**Supplemental Appendix**

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**Figure 1.**

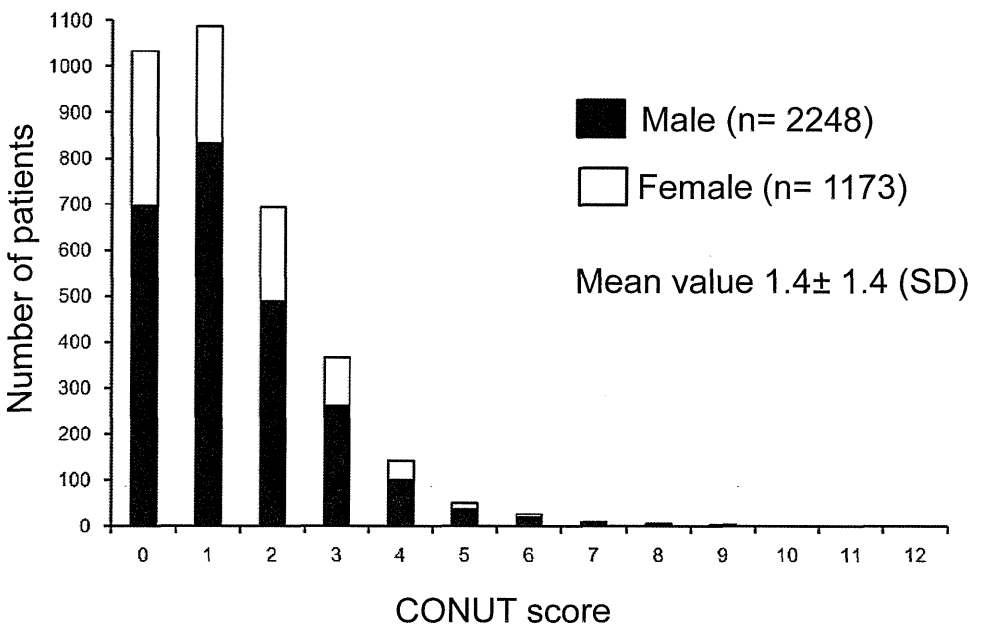

1100
1000
900
800
700
600
500
400
300
200
100
0
Number of patients
0
1
2
3
4
5
6
7
8
9
10
11
12
CONUT score
Male (n= 2248)
Female (n= 1173)
Mean value 1.4± 1.4 (SD)

**Figure 2.**

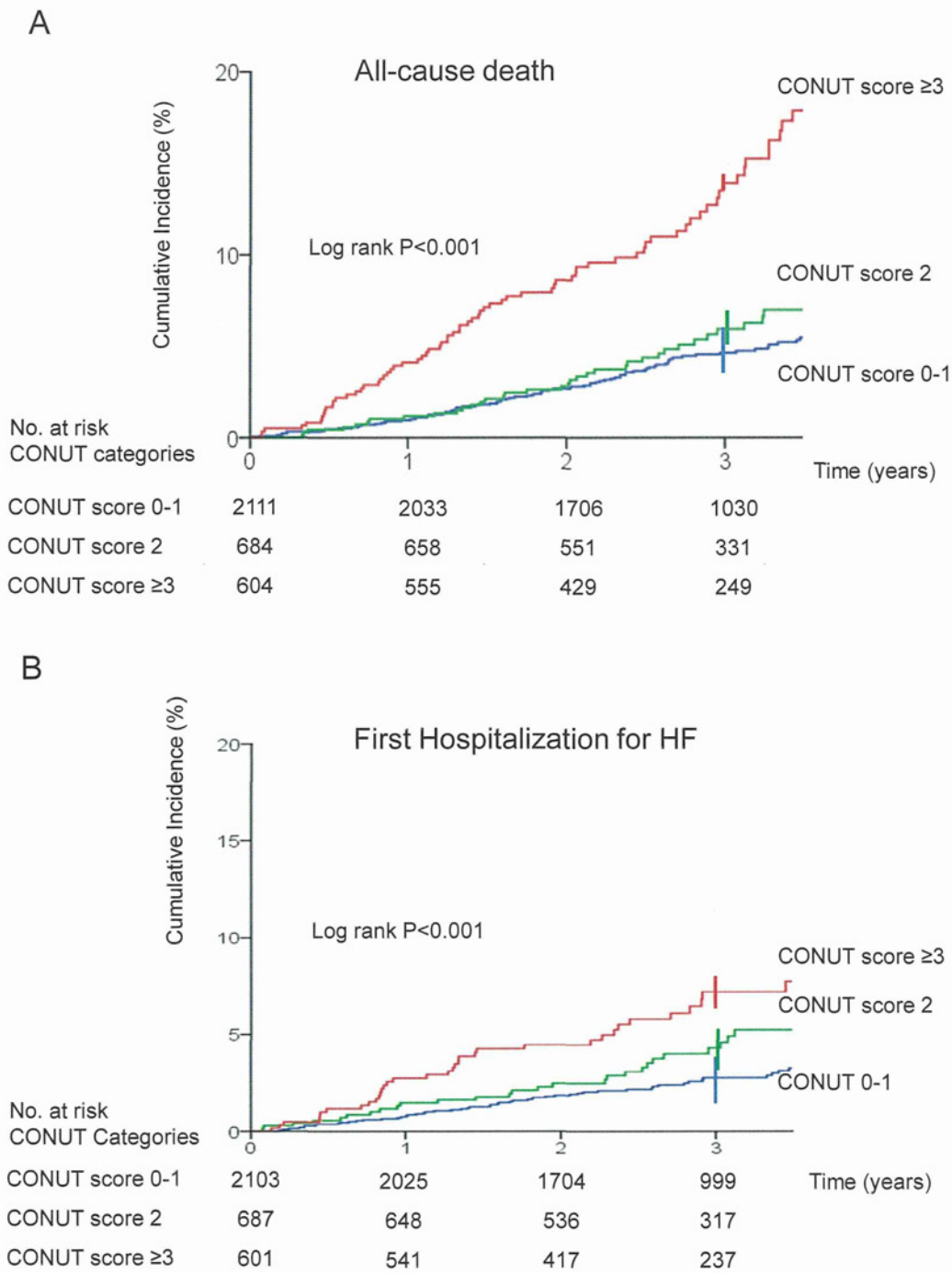
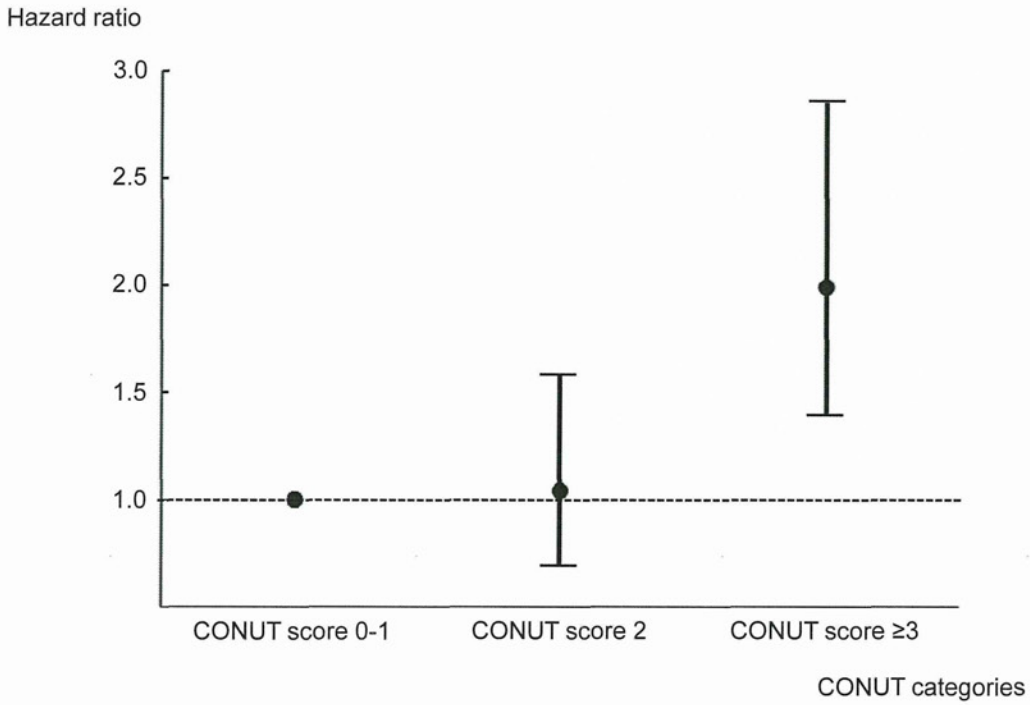

A
All-cause death
Cumulative Incidence (%)
20
10
0
Log rank P<0.001
CONUT score ≥3
CONUT score 2
CONUT score 0-1
No. at risk
CONUT categories
0
1
2
3
Time (years)
CONUT score 0-1 2111 2033 1706 1030
CONUT score 2 684 658 551 331
CONUT score ≥3 604 555 429 249
B
First Hospitalization for HF
Cumulative Incidence (%)
20
15
10
5
0
Log rank P<0.001
CONUT score ≥3
CONUT score 2
CONUT 0-1
No. at risk
CONUT Categories
0
1
2
3
Time (years)
CONUT score 0-1 2103 2025 1704 999
CONUT score 2 687 648 536 317
CONUT score ≥3 601 541 417 237

**Figure 3.**


Hazard ratio
3.0
2.5
2.0
1.5
1.0
CONUT score 0-1
CONUT score 2
CONUT score ≥3
CONUT categories

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# Urinary albumin excretion in heart failure with preserved ejection fraction: an interim analysis of the CHART 2 study

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**Aims** Heart failure with preserved ejection fraction (HFpEF) is characterized by multiple co-morbidities, including chronic kidney disease that is one of the prognostic risks for these patients. This study was performed to evaluate the value of determination of albuminuria using a urine dipstick test (UDT), combined with estimated glomerular filtration rate (eGFR), for predicition of mortality in HFpEF.

**Methods and results** We enrolled 2465 consecutive patients with overt HF with EF ≥50% in our Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) study (NCT00418041). We defined trace or more UDT as positive. We divided the patients into the following four groups based on eGFR and UDT; group 1 (G1) (eGFR ≥60, negative UDT), G2 (eGFR ≥60, positive UDT), G3 (eGFR <60, negative UDT), and G4 (eGFR <60, positive UDT). In total, 29.5% of the HFpEF patients had a positive UDT. HFpEF patients with a positive UDT were characterized by higher brain natriuretic peptide levels and frequent histories of hypertension or diabetes. During a mean follow-up of 2.5 years, HFpEF patients with a positive UDT showed higher mortality in each stratum of eGFR levels. A multivariable adjusted Cox model showed that when compared with G1 (reference), the hazard ratio of all-cause death for G2, G3, and G4 was 2.44 (95% confidence interval 1.47–4.05, $P=0.001$), 1.43 (0.92–2.23, $P=0.12$), and 2.71 (1.72–4.27, $P<0.001$), respectively. Furthermore, the prognostic value of a positive UDT was robust for both cardiovascular and non-cardiovascular deaths.

**Conclusions** These results indicate that measurement of albuminuria in addition to eGFR is useful for appropriate risk stratification in HFpEF patients.

**Keywords** Heart failure with preserved ejection fraction • Albuminuria • Urine dipstick test • Estimated glomerular filtration rate

## Introduction

A meta-analysis reported that patients with heart failure with preserved ejection fraction (HFpEF) might have a lower risk of death compared with those with heart failure with reduced ejection fraction (HFrEF); however, the mortality in HFpEF is still high.[1] Furthermore, there are no authorized treatment guidelines for HFpEF due to its pathophysiological heterogeneity.[2,3] Recent guidelines recommend the inclusion of objective evidence of diastolic dysfunction in diagnosing HFpEF;[4] however, diagnostic methods for diastolic dysfunction using echocardiography are clinically difficult. Therefore, simple diagnosing tools are needed for appropriate risk stratification in HFpEF patients.

HFpEF is typically characterized by multiple co-morbidities.[5] The co-existence of HF and chronic kidney disease (CKD) carries an extremely poor prognosis.[6] Furthermore, the prognosis of

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HFpEF patients may be more influenced by the existence of CKD compared with for those with HFrEF.[5,7] Thus, the effective treatment of CKD may be more essential in HFpEF than in HFrEF.

Albuminuria is a well-known independent risk factor for mortality in the general population,[8] and in those with hypertension[9] and diabetes,[10] reflecting glomerular injury, systemic inflammation, and activation of the renin–angiotensin system (RAS). Therefore, the use of the urine albumin to creatinine ratio (UACR) is currently emphasized to evaluate the severity of CKD.[11] However, the severity of CKD is usually defined by a reduced estimated glomerular filtration rate (eGFR). In HF patients, it has been reported that the prevalence of patients with albuminuria (≥30 mg/g) was ~30%.[12,13] Furthermore, HF patients with albuminuria (≥30 mg/g) had poorer prognosis.[13–16] However, most of the HF patients included in these studies had HFrEF.

The aim of this study was to evaluate the prognostic value of albuminuria using a urine dipstick test (UDT) combined with eGFR in HFpEF patients in our Chronic Heart failure Analysis and Registry in the Tohoku district 2 (CHART-2) study.

# Methods

## Population and inclusion criteria

Details of the design, purpose, and basic characteristics of the CHART-2 study have been described previously (NCT00418041).[17] Briefly, eligible patients were aged ≥20 years with significant coronary artery disease or in stage B, C, or D defined by the Guidelines for the Diagnosis and Management of Heart Failure in Adults.[18] Patients were classified as having HF by experienced cardiologists using the criteria of the Framingham Heart Study.[19] We excluded patients consuming alcohol or drugs, using alternative therapies, and undergoing chemotherapy. The present study was approved by the local ethics committee in each participating hospital. Eligible patients were consecutively recruited after written informed consent was obtained. The CHART-2 study was started in October 2006 and the entry period was successfully closed in March 2010 with 10 219 patients registered from the 24 participating hospitals. All data and events will be surveyed at least once a year until March 2013.

In the CHART-2 study, left ventricular ejection fraction (LVEF) was measured by echocardiography at the time of enrolment. In the present study, patients with LVEF ≥50% were classified as having HFpEF, whereas those with LVEF <50% were classified as having HFrEF.[1] The study flow diagram is shown in *Figure 1*. In the present study, we excluded patients in stage B and those with severe valvular heart disease (VHD), congenital heart disease, pulmonary arterial hypertension, pericardial disease, or on haemodialysis (*Figure 1*). Severe VHD was defined by the Guidelines for the management of patients with VHD.[20] We also excluded patients who did not have UDT measurement. Therefore, 2465 HFpEF patients were finally included in the present study (*Figure 1*).

## Measurements of albuminuria

Albuminuria in the study population was qualitatively evaluated using UDT. UDT was performed at the outpatient department of each

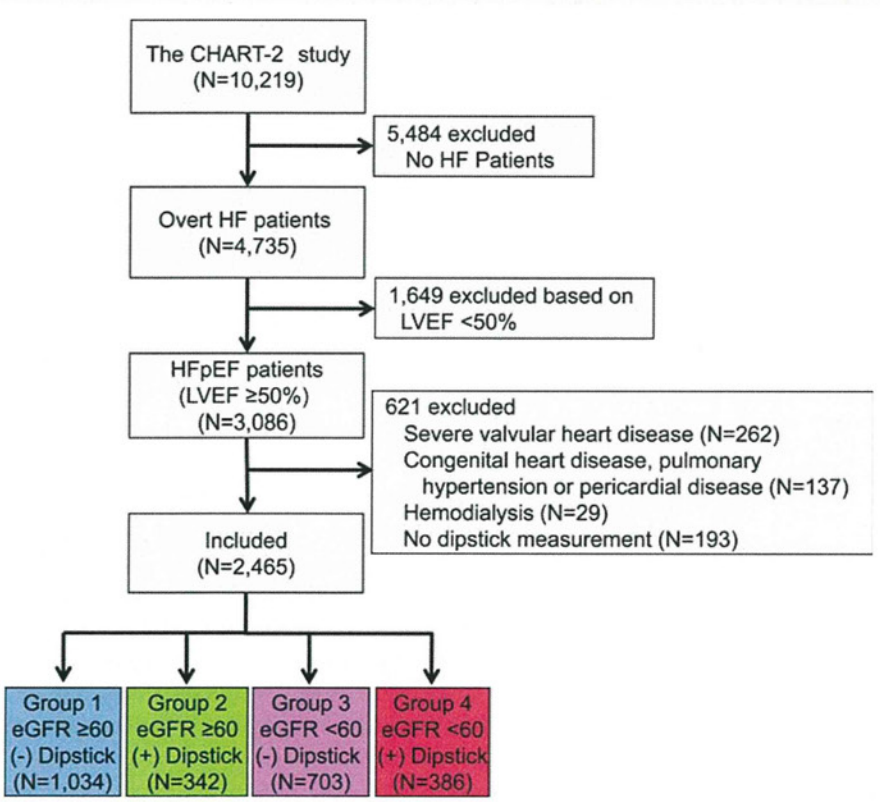


**Figure 1** Study flow diagram. eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction.

institute but not in a central laboratory. In those patients who agreed to participate in this study during their admission for HF, UDT was performed at discharge. Eight kinds of UDTs marketed by five medical corporations were used in the participating hospitals. The names of the corporations and percentage of patients were as follows: ARKLEY, Inc., Kyoto, Japan (39.4%), Eiken Chemical Co. Ltd, Tokyo, Japan (26.2%), Siemens AG, Munich, Germany (21.9%), SYSMEX Corporation, Kobe, Japan (8.6%), Roche Diagnostics, Basel, Switzerland (3.6%), and unknown, 0.4%. All UDTs were calibrated to indicate 1+ qualitatively at a urine protein concentration of ≥0.3 g/L. The dipsticks of the four corporations (ARKELEY, Siemens AG, Eiken Chemical, and SYSMEX) were calibrated to indicate trace proteinuria at ≥0.15 g/L, ≥0.1 g/L, ≥0.15 g/L, and ≥0.1 g/L, respectively.

It has been reported that trace proteinuria evaluated by UDT could be a useful indicator of albuminuria (≥30 mg/g) in subjects at high risk of cardiovascular disease.[21] Furthermore, a recent study reported that trace UDT could identify urine albuminuria (≥30 mg/g) with high specificity and negative predictive value.[22] Thus, in the present study, we defined a positive UDT for proteinuria as trace or more and the remainder as a negative UDT.

### Renal function

Estimated GFR (mL/min/1.73 $m^2$) was calculated using the modified Modification of Diet in Renal Disease equation with the Japanese coefficient[23] at the time of enrolment. We defined reduced eGFR as <60 mL/min/1.73 $m^2$ according to the guideline.[11]

### Follow-up survey and study outcomes

We conducted the first survey of survival in August 2010, and the mean follow-up period of the study population was 2.5 ± 1.0 [standard deviation (SD)] years. The outcomes of this study included all-cause death, cardiovascular death (CVD), and non-cardiovascular death (NCVD). CVD was defined as deaths due to myocardial infarction, HF, cerebrovascular disease, aortic aneurysm rupture, and sudden death. Deaths other than CVD were classified as NCVD. The mode of death was determined by the attending physician and was confirmed by one independent physician who was a member of the Tohoku Heart Failure Association.[17]

### Statistical analysis

To evaluate the usefulness of UDT, we divided the 2465 patients into the following four groups: group 1 (G1) with eGFR ≥60 with a negative UDT ($n$=1043), G2 with eGFR ≥60 with a positive UDT ($n$=342), G3 with eGFR <60 with a negative UDT ($n$=703), and G4 with eGFR <60 with a positive UDT ($n$=386) (*Figure 1*).

Comparisons of data among the four groups were performed by analysis of variance (ANOVA), with reduced eGFR and a positive UDT as factors, including a test for interaction. Continuous data were described as mean ± SD. Kaplan–Meier curves were plotted to evaluate the association between the results of UDT and all-cause death, CVD, and NCVD.

We also constructed the following four Cox proportional hazard regression models: (a) unadjusted; (b) age- and sex-adjusted; (c) adjusted by the clinical status and co-morbidities in addition to model (b); and (d) fully adjusted including medical treatments. In model (c), we included the following covariates that potentially influence the outcomes; age, sex, New York Heart Association class, history of admission for HF and malignant tumour, body mass index, systolic blood pressure,[24] heart rate,[25] serum sodium, serum potassium, co-morbidities[24] (anaemia defined as haemoglobin <12 g/dL in females and <13 g/dL in males, diabetes mellitus, hyperuricaemia, atrial fibrillation, history of coronary artery disease, and cerebrovascular disease), and brands of UDT. In model (d), we included treatment (beta<δελ>β</δελ>-blockers, RAS inhibitors, calcium channel blockers, loop diuretics, and aldosterone antagonists) in addition to model (c). Finally, to determine the prognostic value of UDT in addition to eGFR, we constructed Cox proportional hazard models in patients with eGFR ≥60 or <60 separately including all covariates in model (d) plus eGFR level.

All statistical analyses were performed using SPSS Statistics 19.0 (SPSS Inc., Chicago, IL, USA) and statistical significance was defined as a two-sided $P$-value <0.05.

## Results

### Baseline characteristics (*Table 1*)

Mean age was 69.6 ± 11.7 years and male patients accounted for 68.2% of the study population. Coronary artery disease was observed in 52.1% and the mean LVEF and eGFR were 65.3 ± 9.0% and 62.4 ± 24.3 mL/min/1.73 $m^2$, respectively. The prevalence of patients with eGFR <60 was 44.1% ($n$=1089). The prevalence of patients with a positive UDT was 29.5% ($n$ = 728). Furthermore, the prevalence of patients with a positive UDT and with eGFR <60 was higher (35.4%, $n$ = 386) than that of patients with a positive UDT and with eGFR ≥60 (24.9%, $n$ = 342). Among the positive dipsticks, the prevalence of trace proteinuria was the highest. Male and older patients had higher prevalence of positive UDT. Furthermore, the patients with eGFR <60 had more severe positive dipsticks compared with those with eGFR ≥60.

The patients with eGFR <60 (G3 and G4) were characterized by older age and higher prevalence of HF admission. Furthermore, they had a lower haemoglobin level and were more likely to be taking furosemide, an angiotensin II receptor blocker, and a calcium channel blocker. The G1 and G3 patients had a negative UDT. The patients in G1 who had an eGFR ≥60 were characterized by younger age and had the lowest brain natriuretic peptide (BNP) level compared with other groups. The G3 patients who had eGFR <60 were characterized by more females compared with other groups. There were no differences in the prevalence of past history of coronary artery disease, atrial fibrillation, body mass index, LVEF, or use of beta-blockers among the groups. However, some baseline characteristics of patients with a positive UDT were different from those with a negative UDT. Regardless of eGFR decline, HFpEF patients with a positive UDT (G2 and G4) were characterized by higher prevalence of diabetes mellitus, higher systolic blood pressure, and elevated heart rate compared with those with a negative UDT. Furthermore, those with a positive UDT had a lower haemoglobin level, higher blood urea nitrogen level, lower eGFR level, and higher BNP level with interaction.

### Impact of a positive urine dipstick test for all-cause death

During the mean follow-up period of 2.5 ± 1.0 years, 213 patients (8.6%) died. *Figure 2A* shows Kaplan–Meier survival curves for all-cause death. Groups with a positive UDT (G2 and G4) had poorer prognosis than those with a negative UDT (G1 and G3) within each stratum of eGFR (both $P$<0.001). Importantly, patients with

**Table 1 Baseline characteristics of the study patients**

| | Group 1 ($n=1034$) | Group 2 ($n=342$) | Group 3 ($n=703$) | Group 4 ($n=386$) | *P*-value among the four groups | ANOVA | | |
|---|---|---|---|---|---|---|---|---|
| **Reduced eGFR** | – | – | + | + | | | | |
| **Urine dipstick test** | **Negative** | **Positive** | **Negative** | **Positive** | | **Reduced eGFR** | **Positive UDT** | **Interaction** |
| Age (years) | 66.2 ± 11.8 | 67.3 ± 12.4 | 73.9 ± 9.5 | 73.1 ± 10.8 | <0.001 | <0.001 | 0.001 | 0.98 |
| Male (%) | 69.4 | 76.3 | 62.2 | 68.9 | <0.001 | <0.001 | 0.82 | 0.07 |
| History of admission for HF (%) | 38.8 | 48.4 | 53.1 | 56.1 | <0.001 | 0.86 | 0.42 | 0.06 |
| History of malignant tumour (%) | 9.5 | 12.0 | 13.1 | 13.2 | 0.10 | | | |
| Co-morbidities (%) | | | | | | | | |
| Hypertension | 70.8 | 75.6 | 76.4 | 85.1 | <0.001 | 0.003 | <0.001 | 0.62 |
| Diabetes | 22.0 | 29.2 | 21.6 | 33.2 | <0.001 | 0.35 | <0.001 | 0.62 |
| Hyperuricaemia | 26.0 | 26.6 | 55.0 | 60.1 | <0.001 | <0.001 | 0.17 | 0.28 |
| Atrial fibrillation | 27.8 | 33.0 | 35.2 | 31.7 | 0.05 | | | |
| Coronary artery disease | 52.2 | 48.5 | 51.1 | 56.7 | 0.15 | | | |
| Cerebrovascular disease | 12.2 | 16.7 | 19.8 | 21.5 | <0.001 | <0.001 | 0.06 | 0.40 |
| Clinical status | | | | | | | | |
| NYHA class III and IV (%) | 6.3 | 5.6 | 12.1 | 11.5 | <0.001 | <0.001 | 0.06 | 0.40 |
| Body mass index (kg/m$^2$) | 23.9 ± 4.5 | 23.9 ± 5.6 | 23.7 ± 4.7 | 23.7 ± 4.4 | 0.87 | | | |
| Systolic blood pressure (mmHg) | 127 ± 17.1 | 132 ± 18.9 | 128 ± 19.2 | 133 ± 20.1 | <0.001 | 0.24 | <0.001 | 0.38 |
| Diastolic blood pressure (mmHg) | 74.1 ± 11.1 | 75.1 ± 12.6 | 71.7 ± 12.3 | 72.5 ± 12.1 | <0.001 | <0.001 | 0.08 | 0.82 |
| Heart rate (b.p.m.) | 70.9 ± 13.9 | 73.6 ± 15.8 | 70.7 ± 13.8 | 72.5 ± 12.1 | 0.003 | 0.45 | <0.001 | 0.63 |
| Measurement | | | | | | | | |
| LVEF (%) | 65.2 ± 9.0 | 65.0 ± 9.4 | 65.7 ± 9.1 | 64.8 ± 8.5 | 0.40 | | | |
| LVDd (mm) | 48.8 ± 6.9 | 49.0 ± 7.3 | 48.7 ± 7.5 | 49.1 ± 7.4 | 0.74 | | | |
| Haemoglobin (g/dL) | 13.7 ± 1.7 | 13.8 ± 2.4 | 12.7 ± 2.0 | 12.2 ± 2.1 | <0.001 | <0.001 | 0.002 | 0.001 |
| Blood urea nitrogen (mg/dL) | 15.3 ± 4.2 | 15.5 ± 4.1 | 22.3 ± 8.8 | 26.2 ± 12.0 | <0.001 | <0.001 | <0.001 | <0.001 |
| Serum sodium (mEq/L) | 141 ± 2.6 | 141 ± 2.9 | 141 ± 2.8 | 141 ± 3.2 | 0.40 | | | |
| Serum potassium (mEq/L) | 4.3 ± 0.4 | 4.2 ± 0.4 | 4.5 ± 0.5 | 4.4 ± 0.5 | <0.001 | <0.001 | 0.005 | 0.38 |
| GFR (mL/min/1.73 m$^2$) | 76.5 ± 29.6 | 77.3 ± 15.7 | 45.6 ± 11.0 | 40.5 ± 12.9 | <0.001 | <0.001 | 0.002 | <0.001 |
| Brain natriuretic peptide (pg/mL) | 95 ± 118 | 135 ± 162 | 160 ± 177 | 242 ± 467 | <0.001 | <0.001 | <0.001 | 0.047 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Medications | | | | | | | | |
| ACE inhibitor (%) | 40.9 | 50.3 | 43.5 | 39.4 | 0.01 | 0.06 | 0.23 | 0.002 |
| ARB (%) | 30.7 | 27.2 | 37.4 | 40.9 | <0.001 | <0.001 | 0.96 | 0.09 |
| Beta-blocker (%) | 43.0 | 49.7 | 44.4 | 44.8 | 0.20 | | | |
| Calcium channel blocker (%) | 41.8 | 48.0 | 48.4 | 59.3 | 0.03 | <0.001 | <0.001 | 0.28 |
| Loop diuretics (%) | 32.8 | 34.8 | 52.3 | 52.8 | <0.001 | <0.001 | 0.56 | 0.73 |
| Furosemide dose (mg) | 6.8 ± 13.7 | 8.7 ± 17.0 | 12.6 ± 19.2 | 13.4 ± 19.1 | <0.001 | <0.001 | 0.08 | 0.51 |
| Aldosterone inhibitor (%) | 14.1 | 16.1 | 23.8 | 17.4 | <0.001 | 0.001 | 0.19 | 0.01 |
| Statin (%) | 40.1 | 35.7 | 41.8 | 43.3 | 0.17 | | | |

Analysis of variance (ANOVA) with reduced eGFR and positive urine dipstick test (UDT) as factors, including a test for interaction, was used to identify variables that were associated with reduced eGFR and/or positive urine dipstick test. Numerical data are shown as mean ± standard deviation.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate; HF, heart failure; NYHA, New York Heart Association; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

a positive UDT and eGFR ≥60 (G2) showed significantly poorer prognosis compared with those with a negative UDT and eGFR ≥60 (G1).

*Table 2* shows the results of multivariable Cox proportional hazard regression analysis for all-cause death (the upper portion). In the unadjusted model (a), as compared with G1 (reference), G2, G3, and G4 showed 202, 239, and 500% increases in the risk for all-cause death, respectively (all $P<0.001$). In model (c), as compared with G1, the hazard ratios (HRs) (95% confidence intervals) for all-cause death of G2, G3, and G4 were 2.60 (1.59–4.24), 1.47 (0.94–2.27), and 2.63 (1.67–4.13), respectively. Importantly, the significance of HRs for all-cause death in G2 and G4 remained robust after the adjustment by HF treatments in model (d).

## Impact of a positive urine dipstick test for cardiovascular and non-cardiovascular death

Of the 213 deaths noted, 86 (40.4%) were due to a cardiovascular cause. *Figure 2B* shows Kaplan–Meier survival curves for CVD. G2 showed significantly higher cardiovascular mortality compared with G1 ($P<0.001$). However, there was no significant difference in CVD between G3 and G4. *Table 2* shows the results of multivariable Cox proportional hazard regression analysis for CVD (the middle portion). In the fully adjusted model (d), as compared with G1 (reference), the HRs (95% CI) for CVD of G2, G3, and G4 were 3.58 (1.50–8.58), 2.34 (1.10–4.98), and 3.29 (1.48–7.31), respectively. Importantly, the significance of HRs for CVD in G2 and G4 remained robust in models (b), (c), and (d).

Non-cardiovascular death was observed in 127 patients during the study period. *Figure 2C* shows Kaplan–Meier survival curves for NCVD. Groups with a positive UDT had significantly more NCVDs than those with a negative UDT within each stratum of GFR (both $P<0.001$). *Table 2* shows the results of multivariable Cox proportional hazard regression analysis for NCVD (the lower portion). In model (a), as compared with G1 (reference), the HRs (95% CI) for NCVD of G2, G3, and G4 were 2.75 (1.52–4.98), 2.41 (1.45–4.01), and 5.37 (3.26–8.83), respectively. However, in models (b), (c), and (d), the HR for NCVD in G3 was not significantly higher compared with those in G1 (*Table 2*). Again, the significance of HRs for NCVD in G2 and G4 remained robust in models (b), (c), and (d).

## Prognostic importance of urine dipstick test in addition to estimated glomerular filtration rate

About one-third of HFpEF patients in the present study had a positive UDT. *Figure 3* shows the results of Cox proportional hazard regression analysis for eGFR ≥60 or <60 adjusted by the covariates including eGFR. In HFpEF patients with eGFR ≥60, as compared with G1, G2 showed a 227, 293, and 216% increase in the risk for all-cause death, CVD, and NCVD, respectively (all $P<0.001$). In HFpEF patients with eGFR <60, as compared with G3, G4 showed a 174% and 212% increase in the risk for all-cause mortality and NCVD, respectively, whereas there was no significant difference for CVD.

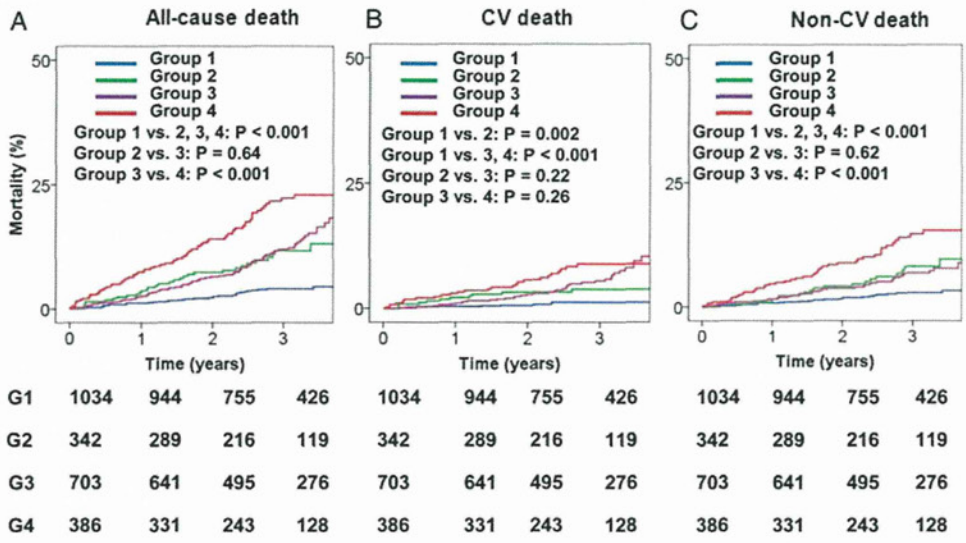


**Figure 2** Kaplan–Meier survival curves for all-cause death (*A*), cardiovascular (CV) death (*B*), and non-CV death (*C*). The four groups were categorized based on the estmated glomerular filtration rate (eGFR) and urine dipstick test (UDT): group 1 (G1) (eGFR ≥60, negative UDT), G2 (eGFR ≥60, positive UDT), G3 (eGFR <60, negative UDT), and G4 (eGFR <60, positive-UDT). *P*-values indicate the comparison between each groups.

# Discussion

The novel findings of the present study are as follows. First, ~30% of the HFpEF patients had a positive UDT. Secondly, HFpEF patients with a positive UDT had significantly higher mortality as compared with those with a negative UDT in each stratum of eGFR levels. Thirdly, the prognostic impact of a positive UDT was significantly enhanced after adjustment by the covariates including eGFR. These findings indicate that we need to perform UDT in addition to eGFR in all HFpEF patients for appropriate risk stratification, especially in HFpEF patients with eGFR ≥60.

## Albuminuria as a marker of cardiorenal syndrome in heart failure with preserved ejection fraction

Albuminuria is known to be an independent risk factor for mortality in the general population and in patients with hypertension or diabetes.[8–10] In HF patients, the prevalence of patients with albuminuria (≥30 mg/g) is ~30%.[12,13] Furthermore, HF patients with albuminuria (≥30 mg/g) had a poorer prognosis independent of diabetes, hypertension, or renal function.[13–16] Anand *et al.* reported that proteinuria was associated with abnormal physical findings and clinical indicators of volume overload, which suggests a possible pathogenic role of increased intravascular volume.[14] Furthermore, RAS activation and inflammation have been suggested to play causal roles in increasing albuminuria.[16] Therefore, HF patients with albuminuria (≥30 mg/g) may have higher RAS activity compared with those without albuminuria. However, most of the HF patients included in these studies had HFrEF.

To our knowledge, this is the first report of the relationship between HFpEF and albuminuria using UDT. In HFpEF patients, the prevalence of albuminuria (≥30 mg/g) was almost similar to that in those with HFrEF. Furthermore, HFpEF patients with a positive UDT had a significantly poorer prognosis. The mechanisms linking albuminuria and HFpEF remain unknown. However, there may not be a large difference between HFrEF and HFpEF in terms of the mechanism of elevated albuminuria.

Chronic kidney disease is a frequent complication of HF, and this close association has been called the cardiorenal syndrome (CRS).[26] Both CKD and HF are associated with an increased activity of the sympathetic nervous system, and RAS activation, oxidative stress, and inflammation.[26] Therefore, we usually pay attention to renal function in HF patients. Compared with HFrEF patients, HFpEF patients were considered to have lower RAS activity.[27] However, according to the pathophysiology of elevated albuminuria in HF patients, HFpEF patients with albuminuria (≥30 mg/g) may have higher RAS activity than those with normal albuminuria. Therefore, the linkage between the heart and kidney in HFpEF patients with albuminuria (≥30 mg/g) may be greater than in HFpEF patients with normal albuminuria. So, the measurement albuminuria is essential to evaluate CRS in addition to eGFR in all HF patients.

## Benefit of the combination of estimated glomerular filtration rate and urine dipstick test in predicting the prognosis in heart failure with preserved ejection fraction

Patients with HFpEF usually tend to be older and female.[1] In most clinical settings, eGFR is calculated by age, sex, and serum creatinine.[23] Therefore, some HFpEF patients may have an eGFR <60 without significant renal damage. Indeed, in the present study,

**Table 2 Cox proportional hazard model for all-cause death, cardiovascular death, and non-cardiovascular death**

| HR categories | | eGFR <60 | Dipstick | No. of events (%) | No. of events/ 100 person/ year | (a) Unadjusted | | | (b) Age- and sex-adjusted | | | (c) All baseline adjusted | | | (d) Fully adjusted including treatment | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | HR | 95% CI | *P*-value | HR | 95% CI | *P*-value | HR | 95% CI | *P*-value | HR | 95% CI | *P*-value |
| All-cause death | | | | | | | | <0.001 | | | <0.001 | | | <0.001 | | | <0.001 |
| | Group 1 (reference) | − | − | 34 (3.3) | 1.5 | 1.00 | | | 1.00 | | | 1.00 | | | 1.00 | | |
| | Group 2 | − | + | 31 (9.0) | 4.0 | 3.02 | 1.85–4.91 | <0.001 | 2.60 | 1.59–4.24 | <0.001 | 2.57 | 1.56–4.25 | <0.001 | 2.44 | 1.47–4.05 | 0.001 |
| | Group 3 | + | − | 78 (11.0) | 4.4 | 3.39 | 2.26–5.07 | <0.001 | 2.07 | 1.37–3.13 | 0.001 | 1.46 | 0.94–2.27 | 0.09 | 1.43 | 0.92–2.23 | 0.12 |
| | Group 4 | + | + | 70 (18.1) | 7.9 | 6.00 | 3.98–9.04 | <0.001 | 3.78 | 2.48–5.74 | <0.001 | 2.63 | 1.67–4.13 | <0.001 | 2.71 | 1.72–4.27 | <0.001 |
| Cardiovascular death | | | | | | | | <0.001 | | | <0.001 | | | <0.001 | | | <0.001 |
| | Group 1 (reference) | − | − | 10 (1.0) | 0.4 | 1.00 | | | 1.00 | | | 1.00 | | | 1.00 | | |
| | Group 2 | − | + | 11 (3.2) | 1.4 | 3.65 | 1.55–8.59 | 0.003 | 3.30 | 1.40–7.80 | 0.006 | 3.66 | 1.53–8.72 | 0.003 | 3.58 | 1.50–8.58 | 0.004 |
| | Group 3 | + | − | 39 (5.5) | 2.2 | 5.72 | 2.85–11.45 | <0.001 | 3.68 | 1.80–7.49 | <0.001 | 2.34 | 1.13–5.09 | 0.023 | 2.34 | 1.10–4.98 | 0.03 |
| | Group 4 | + | + | 26 (6.7) | 2.9 | 7.53 | 3.63–15.63 | <0.001 | 5.06 | 2.40–10.60 | <0.001 | 3.25 | 1.47–7.18 | 0.004 | 3.29 | 1.48–7.31 | 0.003 |
| Non-cardiovascular death | | | | | | | | <0.001 | | | <0.001 | | | <0.001 | | | <0.001 |
| | Group 1 (reference) | − | − | 24 (2.3) | 1.1 | 1.00 | | | 1.00 | | | 1.00 | | | 1.00 | | |
| | Group 2 | − | + | 20 (5.8) | 2.6 | 2.75 | 1.52–4.98 | 0.001 | 2.29 | 1.26–4.16 | 0.007 | 2.03 | 1.09–3.78 | 0.026 | 1.89 | 1.01–3.54 | 0.048 |
| | Group 3 | + | − | 39 (5.5) | 2.2 | 2.41 | 1.45–4.01 | 0.001 | 1.42 | 0.84–2.40 | 0.18 | 1.06 | 0.61–1.86 | 0.83 | 1.05 | 0.60–1.84 | 0.88 |
| | Group 4 | + | + | 44 (11.4) | 5.0 | 5.37 | 3.26–8.83 | <0.001 | 3.24 | 1.95–5.40 | <0.001 | 2.41 | 1.39–4.19 | 0.002 | 2.51 | 1.44–4.37 | 0.001 |

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
In model (c), we adjusted the model by age, sex, and clinical status (New York Heart Association class, systolic blood pressure, heart rate, body mass index, left ventricular ejection fraction), serum sodium, serum potassium, history of malignant tumour, and admission for heart failure, and co-morbidities (diabetes, hyperuricaemia, anaemia, coronary artery disease, cerebrovascular disease, atrial fibrillation), and five urine dipstick test brands. In model (d), in addition to model (c), we adjusted the model by treatment (beta-blocker, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, calcium channel blocker, loop diuretics, aldosterone antagonist).

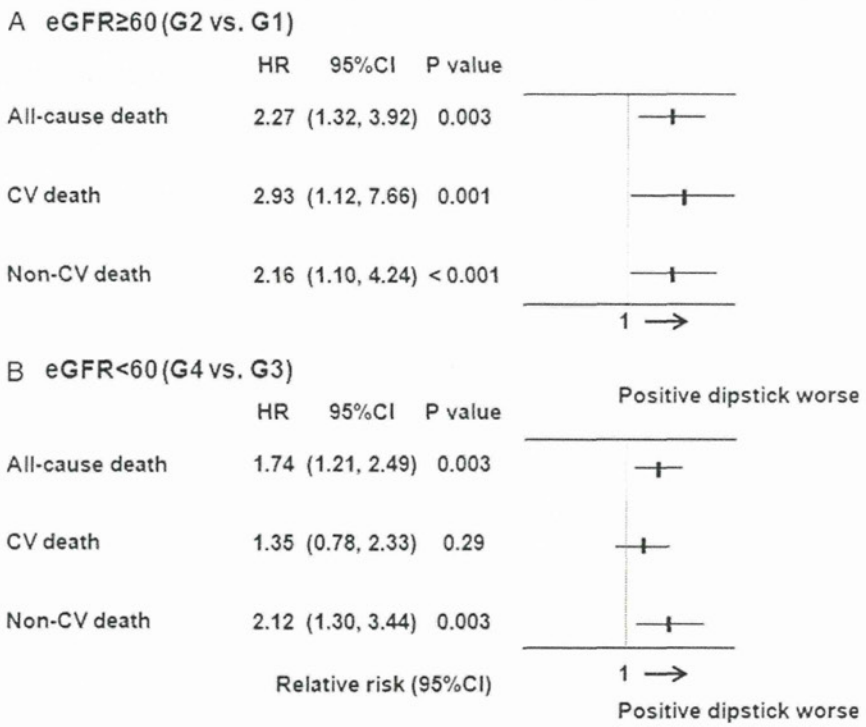


**Figure 3** Hazard ratios (HRs) for all-cause death, cardiovascular (CV) death, and non-CV death after adjustment by multiple covariates including estimated glomerular filtration rate (eGFR). (*A*) eGFR ≥60 (G2 vs. G1), (*B*) eGFR <60 (G4 vs. G3). 95%CI, 95% confidence interval.

HFpEF patients in G3 were older and there were more females as compared with other groups. The present result shows that HFpEF patients with a negative UDT tend to have a better prognosis than those with a positive UDT.

The UDT has been widely used as an initial screening method for evaluation of proteinuria on the basis of low cost and the ability to provide rapid point-of-care information to clinicians and patients.[22] Furthermore, UDT is very sensitive to albumin but is less sensitive to globulins and secreted proteins.[22] Konta *et al.* reported the significant usefulness of trace or more UDT to predict albuminuria (≥30 mg/g) in the general population.[21] Furthermore, the negative predictive value of UDT for identification of albuminuria (≥30 mg/g) was higher than the threshold of ≥1+.[21] Thus, in the present study, we defined positive UDT for albuminuria (≥30 mg/g) when the analysis showed trace or more.

Anand *et al.* reported that the percentage of positive UDTs in HF patients was 8.9%.[14] However, they defined a positive UDT as 1+ or more. In the present study, the prevalence of patients with a positive UDT was 29.5%. Among the patients with a positive UDT, the percentage of trace proteinuria was the highest. Therefore, the difference in the definition of a positive UDT may influence the difference in the percentage. Albuminuria (≥30 mg/g) is observed in approximately one-third of HF patients.[12,13] Thus, our findings indicate that a positive UDT defined as trace or more is useful for detection of albuminuria (≥30 mg/g) and could be a reasonable surrogate of UACR measurement in HFpEF patients.

In HFpEF patients with eGFR ≥60, those with a positive UDT showed about twice as high mortality as those with a negative UDT. Furthermore, in HFpEF patients with eGFR <60, those with a positive UDT also showed significantly higher mortality compared with those with a negative UDT. This result indicates that we should perform UDT in addition to eGFR evaluation in HFpEF patients regardless of the eGFR level.

## Implications of a positive urine dipstick test in heart failure with preserved ejection fraction

The reason for the poorer prognosis of HFpEF patients with a positive UDT remains to be fully clarified. In the present study, HFpEF patients with a positive UDT were characterized by a higher BNP level, suggesting that venous filling pressure is significantly increased. Venous congestion was shown to cause proteinuria in dogs,[28] suggesting that elevated venous pressure may be associated with the development of albuminuria. Furthermore, albuminuria may attenuate the effect of furosemide because filtered albumin may bind furosemide in the tubular fluid and impair the interaction with the luminal co-transporting proteins.[29] Resistance to diuretics may cause a deterioration of the venous congestion status with a resultant vicious cycle of albumin excretion into the urine. Thus, the therapeutic strategy for reducing albuminuria is important in HFpEF patients.

In the present study, 40% of deaths were caused by cardiovascular events. Zile *et al.* also reported that 60% of deaths in HFpEF

patients were CVDs.[30] Albuminuria reflects glomerular injury, systemic inflammation, and endothelial dysfunction that lead to cardiovascular events.[13] Furthermore, albuminuria has been associated with changes in coagulation factors.[31] In the present study, the rate of CVD was relatively low; however, a positive UDT could predict CVD in HFpEF patients, especially in those with an eGFR $\geq$60. In HFpEF patients with eGFR <60, those with a positive UDT showed no significant difference in the development of CVD after adjustment by eGFR compared with those with a negative UDT. This result indicated that the influence of eGFR decline on CVD may be larger than that of albuminuria in patients with eGFR <60. However, Perkins *et al.* reported that cases of early eGFR decline occurred in 9% of the normal albuminuria group and 31% of the albuminuria ($\geq$30 mg/g) group in diabetes patients.[32] Therefore, in the follow-up period, there may be a considerable eGFR decline in patients with a positive UDT compared with those with a negative UDT that leads to poor outcome. Therefore, we need to perform UDT in addition to measurement of eGFR even in HFpEF patients with eGFR <60.

In the present study, a positive UDT was also associated with increased NCVD, a finding consistent with a previous report by Hillege *et al.*[31] Approximately one-third of the NCVDs were due to malignant tumours in the present study. Although the underlying mechanisms remain to be elucidated, patients with advanced malignant tumours have a significantly higher urinary albumin excretion rate than those with localized disease.[33]

In the present study, the remaining one-third of NCVDs were due to infectious diseases. HFpEF patients with albuminuria ($\geq$30 mg/g) tended also to have cerebrovascular disease that leads to impaired activities of daily living (*Table 1*). Such patients are particularly at high risk of contracting infectious disease. The present results also indicate that the prevention of infectious diseases and cerebrovascular disease is important to reduce the mortality of HFpEF patients.

## Treatment strategy of patients with heart failure with preserved ejection fraction with a positive urine dipstick test

The underlying mechanisms of the close relationship between the heart and the kidney include inflammation and an activated RAS and/or sympathetic nervous system.[7] Importantly, these mechanisms are also involved in the pathogenesis of albuminuria.[7] It was reported that RAS inhibitors cause a significant decrease in albuminuria and a trend of a decrease in cardiovascular events in patients with hypertension, LV hypertrophy, and diabetes.[34] On the other hand, RAS inhibition in HFpEF is not associated with a consistent reduction in HF admission or mortality.[27] The overall failure of RAS inhibitors to improve morbidity and mortality of HFpEF patients suggests a relatively smaller contribution of neurohumoral activation on HF progression as compared with the case for HFrEF patients.[27] However, HFpEF patients with a positive UDT may have higher RAS activity than those with a negative UDT. It was reported that telmisartan treatment was associated with an increased risk of adverse renal events in patients without albuminuria, whereas it tended to improve outcomes of patients with albuminuria.[35] Thus, the baseline albuminuria level may be an important factor when selecting patients for treatment with RAS inhibitors.[36] Again, the importance of UDT should be emphasized before we start to use RAS inhibitors for HFpEF patients.

## Study limitations

Several limitations should be mentioned regarding the present study. (i) We had no information on LV function other than the LVEF, and it therefore remains unknown whether the study population had objective evidence of diastolic dysfunction recommended by the recent guidelines in the diagnosis of HFpEF.[4] However, we excluded patients with severe VHD, congenital heart disease, pulmonary arterial hypertension, and pericardial disease. Therefore, our study subjects can be categorized as probable diastolic HF as defined by Vasan *et al.*[2] (ii) UDT is a qualitative measurement of proteinuria and, furthermore, UDT is a less accurate and less sensitive measure of urinary albumin excretion. (iii) In the present study, UDTs from five different companies were used in the participating hospitals. Moreover, UDT was not measured at a central laboratory. Four dipsticks were calibrated to indicate trace at $\geq$0.1 g/L or $\geq$0.15 g/L of proteinuria and one dipstick did not originally indicate trace. Furthermore, the sensitivity and specificity for detecting albuminuria may be different among these dipsticks. However, multivariate analyses including all covariates with the UDT brands clearly showed the significant prognostic impact of a positive UDT in HFpEF patients. (iv) The present results were analysed using data collected at study entry and we did not take into consideration the possible changes in UDT during the follow-up period. (v) The primary design of the present study did not cover chronic lung disease, which has been recognized as one of the important prognostic factors of HFpEF.[5] (vi) All subjects in the CHART-2 study were Japanese people, which may limit extrapolation of the present results to patients in Western countries. Finally, since the CHART-2 study is an observational study, the present results need to be carefully interpreted especially when the effects of treatment are evaluated.

# Conclusions

The present results demonstrate that albuminuria predicts the mortality of HFpEF patients in each stratum of eGFR levels, suggesting its usefulness for appropriate risk stratification in these patients.

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**Conflict of interest:** none declared.

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ORIGINAL ARTICLE
Epidemiology

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

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

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

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

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

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

The incidence and mortality from coronary artery disease (CAD) has been declining in the United States and European countries.[1–4] These declines have been attributed to the control of risk factors (eg, hypertension, dyslipidemia and smoking) and the improvement in critical care (eg, coronary revascularization therapy).[5–7] In contrast to the Western countries, in Japan, a highly developed and racially homogeneous country that is rapidly aging, total cholesterol levels and the prevalence of obesity have been increasing as a result of lifestyle Westernization influence since the 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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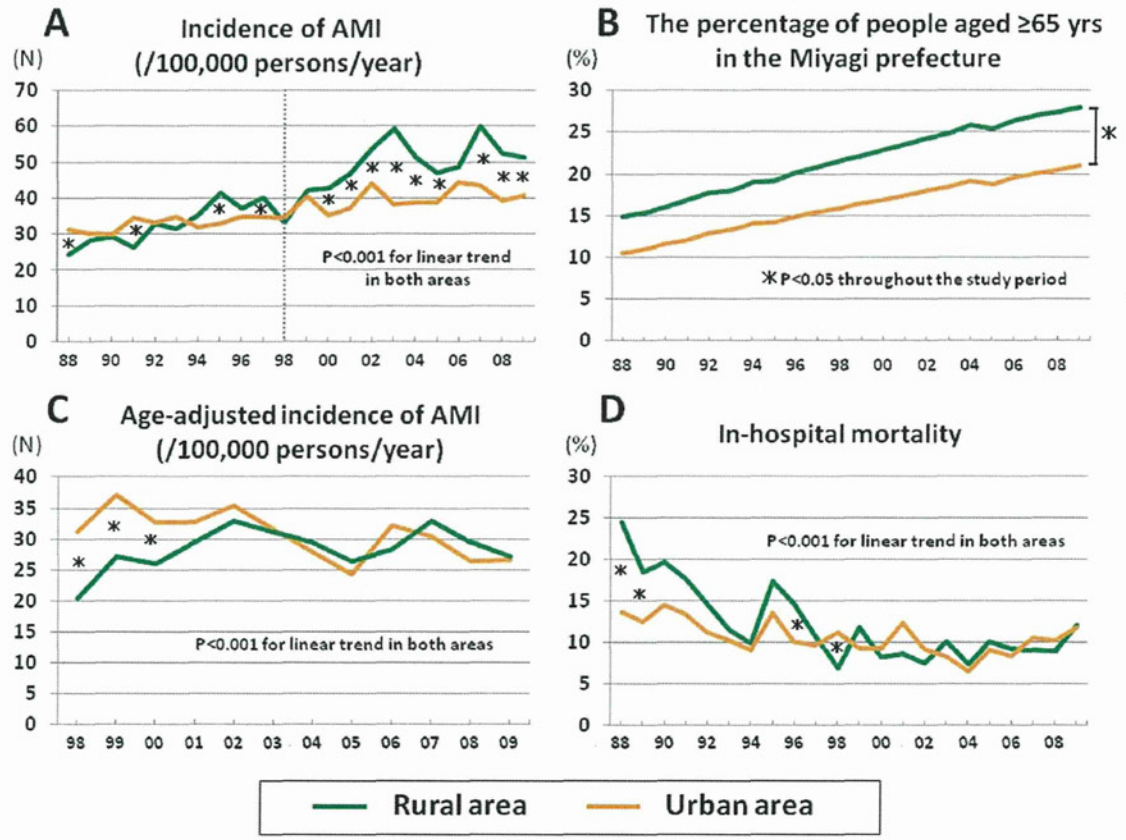


**Figure 1.** The 20-year trend of acute myocardial infarction (AMI) in the Miyagi prefecture. (**A**) The incidence of AMI (/100,000 persons/year) has significantly increased in both areas (both P<0.001) with a greater extent in the urban area over the last 20 years, accompanied with rapid aging in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

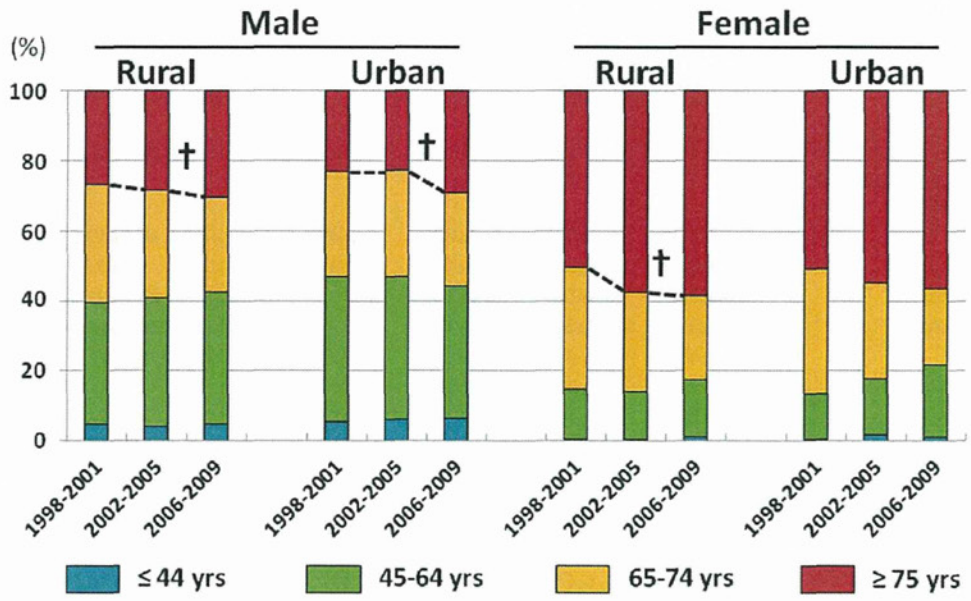


**Figure 2.** Age-distribution of acute myocardial infarction (AMI) patients. The percentage of high-old patients (≥75 years old) was markedly higher in female patients than in the patients in the rural and urban areas and has been increasing significantly in male patients in both areas and rural female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

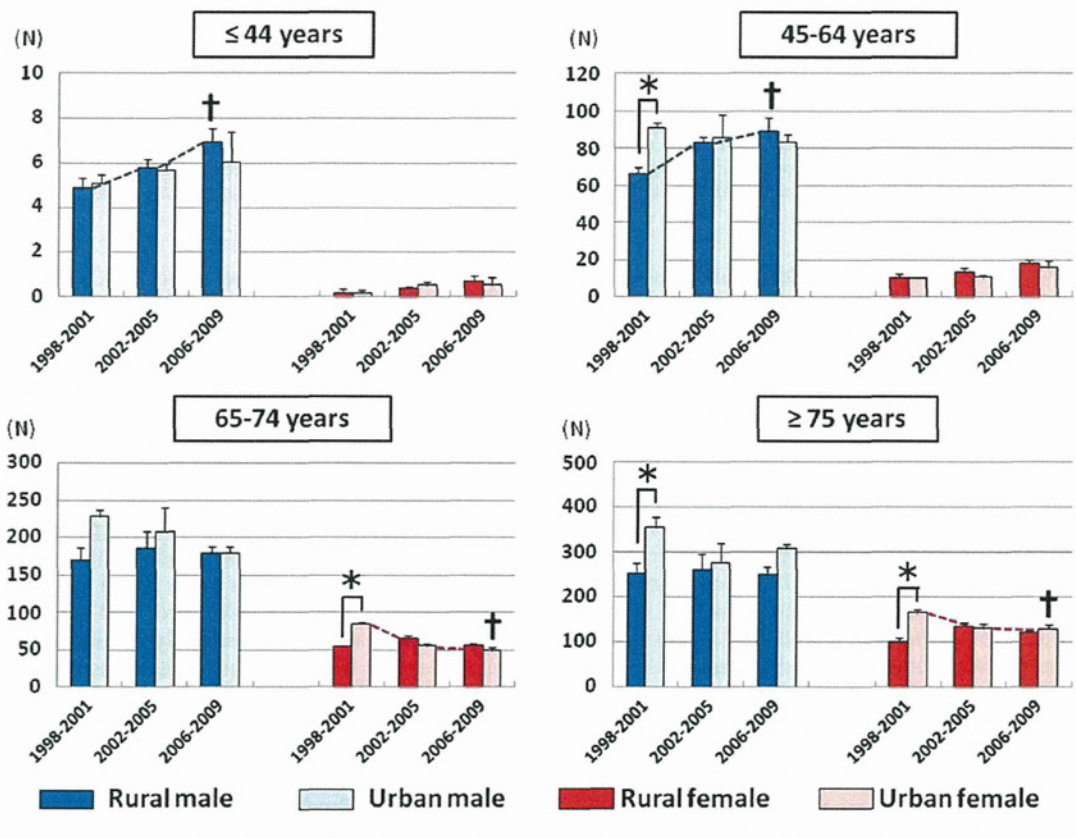


**Figure 3.** Age-specific incidence of acute myocardial infarction (AMI) (/100,000 persons/year). The significant increase in the age-adjusted incidence of AMI was noted in <44 and 45–64 year old rural male patients, and the significant decrease was noted in 65–74 and >75 year old urban female patients.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