefecture. Furthermore, the Japanese national survey reported that, in Miyagi Prefecture, the prevalence of metabolic syndrome (MetS) in the general population was higher compared with other Japanese regions, including Kumamoto Prefecture (17.5% in Miyagi vs.16.3% in Kumamoto in 2010).[32] MetS is a pathological condition with a clustering of metabolic disorders such as central obesity, dyslipidemia, elevated blood pressure, and impaired glucose tolerance.[33,34] Furthermore, MetS has been identified as an additional risk in both Western and Asian countries, including Japan.[35–38] Thus, the prevalence of MetS in the general population could account, at least in part, for the regional difference in the incidence of AMI in Japan.

Trends in the In-Hospital Mortality of AMI

In Western countries, in-hospital mortality of AMI decreased between 1980s and late 2000s, along with the improvements in critical care for AMI such as reperfusion therapy (**Table 2**).[4–8,11] The same trend in reduced in-hospital mortality of AMI was also noted in Korea and Taiwan between late1990s and 2000s (**Table 2**).[12,13] Similarly, in Japan, we also previously reported that in-hospital mortality of AMI markedly decreased between 1980 and 2008.[19] However, the present study revealed that in-hospital mortality of AMI remained unchanged during 2005–2014, irrespective of sex or age (**Table 2**). In the same period, critical care of AMI (e.g., time between onset and admission, and performance rate of primary PCI) significantly improved, whereas the clinical characteristics of AMI patients (age and prevalence of coexisting heart failure on admission) worsened. Thus, it is possible that various counterbalancing factors have resulted in unchanged trends in in-hospital mortality over the last decade. It is important to note that in-hospital mortality of AMI continues to be higher by 2-fold in female patients than in male patients. It is generally considered that the poorer outcome of female AMI patients could be caused by higher age, longer time from onset to admission, poorer condition on admission such as coexisting heart failure, and lower performance rate of primary PCI.[39–41] Those previous findings are consistent with the present study, indicating the necessity of additional approaches to improving the critical care of AMI in female patients.

Perspectives of the Present Study

The present study demonstrated that the incidence of AMI in the elderly turned to decrease during the last decade despite the increased prevalence of hypertension and dyslipidemia in Japan. In contrast, in patients younger than 60 years, both the prevalence of those risk factors and the incidence of AMI continued to increase significantly throughout the past 3 decades. Generally, cardiovascular diseases can be prevented by managing and improving risk factors, such as chronic illnesses and unhealthy lifestyle, as other developed countries have succeeded in doing.[7,8,27] In order to accelerate the decrease in the incidence of AMI in the elderly, and to stop the increase in the incidence in the younger population, we need to more aggressively improve the comorbidity, including hypertension and dyslipidemia, in the general population. However, in Japan, public preventive care programs or projects for coronary risk factors to reduce cardiovascular diseases have not been developed. Thus, we consider that a national project for the management of cardiovascular diseases needs to be developed.

Study Limitations

Several limitations should be mentioned for the present study. First, although almost all AMI patients were transferred to participating hospitals in Miyagi Prefecture, a small number of AMI patients might have been admitted to hospitals not participating in the Miyagi AMI Registry Study. To overcome that limitation, we hold twice-yearly educational seminars for doctors and healthcare workers regarding the critical care of AMI. In the seminars, we emphasize the importance of revascularization therapies in the acute phase of AMI to improve the prognosis and ask the participants to transfer AMI patients to a hospital in the Miyagi AMI Registry Study Group as soon as possible. Second, although the Miyagi AMI Registry Study has been conducted for 37 years, the diagnosis of AMI has been changing.[42] In the present study, the diagnosis of AMI was based on the WHO-MONICA criteria with CPK.[24] Troponins are widely used in recent clinical practice because they are more sensitive and specific biomarkers for myocyte necrosis than CPK.[43] Third, we were unable to distinguish patients with STEMI from those with NSTEMI because of the limitation of the registration system. Fourth, the present study was observational in nature, so the precise mechanisms of the improvement in the critical care of AMI, including shorter elapsed time from onset to admission and increasing performance rate of primary PCI, and the increasing prevalence of heart failure with Killip class ≥2 on admission, remain to be fully elucidated. Fifth, in the Miyagi AMI Registry Study, we only examined in-hospital mortality and we did not have data available for assessing the long-term prognosis.

Conclusions

The present study demonstrated age-specific trends in the incidence and in-hospital mortality of AMI in Japan with rapid population aging, providing a clue to further improve critical care for AMI.

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Disclosures

Conflict of Interest: None.

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Appendix

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