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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.

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 1960 s.[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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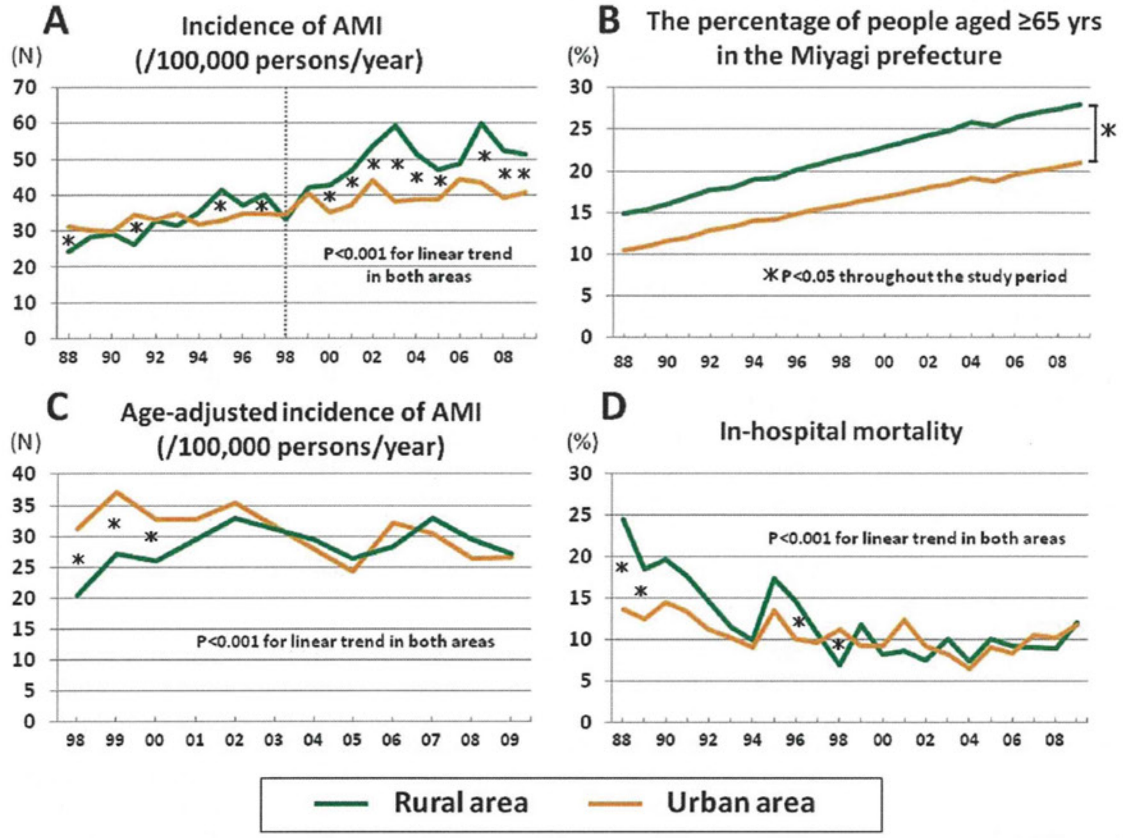

Figure 1. The 20-year trend of acute myocardial infarction (AMI) in the Miyagi prefecture. (**A**) The incidence of AMI (/100,000 persons/year) has significantly increased in both areas (both P<0.001) with a greater extent in the urban area over the last 20 years, accompanied with rapid aging in both 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/km^2 in 2000) has been much higher than that of any other parts of the Miyagi prefecture (209/km^2 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 (480–960×10^3 IU for 30 min) or alteplase (290–435×10^3 IU/kg for 60 min) or with intracoronary administration of urokinase (maximum 960×10^3 IU) or alteplase (maximum 6.4×10^6 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

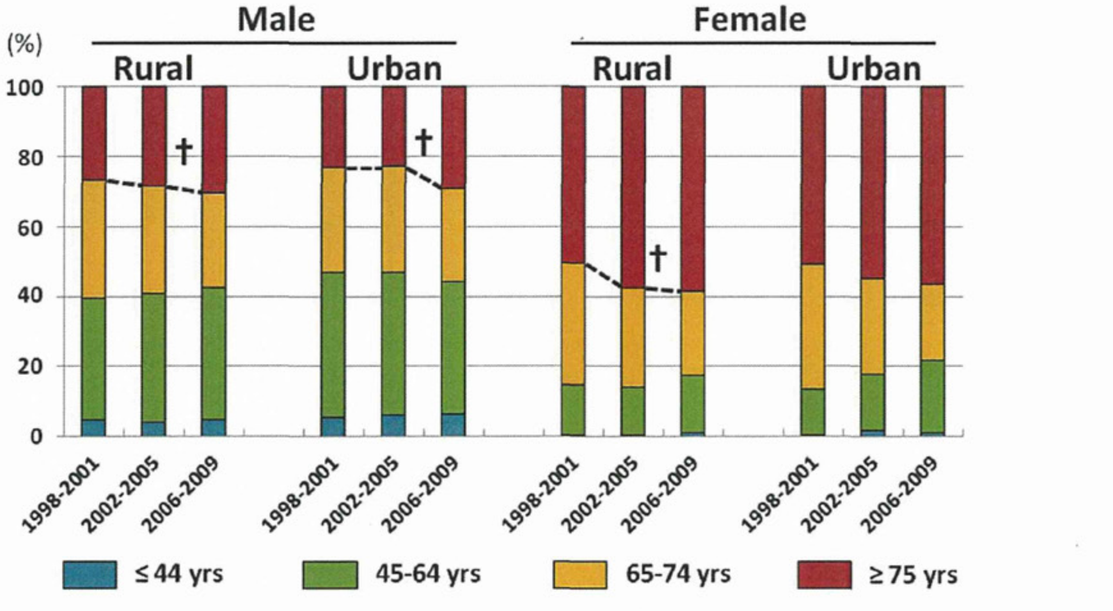

Figure 2. Age-distribution of acute myocardial infarction (AMI) patients. The percentage of high-old patients (≥75 years old) was markedly higher in female patients than in the patients in the rural and urban areas and has been increasing significantly in male patients in both areas and rural female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

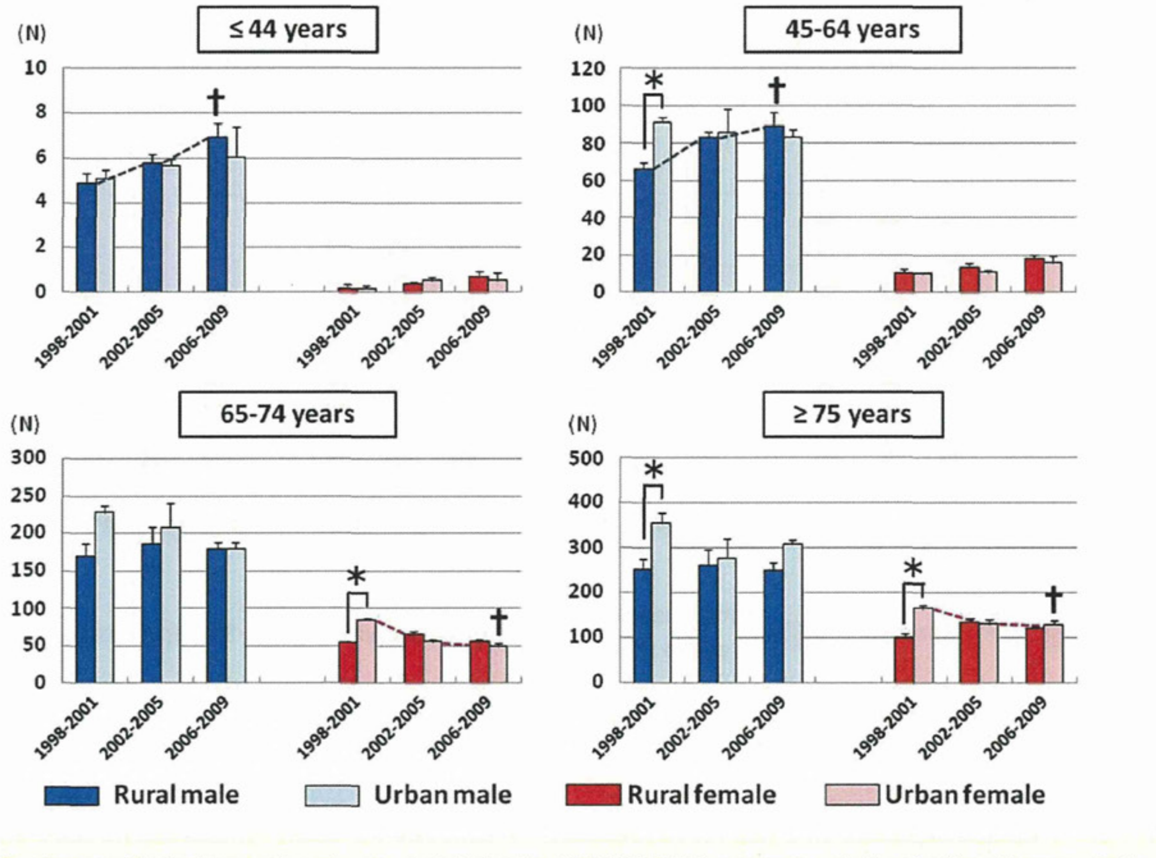

Figure 3. Age-specific incidence of acute myocardial infarction (AMI) (/100,000 persons/year). The significant increase in the age-adjusted incidence of AMI was noted in <44 and 45–64 year old rural male patients, and the significant decrease was noted in 65–74 and >75 year old urban female patients.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

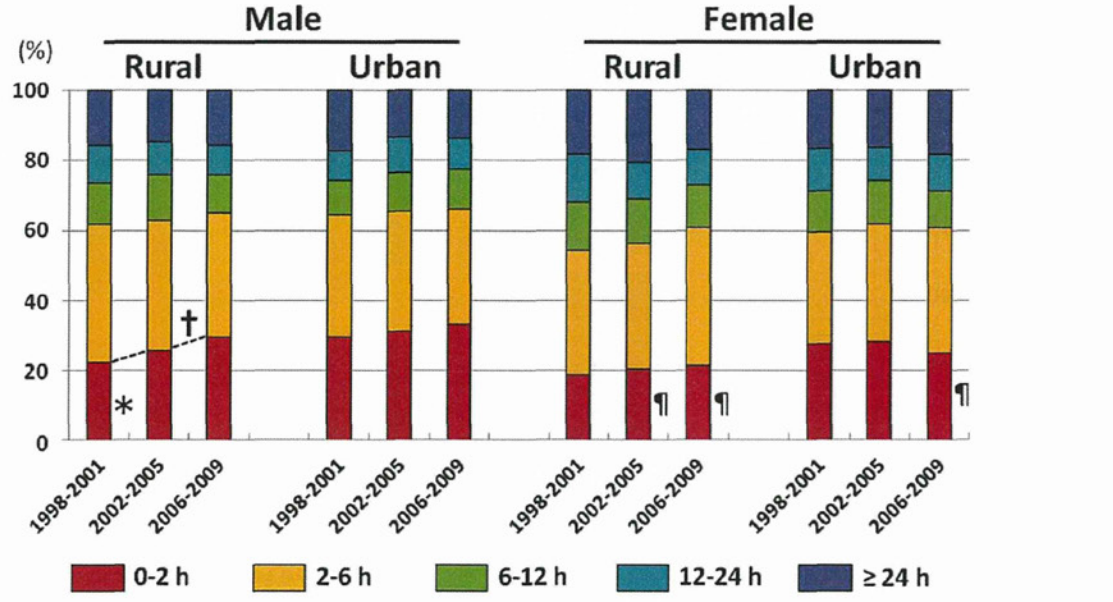

Figure 4. Time interval from the onset of symptoms to hospitalization. The percentage of patients with less than 2 h of elapsing time for hospitalization has significantly increased in rural male patients. The percentage was significantly lower in female patients than in male patients in both areas in 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.

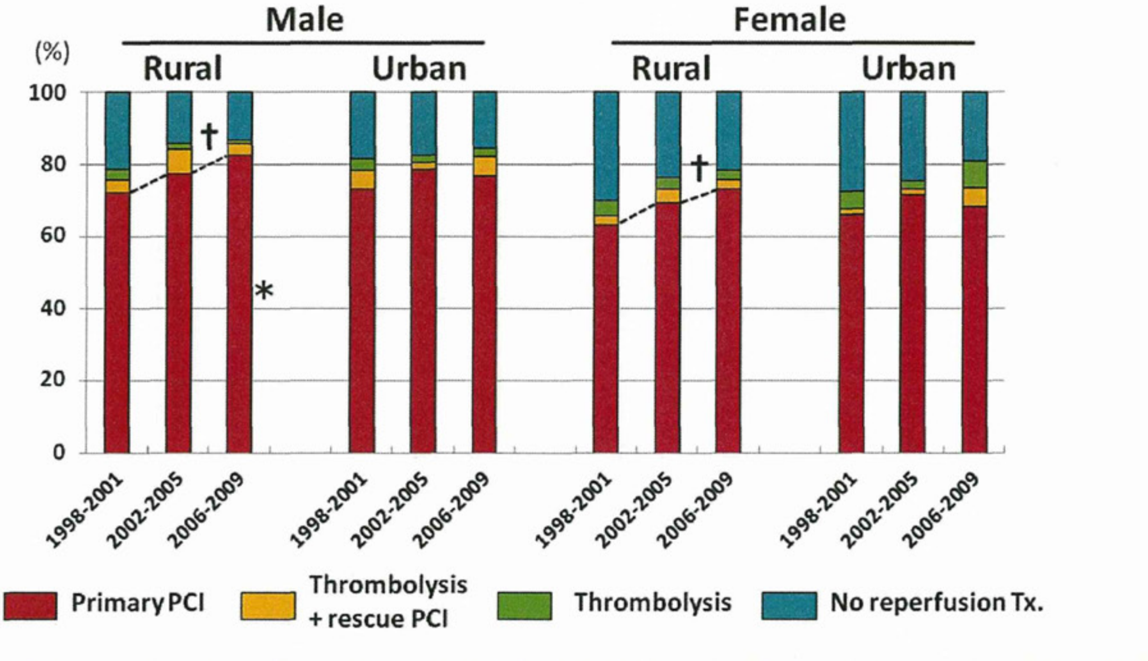

Figure 5. Prevalence of reperfusion therapy for acute myocardial infarction (AMI). The prevalence of primary percutaneous coronary intervention (PCI) steadily increased in the rural area in both sexes. Importantly, the prevalence of PCI was approximately 10% lower in female patients than in male patients 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.

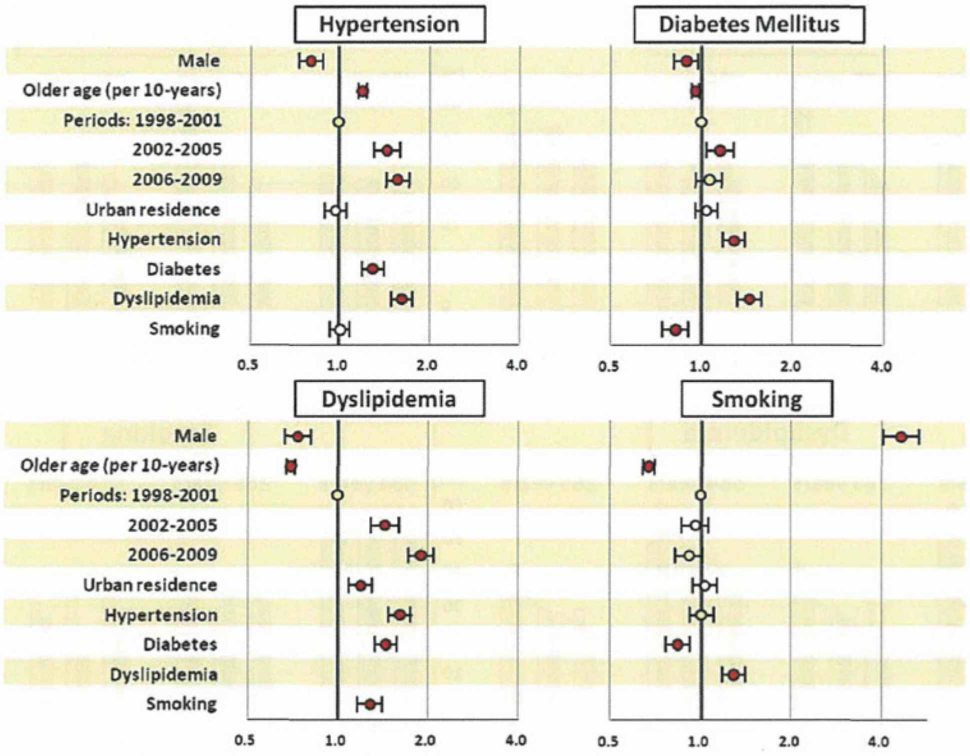

Figure 6. Multivariate analysis of coronary risk factors in acute myocardial infarction (AMI) patients. During the study periods, the prevalence of hypertension and dyslipidemia significantly increased in AMI patients. Hypertension was associated with older age but not with residence, whereas dyslipidemia 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-

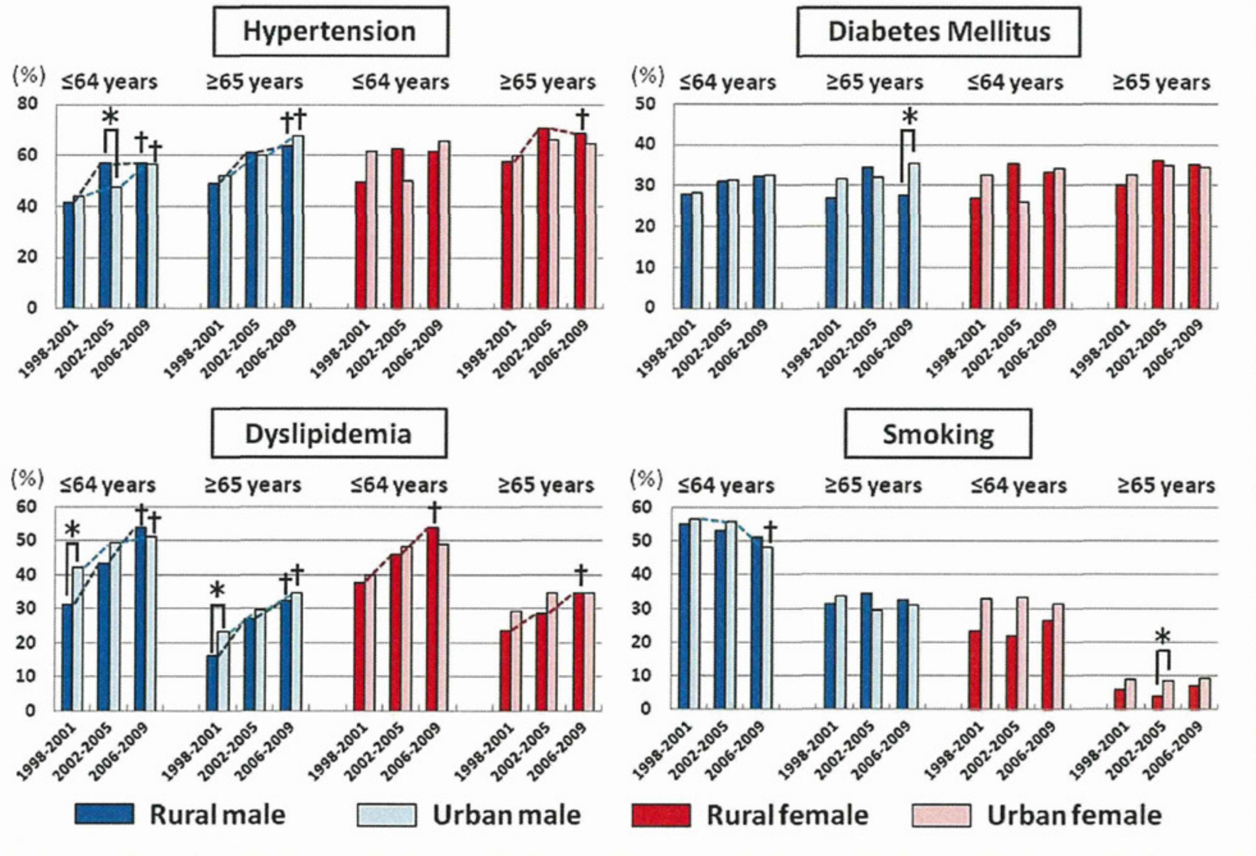

Figure 7. Prevalence of coronary risk factors in acute myocardial infarction (AMI) patients. The prevalence of hypertension and dyslipidemia had a trend of increase in both rural and urban areas. In particular, the prevalence of dyslipidemia in rural male patients aged ≤64 years markedly increased. *P<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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Prospective care of heart failure in Japan: lessons from CHART studies

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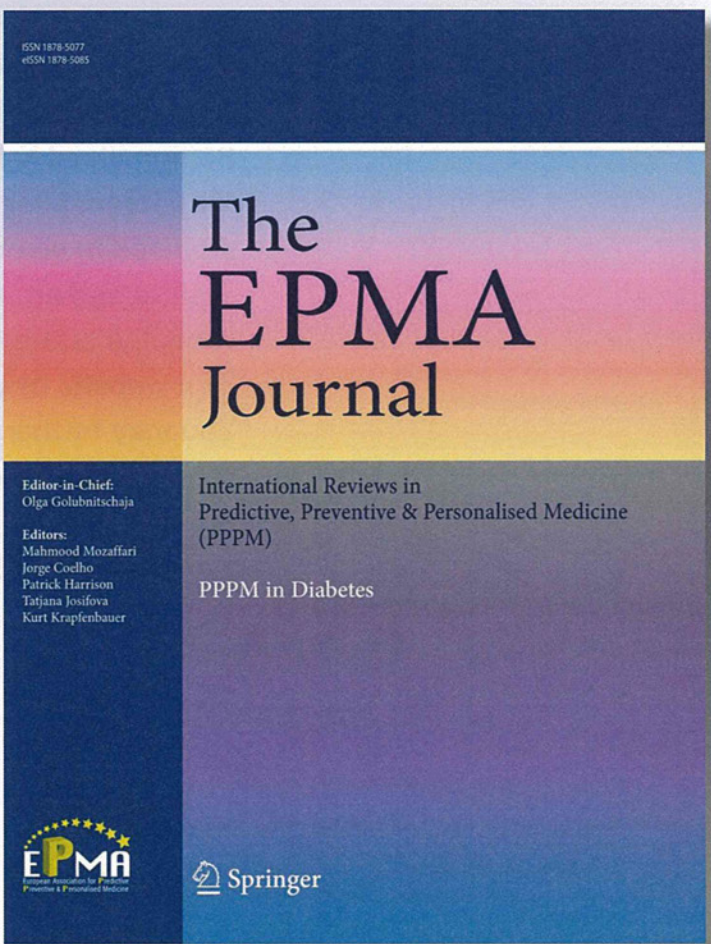

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REVIEW ARTICLE

Prospective care of heart failure in Japan: lessons from CHART studies

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Abstract There are approximately 23 million patients with heart failure (HF) worldwide. The prognosis of patients with HF is still poor and a prospective approach for preventing and treating HF is necessary. The number of HF patients in Japan has been increasing since 1950 mainly because of a rapidly aging population. Furthermore, westernized dietary pattern, reduced physical activity, and obesity have become prominent, particularly in younger Japanese men. There is an increasing trend of diabetes and dyslipidemia, and the prevalence of smoking and hypertension continues to remain high. One of the largest HF cohorts in Japan, the CHART Studies, showed that coronary artery disease (CAD) was the most frequent etiology of HF currently. Thus, prospective strategies including accurate risk stratification, effective prevention of disease progression through evidence-based treatments, optimally personalized treatment particularly in elderly individuals, and life-long control of CAD risk factors are required to manage HF in Japan.

Keywords Prevention · Personalized medicine · Coronary artery disease · Cardiovascular risks · Elderly · Undertreatment

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Worldwide increase in the number of patients with heart failure: importance of a prospective approach

Chronic diseases such as heart disease, stroke, cancer, chronic respiratory diseases, and diabetes mellitus (DM) are the leading causes of morbidity and mortality worldwide [1]. Patients with such diseases account for approximately two-thirds of all healthcare expenses. Typical medical intervention for patients with chronic diseases usually occurs during the latter stages of disease progression and the long-term prognosis remains poor despite the high costs of care. Healthcare systems in the developed countries are now changing their orientation from a disease-based approach to a prospective approach thereby focusing on predictive, preventive, and personalized medicine [2]. A key feature of such new approaches is strategic and personalized health planning. This includes new abilities to detect disease at an earlier stage, identify individuals at a higher risk of certain diseases, prevent disease progression, reduce healthcare costs, and ensure optimal treatment for each patient.

Heart failure (HF) is a complex syndrome that can result from structural or functional cardiac disorders. There has been an increase in the number of HF patients in the developed and developing countries. There are approximately 23 million patients with HF worldwide and 2 million patients are newly diagnosed with HF every year [3]. In the USA, the prevalence of HF in 2007 was 5.7 million and approximately 1 in 9 death certificates mentioned HF as the cause of death [4]. Furthermore, there were 670,000 new cases each year, with approximately 1 million hospitalizations due to worsening HF. The estimated healthcare cost of HF in 2010 was US $39.2 billion [3, 4]. Although the epidemiology of HF in most developing countries is poorly established, an increase in the importance of cardiovascular diseases (CVD) as well as coronary artery disease (CAD), in such countries may lead to an increased incidence and prevalence of HF in the future [5].

Otherwise, the mortality rates due to CVD have been declining in North America, Europe, Australia, and New Zealand since decades. However, mortality rates have been increasing in the former Eastern Bloc countries, Latin and South America, India, China, and Africa [5]. The reasons for the increasing trend of HF worldwide are: (i) advancement in the control of infectious, parasitic, and nutritional diseases in developing countries, which has led to CVDs being increasingly recognized (ii) more people can reach the age at which CVDs manifest (especially in developed countries) (iii) HF usually develops at the final stage in the long-standing process of CVD.

The prevalence of CVD in Japan remains low. The age-adjusted mortality (standardized mortality rate in the Japanese population in 1985) from heart diseases has been declining recently. However, Japan has the most advanced aging society in the world and the crude number of patients who die as a result of heart diseases (of which the major part was considered to be HF) has been increasing dramatically for decades [6, 7]. We have been conducting a multicenter prospective cohort study of HF patients named the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART-1; N= 1278) since 2000. We reported that the mortality rate of HF patients in Japan was high and was comparable with that seen in the Western countries [8, 9].

Guidelines for the diagnosis and management of HF in adults set by the American College of Cardiology (ACC) Foundation / American Heart Association (AHA) have proposed a new classification of HF consisting of stages A, B, C, and D to emphasize the development and progression of HF [10]. Stage-A and -B patients are defined as those with risk factors that clearly dispose toward the development of HF. Stage C denotes patients with current or past symptoms of HF. Stage D denotes patients with truly refractory HF (Fig. 1). This classification shows that there are established risk factors and structural prerequisites for the development of HF. It also shows that the therapeutic interventions introduced even before the manifestation of structural disorders or symptoms can improve the prognosis of HF. Other authoritative HF guidelines published by organizations in several other developed countries have also underscored the importance of thorough care of patients at high risk of developing HF in addition to appropriate treatment for those with overt HF [10–13].

We started a new cohort named the CHART-2 Study in 2006 which included patients at high risk of developing HF as well as those with overt HF, and recently closed the entry period of the study [14]. This review summarizes the recent trends involved in development or exacerbation of HF in Japan as well as the clinical characteristics of Japanese patients with HF. Furthermore, we underscore the importance of a prospective approach in treating patients with CVD or those with a risk of developing HF in order to improve the prognosis of such patients.

The declining birthrate and aging population in Japan

The population of Japan surpassed 100 million in 1967 but the population growth has recently slowed. The annual growth of the population from 1960 to 1980 was approximately 1%. However, the population of Japan began to decrease since 2005, and the total population in 2009 was 127.51 million [7]. The age structure diagram of 1950 shows that Japan had a standard-shaped pyramid characterized by a broad base. However, it represents a constrictive pyramid in 2009, which indicates lower percentage of younger population and longer life expectancy (Fig. 2). In 2009, the population of individuals aged ≥65 years was 29.01 million, constituting 22.7% of the total population. In Japan, the rate of aging has been high since the 1970s compared with that in other Western or Asian countries; the percentage of elderly population (≥65 years) is estimated to reach 39.6% by 2050 (Fig. 3) [15]. The mean life expectancy at birth in Japanese individuals continued to improve after World War II; it was 79.6 years for men and

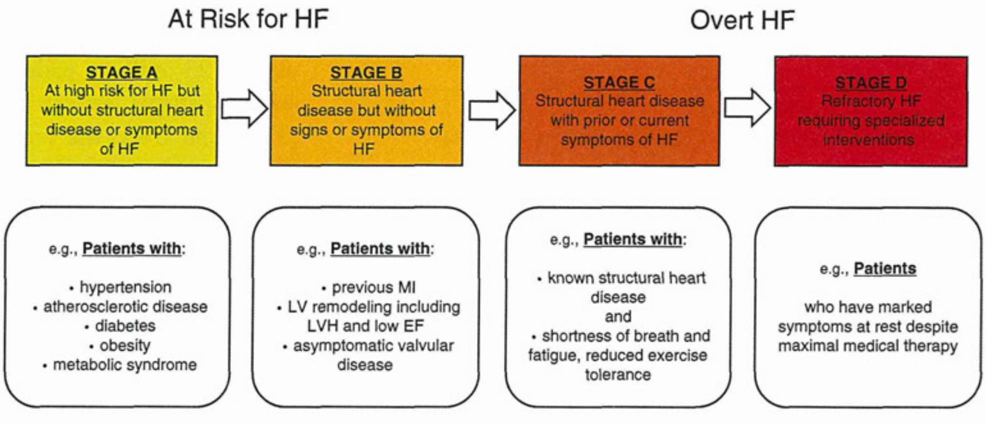

Fig. 1 Stages in the development of heart failure [10]. HF, heart failure; MI, myocardial infarction; LVH, left ventricular hypertrophy; EF, ejection fraction

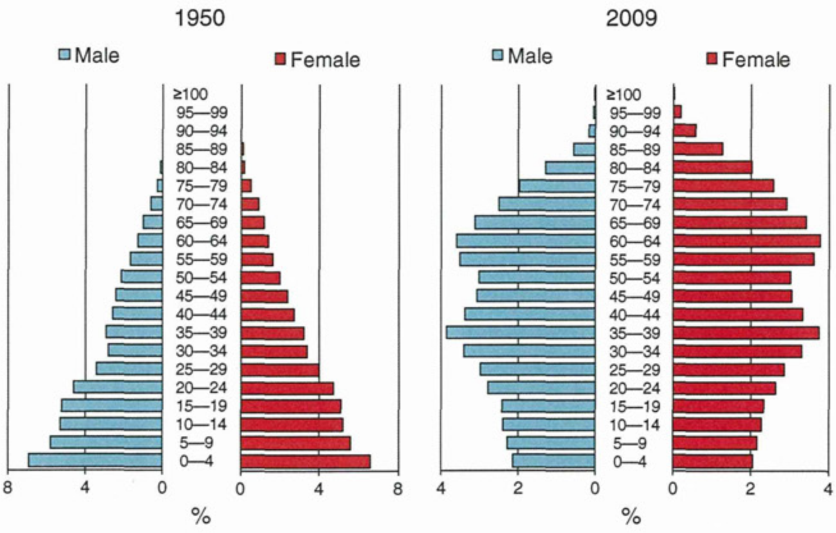

Fig. 2 Population pyramid of Japanese population in 1950 and 2009 [7]

86.4 years for women in 2009 [7]. The percentage of younger age population (0–14 years) has been decreasing since 1982, which was 13.3% of the total population in 2009 [7]. The major reason for this declining trend is the recent low birth rate seen in the Japanese population, which was more prominent since the late 1970s. The birth rate in 2009 was as low as 8.5 per 1,000 population [7].

This trend showing a rapid increase in the elderly population will further increase the number of patients with CVD or HF. These patients would need a more personalized strategy in evaluation and treatment of disease compared with middle-aged patients (see below).

"Lifestyle Westernization" among Japanese people

Multiple dietary factors are strongly associated with atherosclerotic disease (including CAD) and appropriate diet modification can have beneficial effects. A common feature of the diets that help to prevent CAD is the emphasis on plant-based foods. These foods are characterized by a high intake of fiber and a low intake of saturated fat. Furthermore, in Japan, if the total fat intake is >30% kcal, the predominant fat is monounsaturated fats [16]. Although the impact of these dietary patterns in the primary prevention of atherosclerotic disease is important, there are a few clinical trials that directly compare the effect of different diets on CVD risk.

The dietary pattern in Japanese individuals has changed with a higher intake of animal fat and protein, and a lower intake of carbohydrates [17]. The National Nutrition Survey of Japan (NNSJ) reported that the intake of dietary fat as a percentage of energy was approximately 8% in 1950, which has rapidly increased by 3.8-fold over the past 50 years [18]. In men and women, the mean total intake of calories in 2009 was 2073 kcal and 1677 kcal, respectively, whereas percentage intake of energy as fat was 25.1% and 26.7%, respectively. It is important to note that individuals aged 20–29 years who were consuming ≥30% of total energy in the form of fats accounted for 37.0% men and 44.2% women [18].

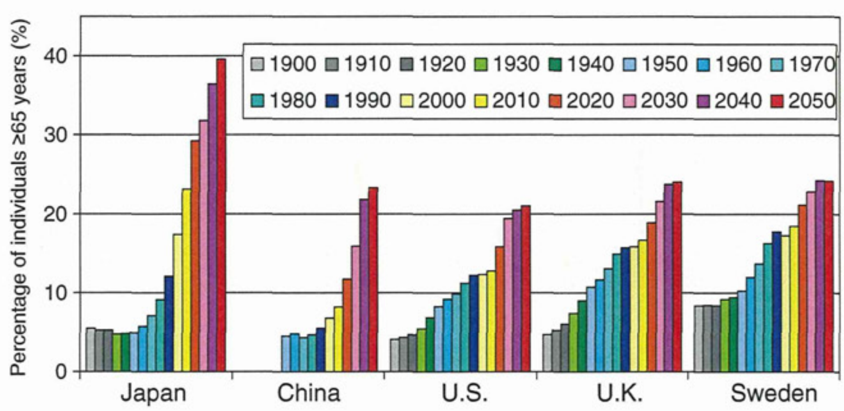

Fig. 3 Trend of percentage of individuals aged ≥65 years in various countries [15]

Studies have shown an inverse association between physical activity and the risk of developing CVDs such as CAD and stroke in men and women [19]. Meta-analyses of prospective observational studies revealed that moderately active men experienced 20-30% less age-adjusted rates of CAD and all-cause mortality compared with the least active men [20]. Regular physical activity of an adequate amount and intensity prevents the development of atherosclerosis and improves several cardiovascular risks which are causally linked to the progression of atherosclerosis (e.g., obesity, hypertension, dyslipidemia, diabetes, and smoking). Shibata et al. evaluated the relationship between physical activity and death from CVD using prospective data involving 12490 Japanese participants. They reported that more physical activity was associated with a reduced risk of death from CVDs [21]. The NNSJ showed an overall increase in the number of individuals who had regular exercise habits since 1987 (Fig. 4) [18]. However, a stable or decreasing trend of physical activity was prominent in men and women aged 20–39 years.

An increased intake of animal fat and relatively less physical activity in the younger Japanese population may have an impact on the development of CVD or HF. These findings warrant long-term monitoring of lifestyle and cardiovascular risks in those individuals.

Trends in risks of CVD and HF in Japan

Hypertension or raised blood pressure (BP) carries a definite risk of developing CVD. Successive lowering of BP will lead to cumulative reduction in the risk of developing CVD. Ueshima et al. reported the long-term trend of BP in a Japanese population using the NNSJ (which has been conducted since World War II) [6]. They reported that systolic blood pressure (SBP) showed a decline since 1965 in men aged ≥50 years and in women of all age groups; the reduction in SBP for individuals aged ≥60 years almost reached ≥15 mmHg during 1965–2000. The prevalence of individuals with hypertension has also decreased since 1980 in all age groups (Fig. 5) [18]. There is clear evidence that increased consumption of salt is a major factor in increasing BP [22] and that the major reason for individuals showing decreasing trend for hypertension in Japan is due to reduced intake of salt. Salt consumption in northern Japan was 26–27 g/day in the 1950s; it decreased significantly to 13 g/day in 2001 and 11 g/day in 2008 [18].

However, Martiniuk et al. reported that the crude prevalence of hypertension in Japan in 2000 was 41.4% and 31.9% in men and women, respectively, and that the prevalence was the second highest in the WHO-defined Western Pacific and South-east Asian regions [23]. They reported that the sex-specific population-attributable fraction of fatal CAD attributable to hypertension was approximately 15% in men and 39% in women. The report of the Asia Pacific Cohort Studies Collaboration (APCSC) showed continuous log–linear associations between SBP and incidence of CAD [24]. A 10-mmHg decrease in SBP was associated with 46%, 24%, and 16% lower CAD risk in individuals aged <60, 60–69, and ≥70 years, respectively. Further reductions in the prevalence of hypertensive individuals should be given high priority in many countries (including Japan) to prevent the development of hypertension-related CVD, which is a major cause of HF.

Individuals with DM are also at an increased risk of death from various types of CVDs. The APCSC analyzed 24 population-based cohort studies from Asia, Australia, and New Zealand [25]. This study included 29089 Japanese individuals (aged 20–96 years) and the mean prevalence of DM at study entry was 3.3%. During a median follow-up of 5.4 years, they showed that age-, sex-, and study-adjusted hazard ratios (HRs) for fatal CAD associated with DM were 2.22 in the Asian population. In addition, there was no significant change in the HR after multivariable adjustment including BP, cholesterol, body mass index (BMI), and smoking status. It is important to note that the relative effect of DM on the risks of CVD and death in Asian populations

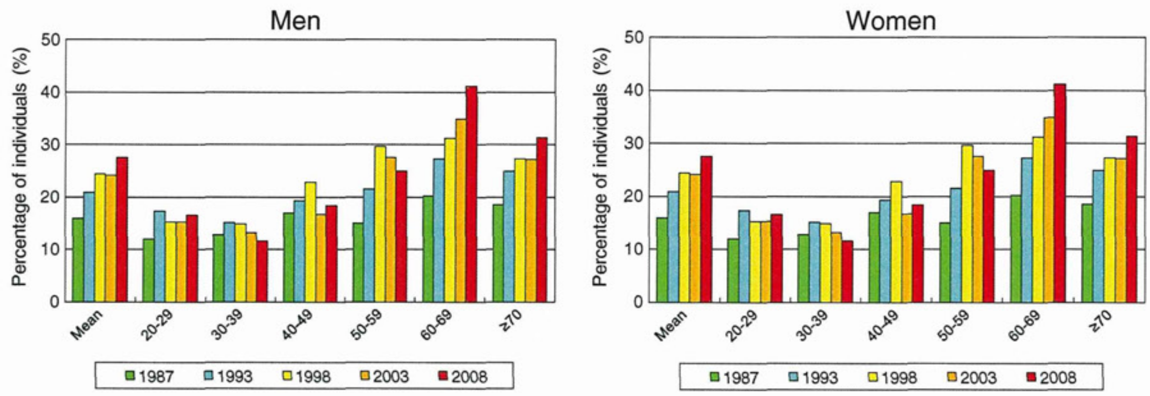

Fig. 4 Trend of regular exercise habit in Japanese individuals [18]

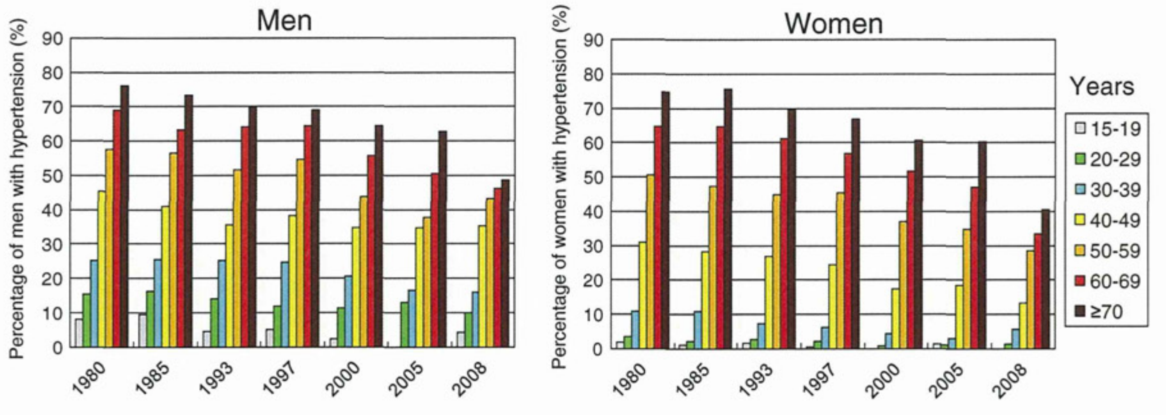

Fig. 5 Trend of percentage of individuals with hypertension by age [18]

was almost identical to that in Caucasian populations. The prevalence of DM has been increasing more rapidly throughout Asia compared with that in the Western countries. Wild et al. reported that individuals with DM in Japan would increase from 6.8 million in 2000 to 8.9 million in 2030 [26]. The NNSJ showed that the prevalence of individuals diagnosed as having DM or whose hemoglobin A1c level was ≥6.1% was 8.2%, 9.0%, and 10.5% in the years 1997, 2002, and 2007, respectively [27]. This survey also revealed that the increase in prevalence was more prominent in individuals aged ≥60 years and that 22.1 million Japanese people were considered to have DM (or the possibility of having glucose intolerance) in 2007 (Fig. 6).

Asian populations are less obese compared with Western populations. The BMI in Asians is approximately 20–24 kg/m^2, whereas it is 26–29 kg/m^2 in the Westerners [28]. However, age-adjusted BMI has increased since 1956 in the Japanese population [29]. The NNSJ revealed that the prevalence of Japanese male individuals with BMI ≥25 kg/m^2 has been increasing (Fig. 7) and the mean prevalence was 16.8%, 25.8%, and 30.5% in the years 1979, 1999, and 2009, respectively [18]. The BMI of Japanese women has been relatively stable for the last 30 years (Fig. 7) and the mean prevalence of Japanese females with a BMI ≥25 kg/m^2 was approximately 20% [18]. Increased BMI is also associated with raised BP, glucose intolerance, dyslipidemia, and development of CVD in Japanese population. The analysis of NIPPON DATA showed that there was a significant dose–response relationship between the BMI and odds ratio for hypertension in men and women [30]. This analysis also revealed that the percentage of individuals with hypertension attributable to obesity in 1980 and 1990 was 11.4% and 15.3% for men and 19.3% and 22.3% for women, respectively. Furthermore, Shiraishi et al. reported that a BMI ≥25 kg/m^2 was significantly associated with the development of acute myocardial infarction (AMI) in young and middle-aged Japanese men [31]. These findings suggest that obesity is now playing an important role in the development of cardiovascular risks and CVD in Japan.

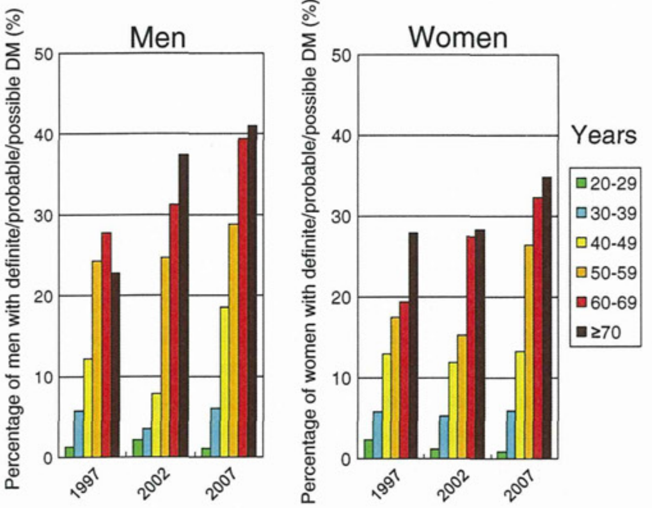

Fig. 6 Recent trend of percentage of individuals with DM by age [27]. DM, diabetes mellitus

Cigarette smoking has been associated with atherosclerotic disease (including CAD and stroke) throughout the world. The report of the APCSC in 2005 stated that 51–76% of men and 1–17% of women in Japan were current smokers from 1974 to1997 [32]. This study revealed that the HR of current smokers for CAD was 1.60 compared with non-smokers in Asia, Australia, and New Zealand; there was a clear dose–response relationship between the number of cigarettes smoked per day and the incidence of CAD. The prevalence of smoking in Japanese men declined from 46.8% in 2003 to 38.2% in 2009, whereas that in Japanese women is relatively lower compared with that in men, but remains high (11.3% in 2003 and 10.9% in 2009) [18, 28]. Martiniuk et al. reported that the fraction of CAD attributable to smoking in Japanese men and women in year 2000 was 22% and 7%, respectively [33]. Smoking control must be more emphasized to reduce the prevalence of CVD in Japanese men and women.

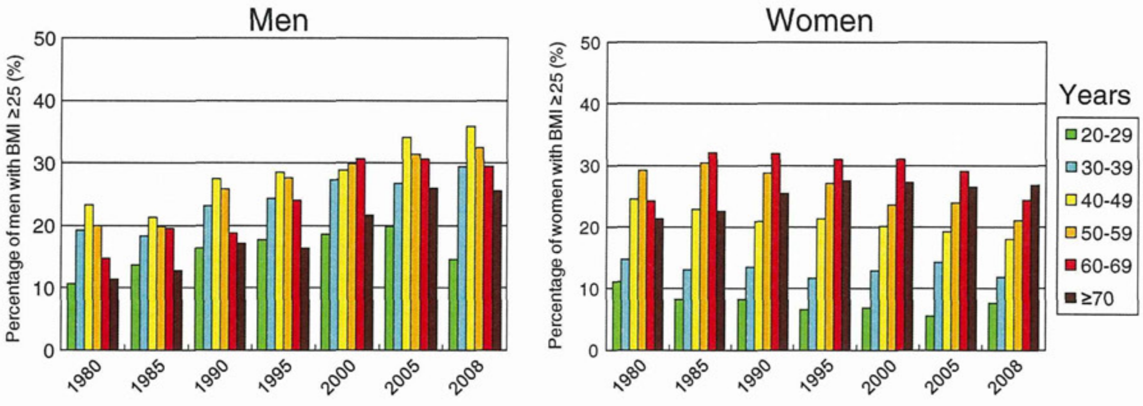

Fig. 7 Trend of percentage of individuals with BMI ≥25 kg/m^2 by age [18]. BMI, body mass index

Dyslipidemia is a well-established risk factor for CAD. Serum levels of total cholesterol (TC) in individuals of Asian countries (except Singapore) are generally far lower than those in the USA and other Western countries [28]. It was <190 mg/dL in 1980 in all age groups, and has significantly increased in recent years (>200 mg/dL in middle-aged men) (Fig. 8). However, the serum level of TC in the elderly Japanese population is lower than that of Western populations [34]. Although Japanese women aged 50–69 years showed a relatively high serum TC level (Fig. 8), the impact of raised TC or low-density lipoprotein cholesterol (LDL-C) between men and women might be different. Noda et al. after evaluating 91219 Japanese individuals without stroke and CAD, reported that a higher LDL-C level was associated with an increased risk of mortality from CAD in men but not in women [35]. Arai et al. evaluated the 40-year trend of lipid profiles in 12839 Japanese individuals [36]; they reported that the increase in TC level was attributed to an increase in the level of high-density lipoprotein cholesterol, and not LDL-C. The triglyceride level in Japanese population increased over the last 10 years, which was mainly attributed to the increase of that in middle-aged men; the authors anticipate a further increase in the incidence of hypertriglyceridemia in the future. In Japan, high consumption of fish and rice have contributed in keeping the serum level of TC lower than that of Western countries [34, 37]. Recently, the intake of animal protein and fat in the Japanese population has increased significantly [38]. The impact of such alterations in dietary habits on the lipid profile should be evaluated.

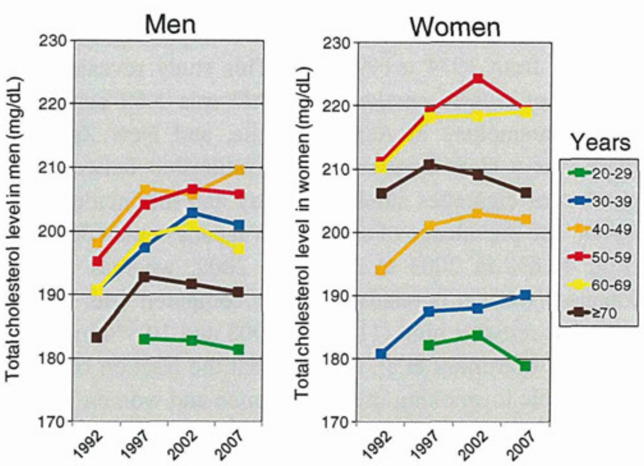

Fig. 8 Recent trend of total cholesterol level by age [18]

Trends in mortality and incidence of CAD in Japan

Japan has the lowest mortality rate from CAD among the industrialized countries [19]. Mortality from CAD began to decline by 1970 in most countries. Age-adjusted mortality due to all heart diseases and CAD in Japan increased until 1970 and then continued to decrease gradually (Fig. 9) [7]. However, the crude mortality rate from all heart diseases, CAD other than AMI and HF has been increasing since the 1970s; crude mortality from AMI has decreased gradually since 1995 (Fig. 9). The major reason for such trends includes the rapidly aging Japanese society. The incidence rate of AMI was much lower than that in other industrialized countries [34]. Several reports from the USA showed a substantial decrease in CAD incidence beginning in 1970 [39, 40]. However, it remains controversial whether the incidence rate of AMI in Japan has decreased or not. Kodama et al. evaluated the incidence of CAD from a 26-year follow-up study, which included 19961 subjects and reported that the age-adjusted incidence of AMI remained almost constant from 1958 to 1984, averaging 2.1/1000 person-years in men and 0.79/1000 person-years in women [41]. Kitamura et al. reported an increasing trend of age-adjusted CAD incidence in Japanese men since 1980 in the rural and urban areas [42]. The Hisayama Study, using three study cohorts from 1961, 1974, and 1988, reported that the age-standardized incidence of CAD had been increasing in individuals aged ≥80 years [43].

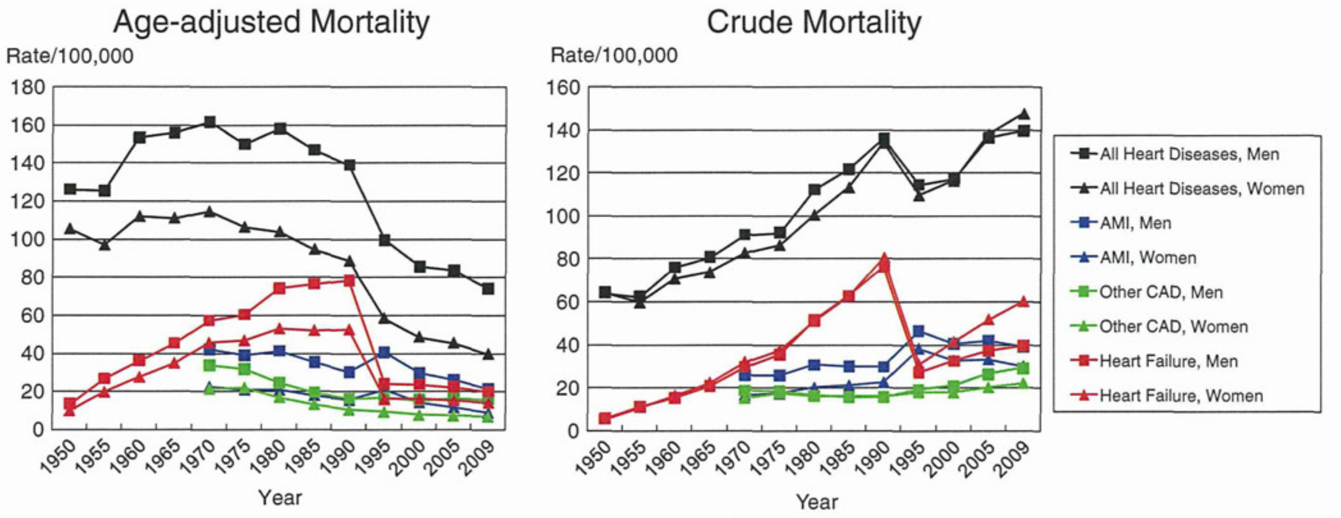

Fig. 9 Trend of mortality rate by various heart diseases [7]. AMI, acute myocardial infarction; CAD, coronary artery disease

The mechanisms of increasing trend of AMI in Japan include westernization of lifestyle, increased prevalence of DM, increased levels of TC in serum, increased BMI in men, and a high prevalence of hypertension and smoking. Although the incidence rate of AMI in Japan remains low, aggressive reduction of such cardiovascular risks must be emphasized to prevent the development of AMI.

Elderly individuals and CVD

In general, atherosclerosis takes a long time to develop. Most elderly individuals have some degree of atherosclerosis, and >80% of all cardiovascular deaths occur in individuals aged ≥65 years [44]. In many countries, the mortality rate from CAD and stroke has been decreasing steadily since the late 1960s. However, the reduction in mortality has been particularly observed in middle-aged men; the elderly population has not shown a substantial decrease in cardiovascular mortality [44]. Statistical data from Japan have also shown a decreasing trend in the crude cardiovascular mortality rate across all age groups since 1990. However, since 1950, there has been a dramatic increase in the mortality from heart diseases among individuals aged ≥75 years and a moderate increase in the mortality from heart disease was observed in men aged 65–74 years (Fig. 10) [7]. The Tokyo Fire Department of the Fire and Disaster Management Agency in Japan sent 700808 ambulance services in 2010. It reported that the number of individuals aged ≥65 years who utilized the service for a sudden illness was 277077 (39.5%), which was an increase in the figure from 2003 (Fig. 11); one of the major reasons for this trend was the rapid increase in the elderly population in Tokyo [45].

Many of the elderly individuals are at a much higher cardiovascular risk than any other age group. However, the magnitude of risks and benefits of risk mitigation between the elderly and the younger or middle-aged population might be different.

Hypercholesterolemia or a high level of LDL-C is a major risk factor for developing CAD in the general population. However, in observational studies, this association in the older population is controversial [46]. One of reasons for the discrepancy in this association between middle-aged and older populations is that comorbidity is frequently observed in the elderly and this may cause acquired low levels of cholesterol. There were several reports showing that lipid-lowering treatment using 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors significantly reduced coronary events in the older age group similar to those in the middle-aged population in primary and secondary prevention trials [46, 47].

Hypertension is a definite risk factor for the development of CVD in the elderly population [48]. Many large prospective trials also documented the clear benefit of antihypertensive treatment in elderly patients with hypertension. A meta-analysis involving 5 trials in hypertensive patients aged ≥60 years showed that antihypertensive agents resulted in a 19% reduction in CAD, which was similar to that seen in younger individuals [49]. Furthermore, Mulrow et al. reported that the short-term benefits in morbidity and mortality of treatment were greater in elderly than in younger patients [50]. The Hypertension in the Very Elderly Trial reported that antihypertensive treatment with indapamide in patients aged ≥80 years was beneficial with significant reduction in death rate from cardiovascular causes or the development of HF [51].

Smoking is an established risk for the development of new CVDs in the elderly, although its relative contribution decreases with increasing age [52]. Furthermore, older people who cease smoking after 70 years of age showed a

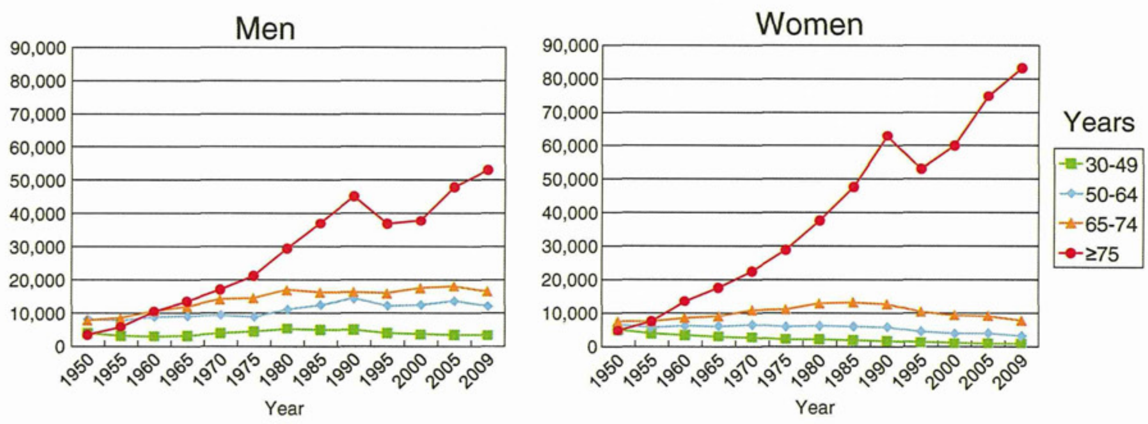

Fig. 10 Trend of number of individuals who died from heart diseases by age [7]

significant reduction in the development of new myocardial infarction or death [53].

DM or poor glycemic control are associated with an increased incidence of cardiovascular events in elderly men and women [54, 55]. However, the relative effects of DM on CVDs are weaker among older patients compared with younger patients [56].

Atherosclerosis is not the only abnormality associated with the development of symptomatic CVD. Triggering factors (e.g., increased coagulation activity, increased activity of sympathetic nervous system, vasoactive hormone, smoking) which might be more frequently observed in elderly individuals also play an important role (especially in artery-occlusive diseases). The most effective strategies preventing the development of HF and the progression of CVD are reduction of modifiable cardiovascular risks and elimination of triggering factors that causes sudden arterial occlusion or decompensation of HF. However, under-treatment or insufficient control of cardiovascular risks may be more prominent in elderly patients. National Health and Nutrition Examination Survey III showed that only 23–46% of patients with hypertension aged >70 years showed adequate control of BP [57]. Our previous cohort study of HF patients: (the CHART-1 Study) revealed that the penetration rate of standard HF treatment such as renin-angiotensin system (RAS) inhibitors and β-blockers was significantly lower in elderly patients, which was validated by multivariate logistic regression analyses [58].

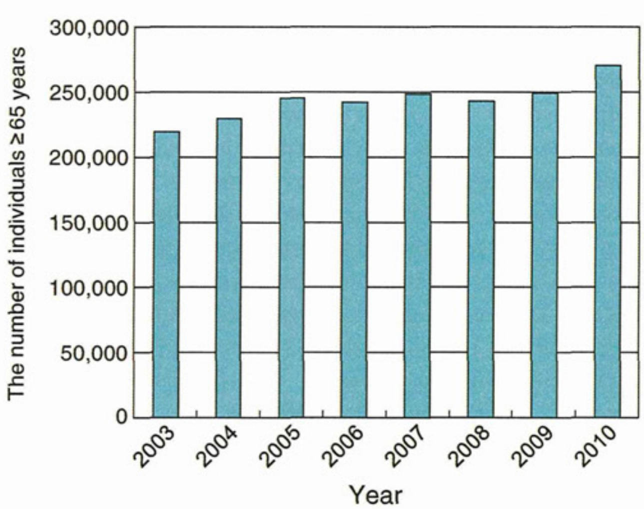

Fig. 11 Number of ambulance service in the Tokyo Fire Department [45]

Some elderly individuals have comorbidities that represent a significant association with CVD. Chronic kidney disease (CKD) is an extensive public-health problem and is observed in 9–13% of the general population [59]. The prevalence of CKD increases with age and many reports have clarified that CKD is an important risk factor for the development and worsening of CVD [59, 60]. Chronic obstructive pulmonary disease (COPD) is the fourth most frequent cause of death; approximately 400000 deaths occur each year from COPD in developed countries [61]. COPD is one of the persistent systemic inflammatory disorders (like CVD or HF) and is strongly associated with the elderly population (probably as a result of the long-term exposure to risk factors such as cigarette smoking) [61]. Recent reports showed that COPD was a significant risk factor for developing CVD and cardiovascular death. Mazza et al. reported that COPD was an independent risk factor for cardiovascular mortality in hypertensive individuals [62]. Kjøller et al. also revealed that COPD was a predictor of mortality in patients with AMI when evaluating 6669 subjects included in the Trandolapril Cardiac Evaluation Study [63]. Further research should be emphasized to evaluate such extra cardiac risks for CVD and to recognize novel prognostic risks (particularly in the elderly population).

The pathophysiology of CVD or HF is more complicated and heterogeneous in elderly patients. Furthermore, such patients usually have non-cardiovascular comorbidities (including chronic diseases) which sometimes complicate appropriate diagnosis and treatment. Conventional diagnostic tools may be less useful in such patients compared with younger or middle-aged patients. Importantly, there is no sufficient clinical evidence for treating elderly patients with CVD or HF. Thus a personalized approach is necessary in the prevention and management of HF in elderly patients.

CHART-2 study

The prevalence and crude mortality rate of CVD has been relatively lower in Japan compared with that in Western countries. However, it has been rapidly increasing due to the westernization of lifestyle, increased risk of atherosclerosis, and a rapidly aging population [7, 9]. Our previous cohort study of HF patients, the CHART-1 Study, revealed that the most prevalent etiology of HF in Japan was non-ischemic cardiomyopathy (28.6%) and only 25.4% of HF was attributed to CAD (which is the leading cause of HF in most Western countries) [8]. We started a multicenter prospective cohort study, the CHART-2 Study, in October 2006 to evaluate the clinical characteristics and prognosis of Japanese patients at high risk for disease progression of CVD or those with overt HF [14]. The study was conducted in collaboration with 24 hospitals in the Tohoku district; this is in the north-east of Japan and has a population of 9.8 million. Stable patients aged ≥20 years were consecutively enrolled in the study who were suffering from CAD or were in stage B, C, or D as defined by the Guidelines for the Diagnosis and Management of HF in Adults of the ACC Foundation/AHA [10]. The entry period of the CHART-2 Study was closed in March 2010 (N=10219), which made this study the largest-scale cohort of CVD in Japan [64].

Characteristics of Japanese patients with CVD but without HF

The CHART-2 cohort involved 5484 patients (53.7%) with CVD but without HF. These patients were characterized by younger age (67.6±12.2 years), higher number of males (71.0%), less severe symptom, and higher values of ejection fraction (EF, 65.5±11.7%) compared with those in stage C or D. However, the prevalence of cardiovascular risks such as hypertension (75.4%), DM (21.9%), and dyslipidemia (72.7%) was similarly high. The prevalence of current smokers was also high, 23.3% (men) and 5.9% (women). CAD was the most prevalent etiology accounting for 58.2% of patients in stage B. Furthermore, B-type natriuretic peptide (BNP) level was mildly elevated in patients in this category (97.6±188.1 pg/mL) and 32.4% of patients had CKD. Usage rates of RAS inhibitors and β-blockers were 57.9% and 33.0%, respectively.

HF stage progression and exacerbation in prognostic risks

Background characteristics of CHART-2 patients showed a graded appearance of HF stage on CVD severity [14]. For example, as the HF stage progressed from stage B to stage D, left ventricular end-diastolic dimension increased, left ventricular EF decreased, and BNP level increased significantly (Fig. 12). Furthermore, recently underscored kidney-related risks were also exacerbated with progression of HF stage; the estimated glomerular filtration rate (GFR) decreased, hemoglobin level decreased, and the urine albumin creatinine ratio increased significantly (Fig. 13).

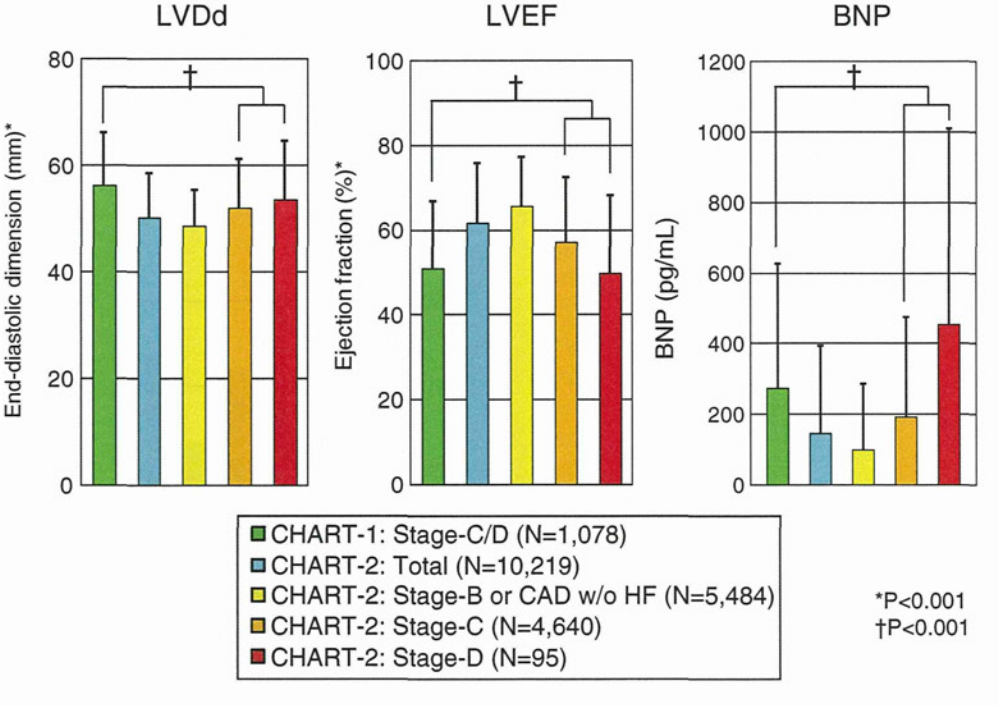

Fig. 12 LV dimension, EF, and BNP of CHART-1 and CHART-2 patients [14]. BNP, B-type natriuretic peptide; CAD, coronary artery disease; Dd, diastolic dimension; EF, ejection fraction; LV, left ventricular