

「急性心筋梗塞の再灌流療法における性差についての研究」

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研究要旨

最近3年間に24時間以内に再灌流療法を施行された1199名(男性 898名、女性 301名)を対象としてAMI発症から再灌流するまでの時間経過を男女間で比較した。発症から再灌流達成までの時間は男性に比して女性において有意に長く(285 vs. 235分, $P<0.01$)、その差は発症から入院までに女性でより時間を要していることに起因していた。特に郊外部に住む女性において顕著であった。

A. 研究目的

以前我々は急性心筋梗塞(AMI)後の院内死亡率が男性に比して女性で高率であることを報告したがその原因はよく分かっていない。本研究ではAMI発症から再灌流するまでの時間経過の性差を検討した。

B. 研究方法

MIYAGI-AMI registryにて登録された患者の内、2008年から2010年の間に登録された3119名(男性2219名、女性900名)を対象とした。そのうちAMI発症からCAG開始までの時間が24時間以上経過している症例は除外し、最終的に1199症例(男性898名、女性301名)を解析の対象とした。各群においてAMI発症後の時間経過、PCI施行率、院内死亡率を検討した。また患者の居住地により仙台市内(都市部)と仙台市外(郡部)の2群に分けた。

(倫理面への配慮) 本研究は「疫学研究に関する倫理指針」を遵守して研究を計画・実施した。調査されたデータは個人情報情報を除外した上で暗号化されて事務局のデータベースに登録される。システムへのアクセスは、パスワードで厳重に制限されて

いる。

C. 研究結果

対象患者3119名における院内死亡率は女性で有意に高く(男性9.2% vs. 女性14.3%, $P<0.01$)、PCI施行率は女性で有意に低率であった(男性82.2% vs. 女性70.3%)。24時間以内に再灌流された1199名を対象とすると、AMI発症から再灌流まで、男性に比べ女性で有意に時間を要していた(中央値男性235分 vs. 女性285分, $P<0.01$)。病院に搬送されてから再灌流まで要した時間、いわゆるドアツーバルーン時間に男女差は無く、AMI発症から入院まで女性において有意に長く時間を要していることに起因していた(男性150分 vs. 女性190分, $P<0.01$)。特に仙台市内の男性と郊外部の女性間でその差は顕著であった(140分 vs. 207分)。

D. 考察

本検討においてAMI発症から再灌流まで男性に比べ女性において時間を要しており、その主因としてはAMI発症から入院までの時間経過に起因することがわかった。特に郊外部に住む女性でその傾向は顕著で

あり、女性において高率な AMI 院内死亡率の低下を計るためにはこれらの対象における啓蒙・教育が必要と思われる。また、病院に搬送されてから再灌流までの経過に男女差、住居地による差は認められず、宮城県全体で一律な加療が行われていると推測できる。

E. 結論

男性に比して女性において AMI 発症から来院するまでの時間が長く、結果的に再灌流まで時間を要していた。その差は郊外に住む女性で顕著であった。

F. 健康危険情報

総括研究報告書参照

G. 研究発表

1. 論文発表

なし

2. 学会発表

なし

H. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

Factors Influencing the Gender Difference in the Outcome of Reperfusion Therapy in Patients with Acute Myocardial Infarction

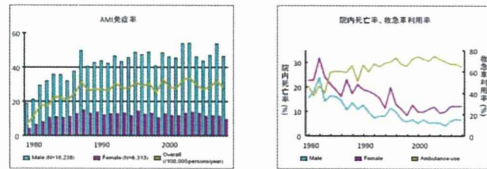
Report from the MIYAGI-AMI Registry Study

Abstract

- Background:** We have previously demonstrated that the in-hospital mortality of patients with acute myocardial infarction (AMI) is higher in female than in male patients in our MIYAGI-AMI Registry. In this study, we aimed to elucidate the factors influencing the gender difference.
- Methods and Results:** In our registry study with a total of 3,119 patients with AMI (M:F, 2,219:900) between 2008 and 2010, in-hospital mortality was higher (14.3% vs. 9.2%, $P < 0.01$) and the prevalence of primary percutaneous coronary intervention (PCI) (70.3% vs. 82.2%, $P < 0.01$) was lower in female than in male patients. In 1,199 patients (F/M, 301:898) who admitted within 24 hours after the onset, the time from symptom onset to reperfusion was significantly longer in female than in male patients (median F, 285 vs. M, 235 min, $P < 0.01$). This was mainly due to the longer time from symptom onset to admission in female patients (F, 190 vs. M, 150 min, $P < 0.01$), whereas door-to-balloon time was comparable between both sexes. Importantly, the time difference was most remarkable, when comparing rural female patients (outside of Sendai City) with urban male patients (inside it) (207 vs. 140 min, $P = 0.02$).
- Conclusions:** These results suggest that several factors are involved in the higher in-hospital mortality in female patients, including low prevalence of PCI and the time delay from the symptom onset to admission, especially in the rural area.

背景

宮城心筋梗塞対策協議会(MIYAGI-AMI registry)では1979年以降宮城県内のほぼ全ての急性心筋梗塞(AMI)患者を前向き登録している。この過去30年間にわたる調査の結果、AMIの発症率は近年増加しているが救急車の利用や経皮的冠動脈形成術(PCI)の普及により院内死亡率が減少していること、また男性と比較し女性では院内死亡率が高いこと等を報告した¹⁾。



AMI後の予後に関して性差が認められることは以前から報告されており、女性においてAMI発症からの時間経過が長いことがその一因であるという報告もある。そこで今回我々は、AMI発症後の時間経過を解析し、院内死亡率の性差に関してどのように影響しているか検討した。

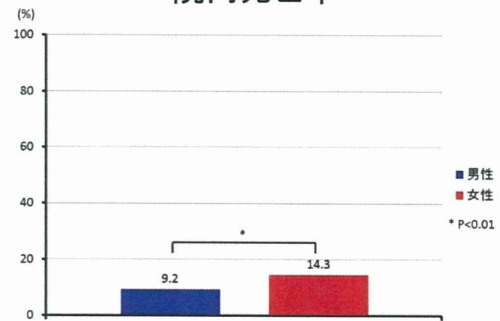
方法

- MIYAGI-AMI registryにて2008年から2010年までに登録された患者3119名(男性2219名、女性900名)を解析した。
- AMI発症からCAG開始までが24時間以内の1199名(男性898名、女性301名)を時間経過の解析の対象とした。

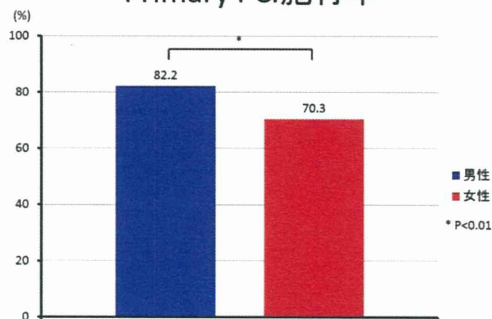
患者背景

	男性	女性	P値
人数	898	301	
年齢	66.5	75.8	<0.01
高血圧症(人数(%))	594 (76.9)	210 (78.4)	0.67
脂質異常症(人数(%))	450 (62.0)	143 (61.9)	1.00
糖尿病(人数(%))	319 (47.1)	100 (45.1)	0.64
喫煙(人数(%))	229 (64.9)	20 (29.9)	<0.01
市内(人数(%))	355 (39.5)	96 (31.9)	<0.05

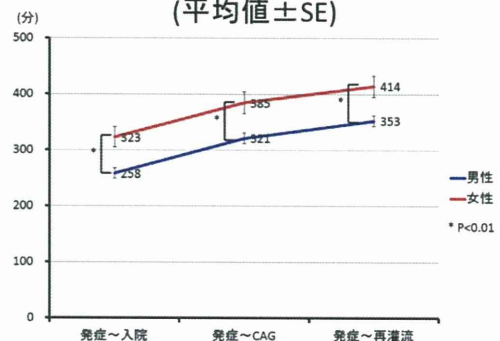
院内死亡率

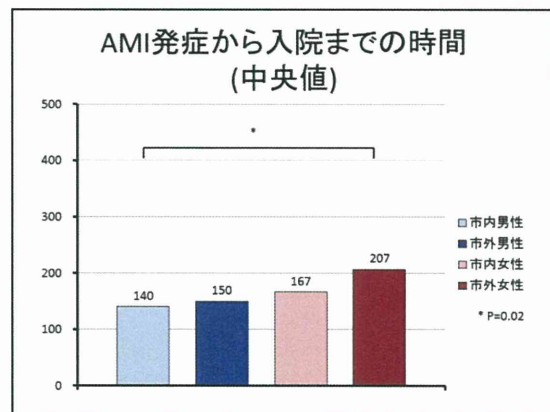
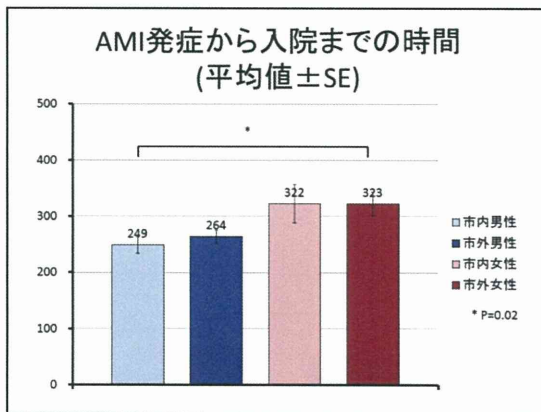
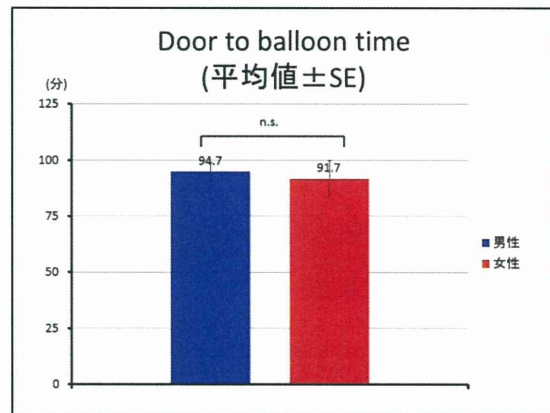
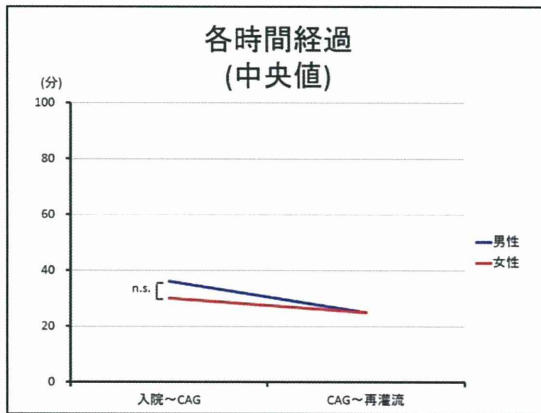
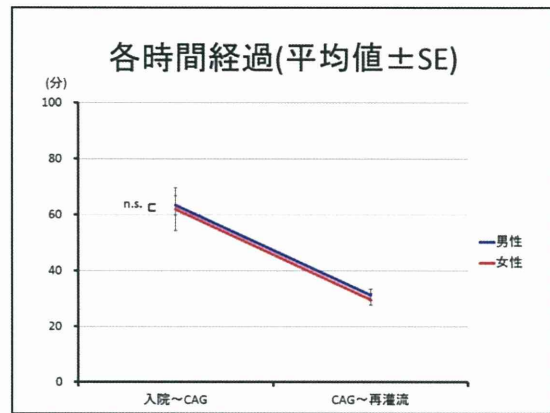
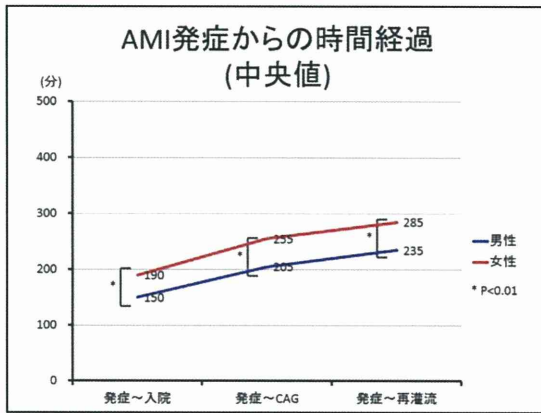


Primary PCI施行率



AMI発症からの時間経過(平均値±SE)





結論

- 男性と比して女性ではPCI施行率が低いことや、AMI発症から来院するまでに長い時間を要していることが、女性におけるAMI後の院内死亡率が高率であることに関与している可能性が考えられた。
- 来院してからの時間経過に性差は認められず、女性(特に郊外部に住む)においてAMI発症から来院までの時間を短縮するための啓蒙活動が必要であると考えられる。

厚生労働科学研究費補助金（循環器疾患・糖尿病等生活習慣病対策総合研究事業）
分担研究報告書

「急性心筋梗塞に対する病院前救護を含めた超急性期診療体制の構築に関する研究」
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研究要旨

急性心筋梗塞症では「発症から120分以内の再灌流のために、救急隊が現場到着後90分以内の冠動脈インターベンション(PCI)施行」が推奨されている。都市部では、係り付け医を介しての受診や病院の選択・交通事情などで時間を要する場合がある一方で、郡部では病院の拠点化・医療圏の拡大により搬送に時間がかかる場合があること、常駐する医療スタッフ数にも制限があることより治療内容やその結果としての救命率に地域差があることが懸念される。本研究では、2005年～2008年の4年間における宮城県内の各救急隊によりウツタイン形式で記録された救急医療活動データを利用し、都市部・郡部における心原性院外心停止患者の救急医療における時間経過の実態を解析した。

A. 研究目的

急性心筋梗塞は院外死を含めるとその致命率は依然として高い重篤な疾患である。心筋梗塞発症から再灌流までの時間が予後の重要な規定因子であり、ガイドライン(Circulation 2004;110:586-636)でも「発症から120分以内の再灌流のために、救急隊が現場到着後90分以内の冠動脈インターベンション(PCI)施行」が推奨されている。しかしながら我が国においては、発症から搬送・再灌流までの時間経過を含めた診療体制に関するデータが不十分であるのが現状である。都市部では、係り付け医を介しての受診や病院の選択・交通事情などで時間を要する場合がある一方で、郡部では病院の拠点化・医療圏の拡大により搬送に時間がかかる場合があること、常駐する医療スタッフ数にも制限があることより治療内容やその結果としての救命率に地域差があることが懸念される。

急性心筋梗塞や致死性不整脈等の結果として発生する心原性院外心停止患者の予後を改善するためには、市民による一次救命処置や医療施設における二次救命処置を含めた包括的な救急活動が求められる。近年自動体外式除細動器(AED)の普及により院外心停止患者の予後が改善したことも報告されており(Kitamura T, et al. N Eng J 2010)、その予後の改善には医療資源への迅速なアクセスが必要と考えられている。宮城県は人口約234万人で、その内全人口の約43%を占める100万政令都市仙台市(都市部)とそれ以外の仙台市外(郡部)とに分けられ、中核都市部と郡部(農漁村部)が混在するモデル地域としての特徴を有する。患者の居住地によって医療資源へのアクセスのしやすさ(病院までの距離、AEDの普及率、各救急隊の活動範囲など)は異なっている可能性があり、この事が心原性院外心停止患者に対する救急医療活動やその予後にどのよ

うに関与しているかに関してあまり多くは知られていない。本研究は、宮城県内の各救急隊から得られたウツタイン形式で記録された救急医療活動データを活用し、心筋梗塞の最重症型である院外心停止例における来院までの救急医療体制に関する実態調査を行い、その問題点を明らかにすることを目的とする。この結果は「急性心筋梗塞患者の予後改善のための高度医療を時間の遅延なくまた地域の別なく効果的に提供できる救急医療システム構築」という厚生労働政策医療に役立つデータとして活用されることが期待される。

B. 研究方法

2005年から2008年の4年間に宮城県内の各救急隊で救急搬送されウツタイン形式のデータが得られた8,650名の院外心停止患者のうち、心原性の院外心停止患者と考えられた5,066名を解析の対象とした。患者を救急隊の所在地により仙台市内(都市部)と仙台市外(郡部)の2群に分け解析を行った。各群において覚知からの時間経過(覚知～現着、覚知～接触、覚知～CPR開始、覚知～病院収容)、バイスタンダーCPRの施行率、初期リズムが心室細動であった頻度、一ヶ月後生存率等を解析した。

(倫理面への配慮) 各救急隊から得られたウツタイン形式データには個人を特定する情報は含まれていないため、倫理面の問題は無いと判断した。

C. 研究結果

2005～2008年の4年間に登録された8,650名の院外心停止症例の内、5,066名(男性2,900名、女性2,166名)の心原性院外心停止症例を解析対象とした。救急隊の所在地により都市部(1,925名)と郡部

(3,141名)の2群に分け、各群間で比較検討した。時間経過における解析では(各データは中央値)、覚知から現場到着までの時間(都市部7 vs. 郡部8分)、覚知から患者接触までの時間(都市部8 vs. 郡部9分)、覚知から心肺蘇生(CPR)開始までの時間(都市部9 vs. 郡部9分)、覚知から病院到着までの時間(都市部31 vs. 郡部31分)に両群間で差異は認められなかった(図1)。バイスタンダーCPRの施行率CPR(都市部27.0 vs. 郡部27.2%, 図2)、初期リズムが心室細動であった頻度(都市部15.1 vs. 郡部13.3%, 図3)共に同等であったものの、1ヶ月生存率は都市部に比し郡部で有意に低率であった(都市部4.3 vs. 郡部2.4%, $P < 0.001$, 図4)。

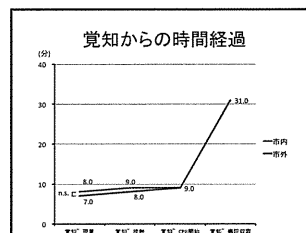


図 1: 覚知からの時間経過

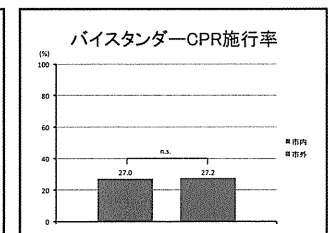


図 2: バイスタンダーCPR 施行率

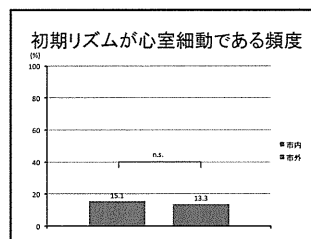


図 3: 初期リズムが心室細動である頻度

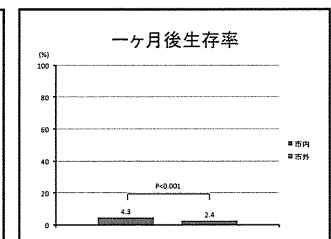


図 4: 一ヶ月後生存率

D. 考察

本研究結果により、宮城県内の心原性院外心停止患者に対する救急医療に関して、

都市部・郡部において覚知からの時間経過には差異は認められないことが明らかになった。このことから、救急隊による救急医療は宮城県内で均質的に行われていることが判明した。またバイスタンダーCPR 施行率や初期リズムが心室細動である頻度も両群間では差異は認められないことから、急性心筋梗塞発症から来院するまでに市民により行われている救急処置も両群間で同等であることが判明した。一ヶ月後生存率が郡部で有意に低いことから、来院後の高度専門医療に地域差があることを示唆する結果と考えられた。

なし

E. 結論

宮城県内では、心原性院外心停止患者に対して居住地に関わらず均質的な救急医療を提供している事、急性心筋梗塞発症から来院するまでに市民により行われている救急処置が両群間で同等であることが判明した。郡部で一ヶ月後生存率が有意に低く、来院後の高度救急医療に関して地域差がある可能性が考えられた。

F. 健康危険情報

総括研究報告書参照

G. 研究発表

1. 論文発表

なし

2. 学会発表

第76回日本循環器学会学術集会一般演題
ポスター発表(2012年3月16日、福岡)

H. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書 籍 名	出版社名	出版地	出版年	ページ
安田 聡、 瀧井 楊、 伊藤健太、 下川宏明	我が国の心筋梗塞コホート 研究－宮城県心筋梗塞対策 協議会	古山 正史	月刊「臨床と研究」	大道学館出版部	福岡	2012	pp.78-82
伊藤健太、 下川宏明	虚血性心疾患 (狭心症・心筋梗塞)	泉 孝英	ガイドライン外来診療	日経メディカル開発	東京	2012	pp.75-87

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Takii T, Yasuda S, et al.	Trends in acute myocardial infarction incidence and mortality over 30 years in Japan: report from the MIYAGI-AMI Registry Study.	Circ J.	74	pp.93-100	2010
Hao K, Yasuda S, Takii T, Ito Y, Takahashi J, Ito K, Nakayama M, Shiba N, Fukumoto Y, Shimokawa H.	Urbanization, life-style changes and incidence and in-hospital mortality from acute myocardial infarction in Japan –Report from the MIYAGI-AMI Registry-	Circ J.	in press	in press	2012
Ito K, Fukumoto Y, Shimokawa H.	Extracorporeal shock wave therapy for ischemic cardiovascular disorders.	Am J Cardiovasc Drugs.	11	pp.295-302	2011

IV. 研究成果の刊行物・別刷



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}

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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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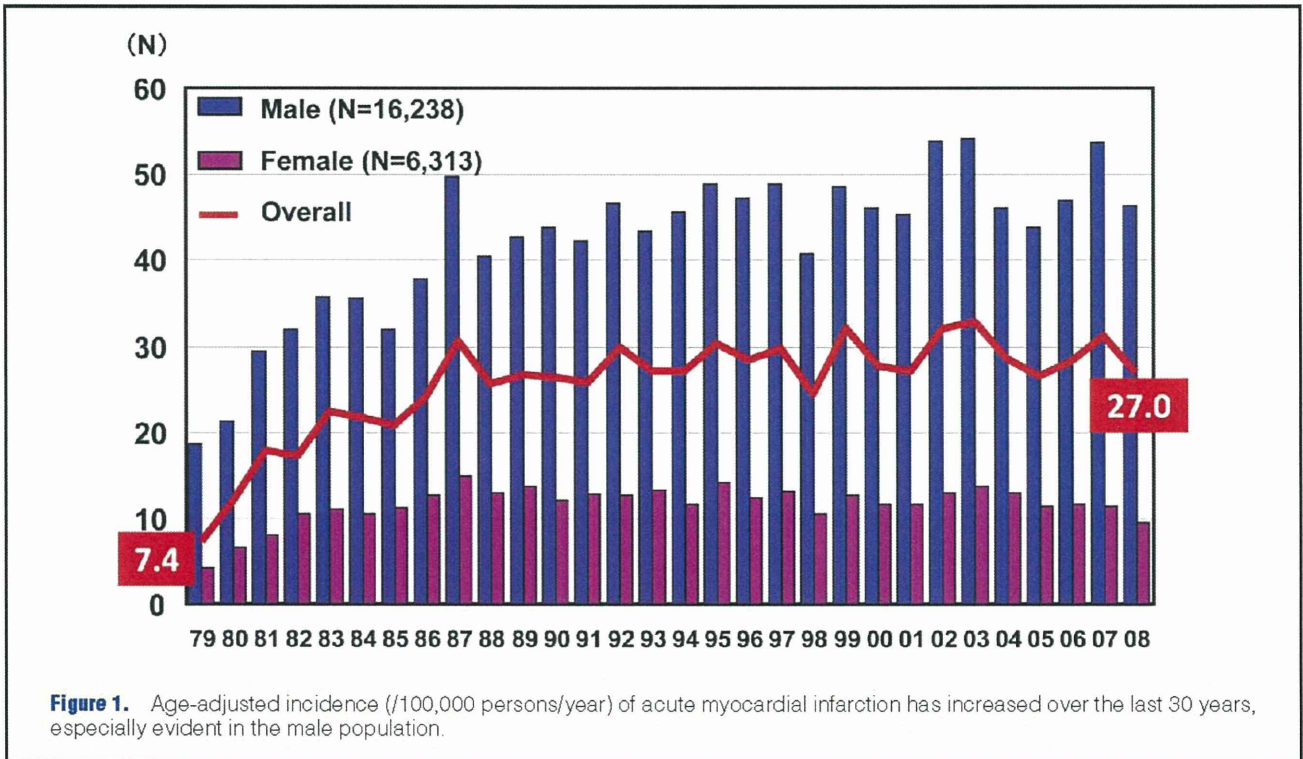


Figure 1. Age-adjusted incidence (/100,000 persons/year) of acute myocardial infarction has increased over the last 30 years, especially evident in the male population.

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 thrombolysis was unsuccessful in terms of symptoms, ECG changes and/or coronary blood flow.

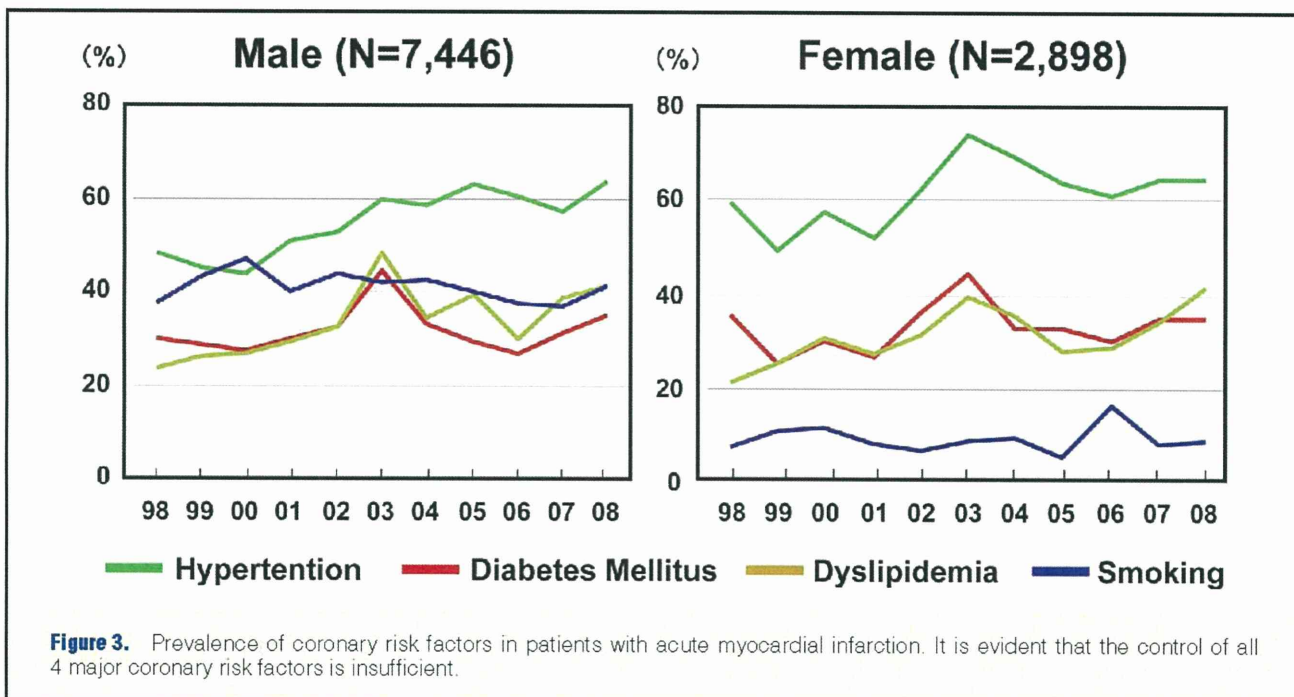
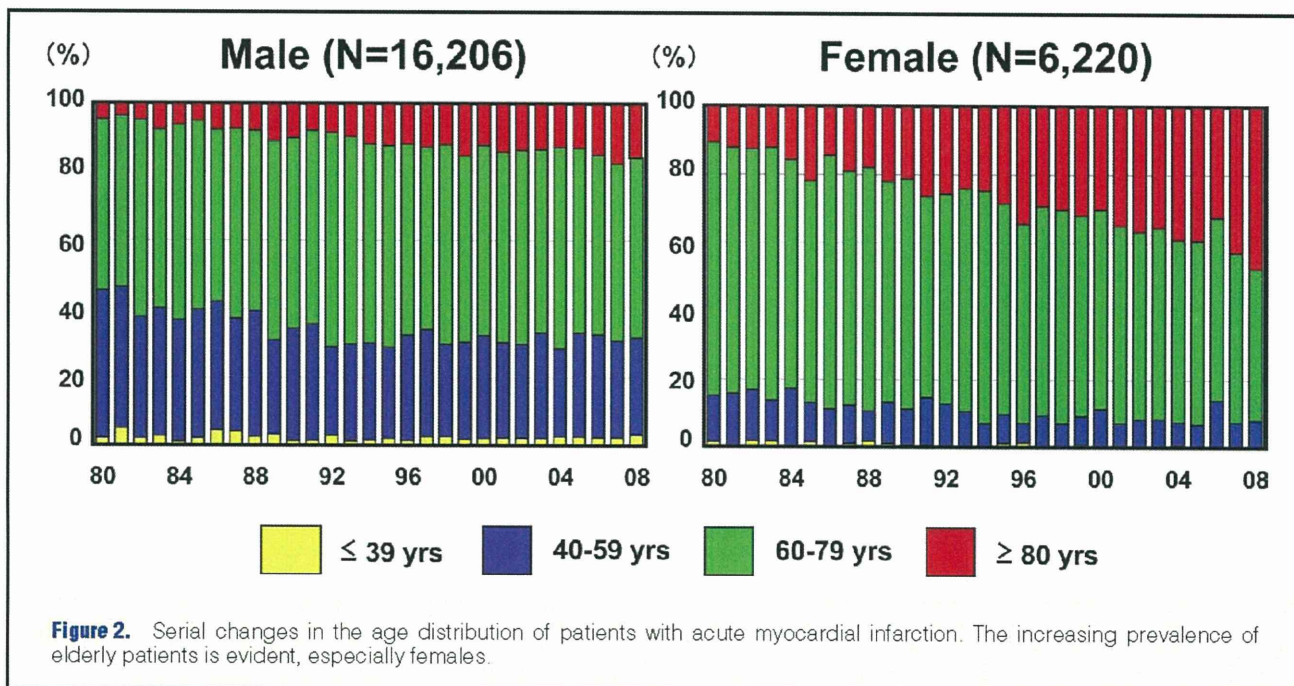
Data Analysis

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 χ^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



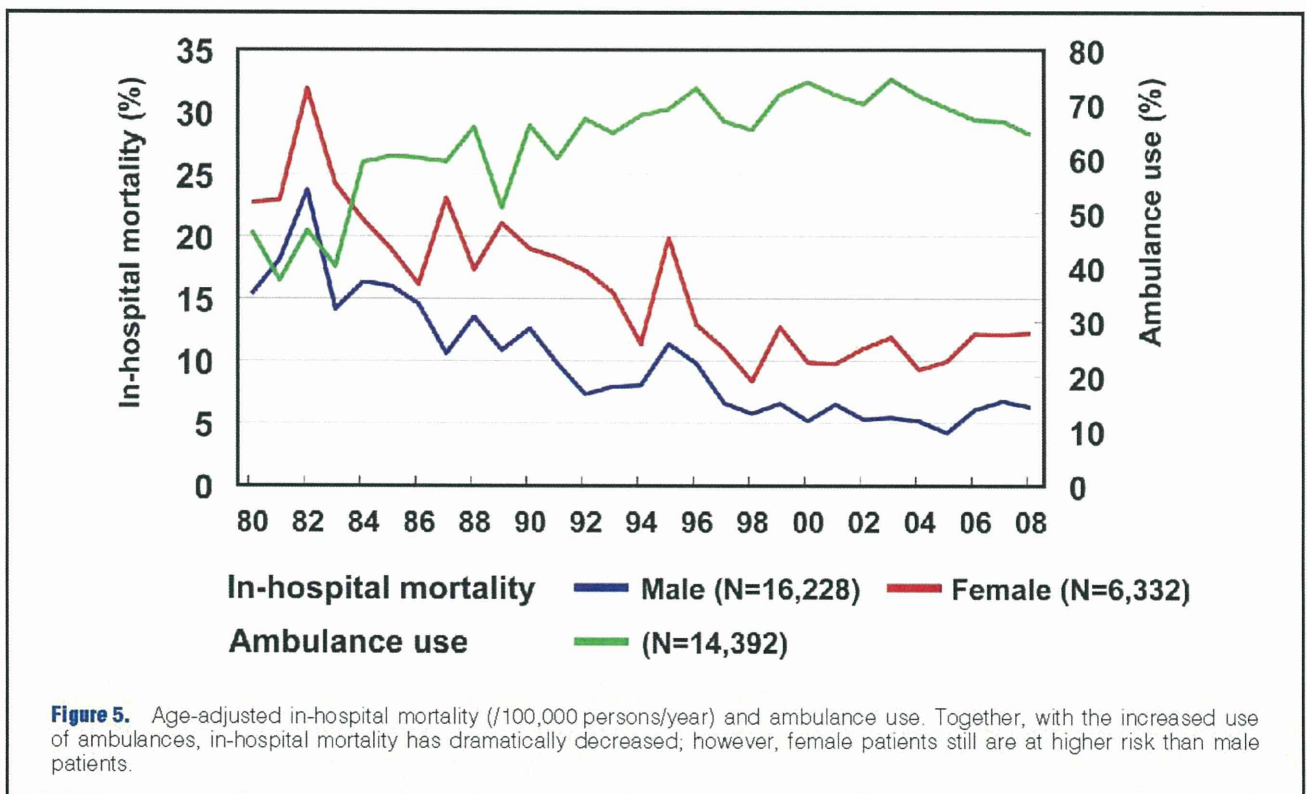
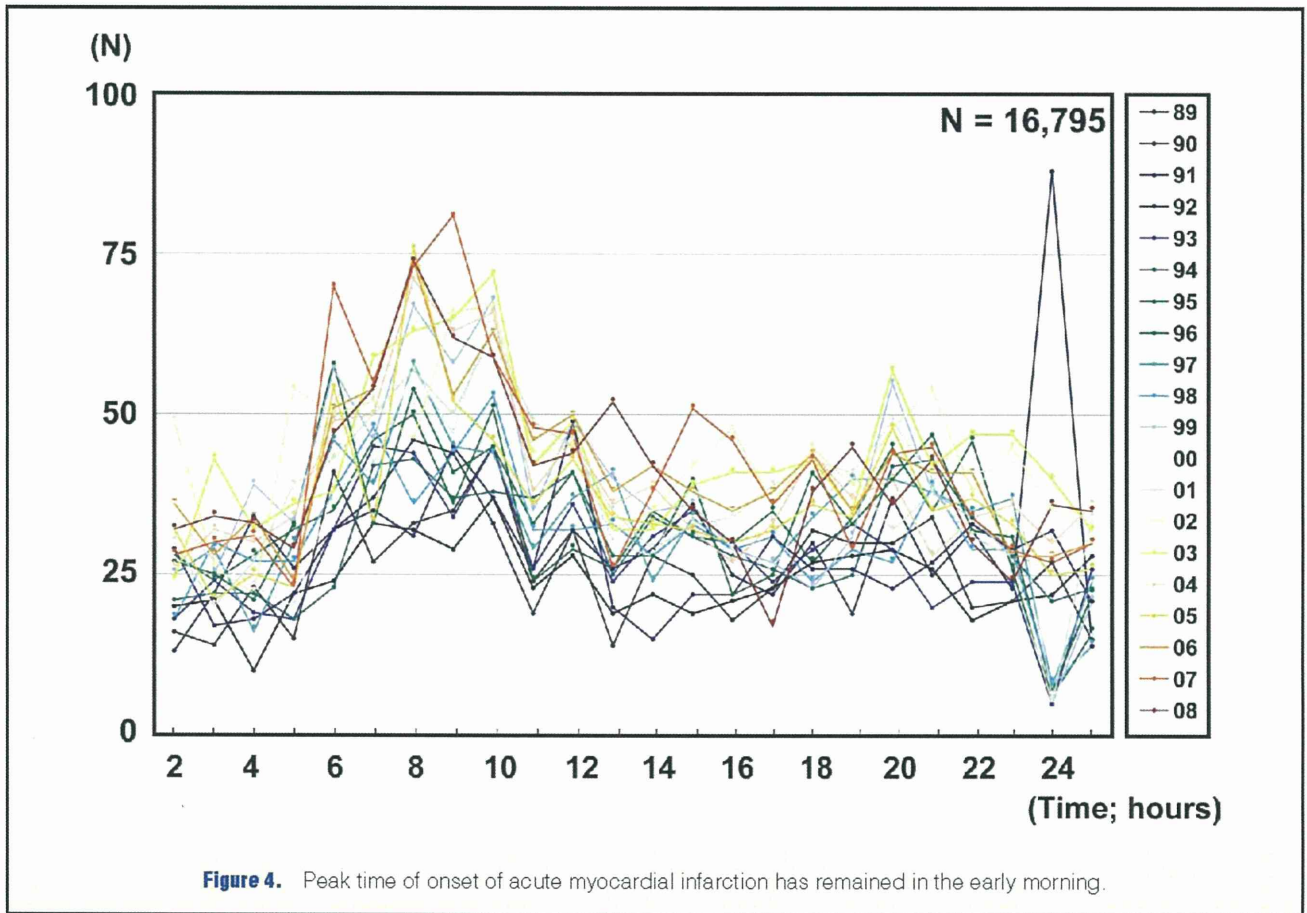
2.3-fold, from 4.2 in 1979 to 9.6 in 2008, but did not reach a statistically significant level ($P=0.15$).

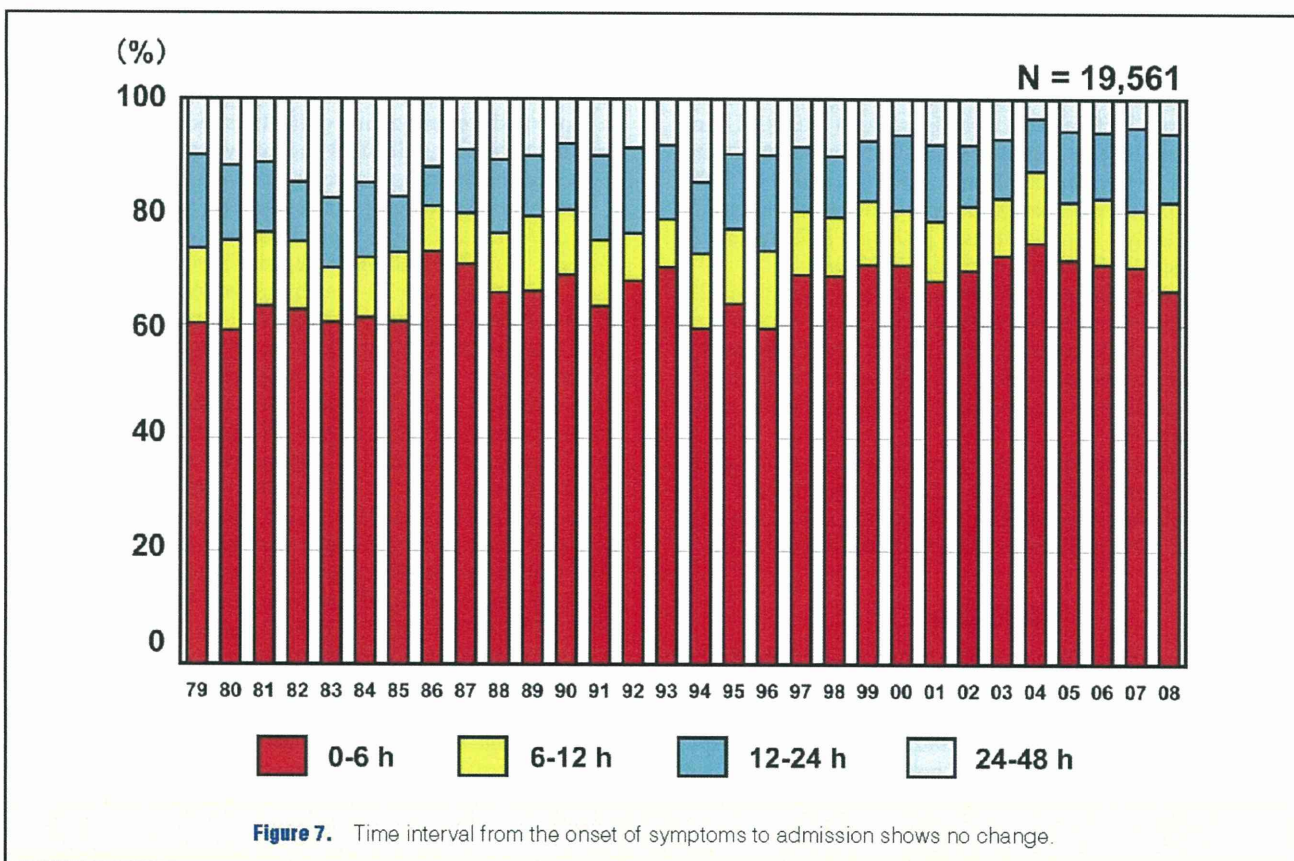
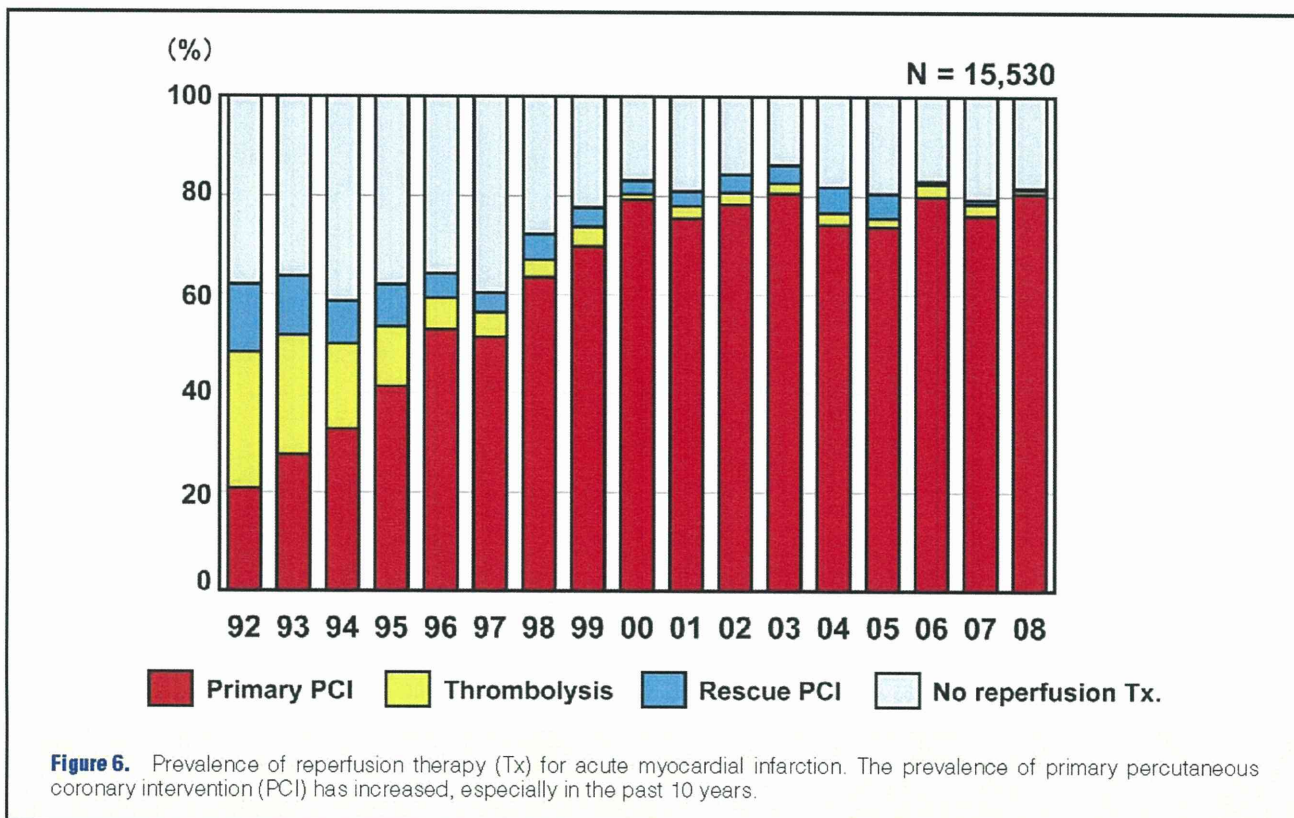
The distribution of age significantly changed with the increased population of elderly patients, especially that of ≥ 80 -year-old patients, in both sexes (both $P<0.001$) (Figure 2). Moreover, the prevalence of hypertension, diabetes mellitus, and dyslipidemia also significantly increased over time in both sexes (all $P<0.01$) (Figure 3). Smoking habit also remained at $\sim 40\%$ in male and $\sim 10\%$ 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

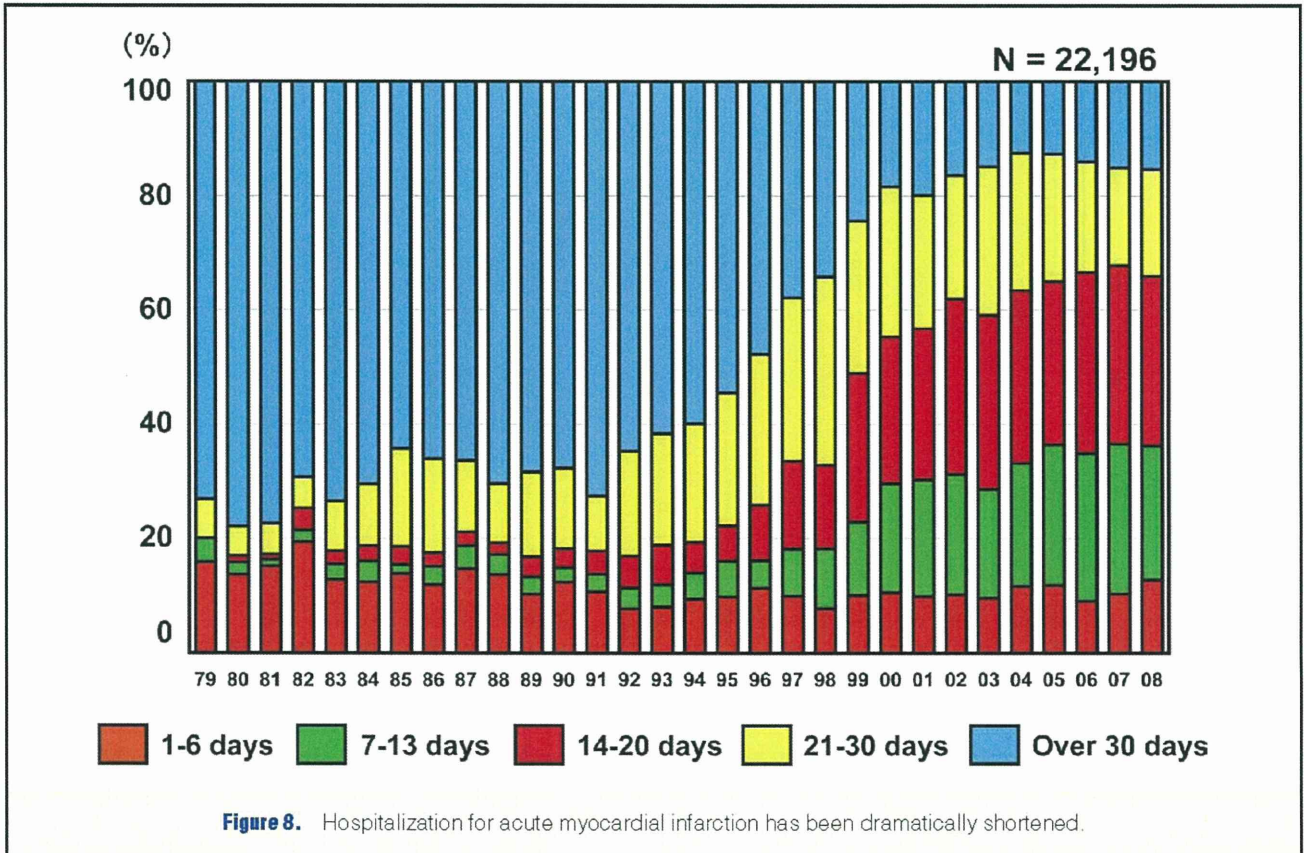
anterior wall in 45%, inferior/posterior wall in 43%, and other in 12%.

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







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 12 h from the onset of AMI to hospitalization, while 60% of patients were hospitalized within 6 h after the onset (Figure 7). This tendency for the majority of AMI patients to be hospitalized within 6 h 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 Japan²⁶ 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 mortality 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 6 h (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.

Acknowledgments

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Appendix 1

List of Participating Hospitals

Fukaya Hospital, Hiroshi Akiho, MD; Higarigaoka Spellman Hospital, Tomofumi Mimata, MD; Ishinomaki Municipal Hospital, Kenjiro Akai, MD; Ishinomaki Red-Cross Hospital, Hiroyasu Sukeyama, 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; NIT EAST Tohoku Hospital, Aki Yamada, MD; Oizumi Memorial Hospital, Yoshiro 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, Taiichiro 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.



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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on behalf of the MIYAGI-AMI Study Investigators

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 cities, 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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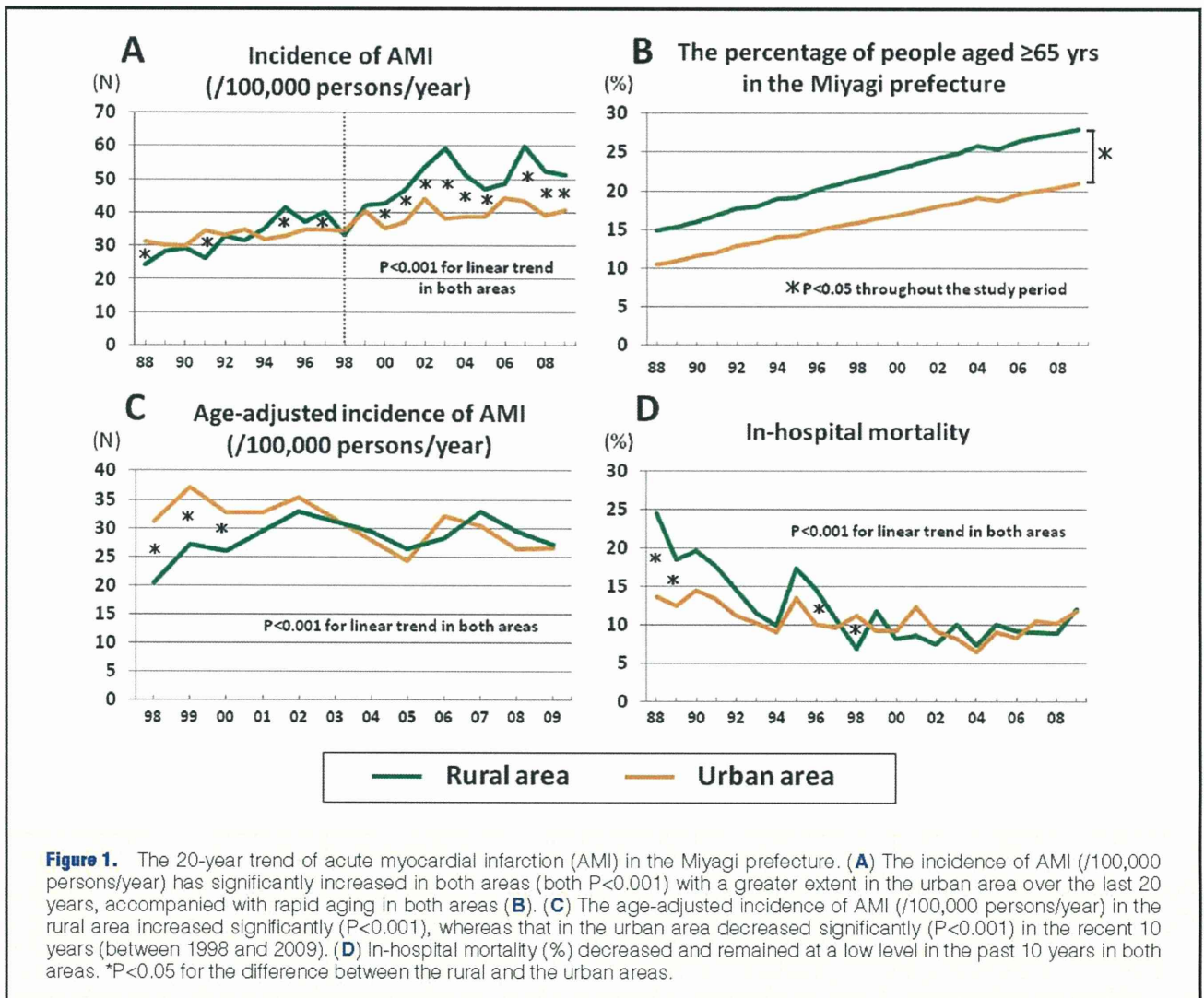


Figure 1. The 20-year trend of acute myocardial infarction (AMI) in the Miyagi prefecture. (A) The incidence of AMI (/100,000 persons/year) has significantly increased in both areas (both $P < 0.001$) with a greater extent in the urban area over the last 20 years, accompanied with rapid aging in both 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, multi-center 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 Board 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-