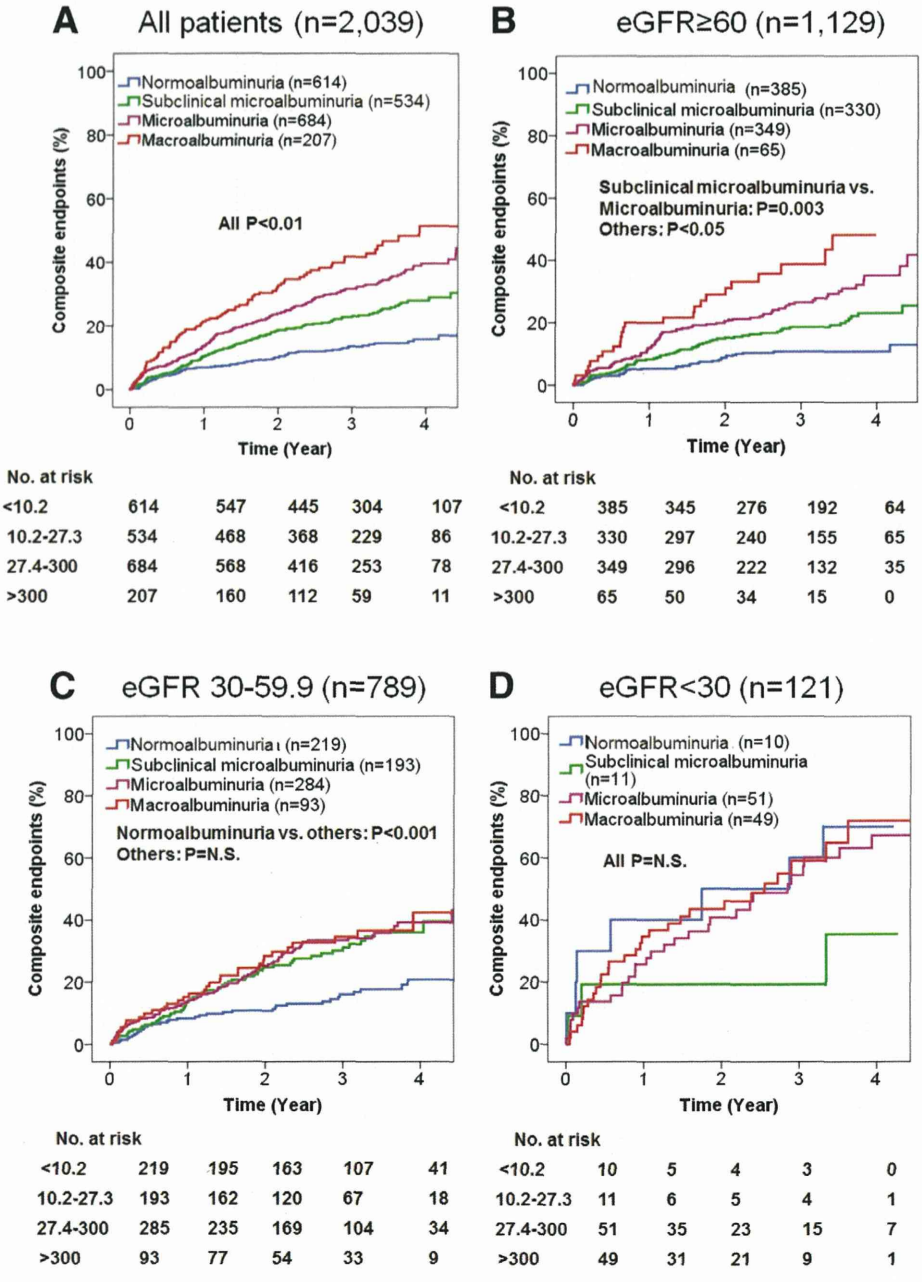

Figure 3. Kaplan-Meier curves for composite endpoints. (**A**) All patients; (**B**) estimated glomerular filtration rate (eGFR) ≥60 ml·min^{-1}·1.73m^{-2}; (**C**) eGFR 30–59.9 ml·min^{-1}·1.73m^{-2}; (**D**) eGFR <30 ml·min^{-1}·1.73m^{-2}.

67.4 years and male patients accounted for 68.9%. History of ischemic heart disease was noted in 46.2% and mean LVEF and eGFR were 55.3±15.7% and 62.8±20.9 ml·min^{-1}·1.73m^{-2}, respectively. The prevalence of eGFR <60 ml·min^{-1}·1.73 m^{-2} was 44.6% (n=910), and median UACR was 21.5 mg/g. On CART analysis UACR=27.4 mg/g and 10.2 mg/g were identified as the first and the second discriminating points to stratify risk for composite endpoints, respectively (**Figure 1**). Thus, normoalbuminuria, subclinical microalbuminuria, microalbuminuria and macroalbuminuria were defined as UACR (mg/g) <10.2, 10.2–27.3, 27.4–300, and >300, respectively. The prevalence of normoalbuminuria, subclinical microalbuminuria, microalbuminuria and macroalbuminuria was 30.1%, 26.2%, 33.5%, and 10.2%, respectively. As shown in **Figure 2**, the prevalence of normoalbuminuria was decreased along with a decrease in eGFR categories. It was noted that, even in patients with preserved eGFR and mildly reduced eGFR, the prevalence of subclinical microalbuminuria was 29.2% and 24.5%, respectively. The characteristics of the patients with subclinical microalbuminuria or microalbuminuria were generally intermediate between those with normoalbuminuria and those with macroalbuminuria, in terms of age, comorbidity, NYHA class,

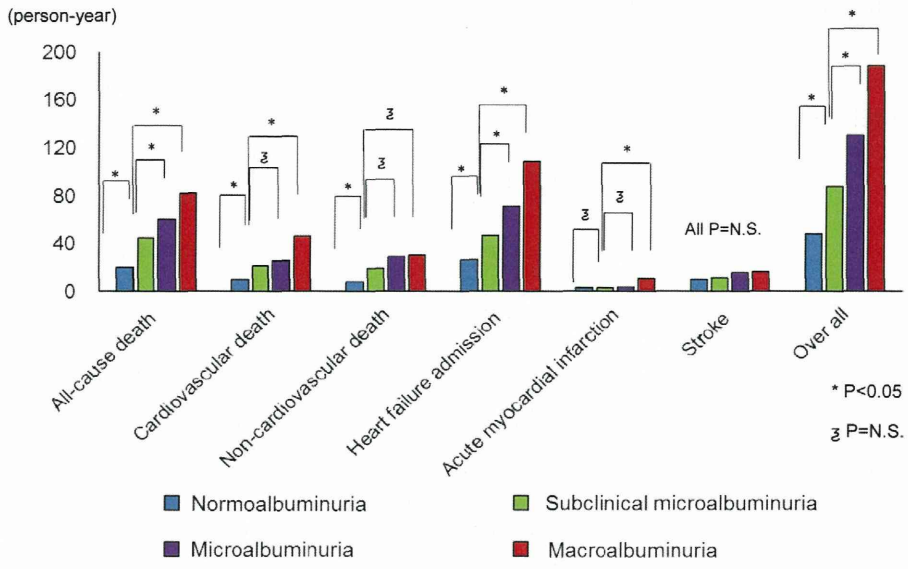

Figure 4. Incidence of composite endpoints. The patients with subclinical microalbuminuria had significantly higher event rates of death, heart failure admission.

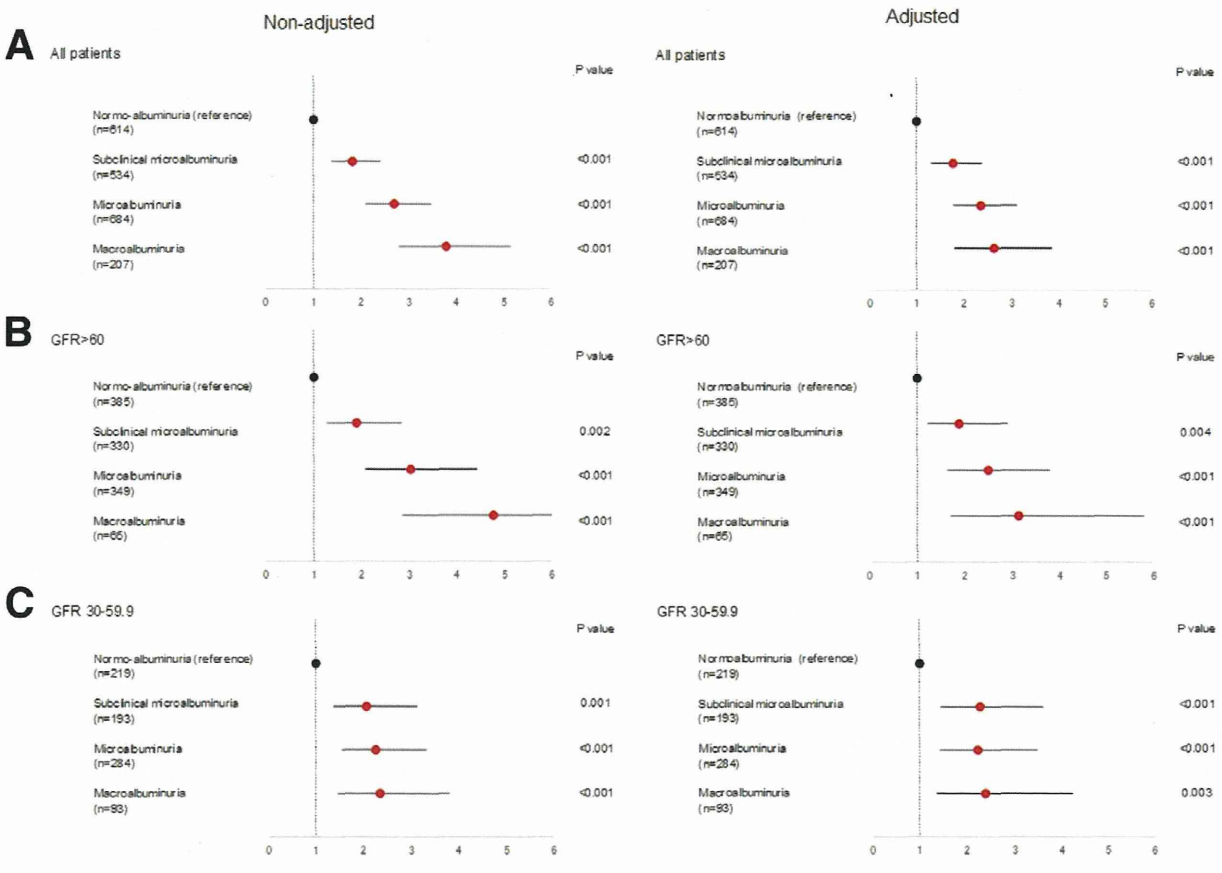

Figure 5. Non-adjusted and adjusted Cox hazard model adjusted for covariates that could potentially influence outcome: (**A**) all patients; (**B**) estimated glomerular filtration rate (eGFR) ≥60 ml·min^{-1}·1.73m^{-2}; and (**C**) eGFR 30–59.9 ml·min^{-1}·1.73m^{-2}.

Table 2. Subgroup Analysis for Composite Endpoints

	HR	95% CI	P-value	HR	95% CI	P-value	P for interaction
	Male			Female			
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.96	1.37–2.79	<0.001	1.35	0.75–2.43	0.320	0.40
Microalbuminuria	2.27	1.61–3.19	<0.001	2.25	1.32–3.85	0.003	0.45
Macroalbuminuria	2.71	1.73–4.23	<0.001	3.10	1.50–6.41	0.002	0.33
	Age ≥69 years			Age <69 years			
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	2.04	1.37–3.05	<0.001	1.66	1.02–2.68	0.040	0.35
Microalbuminuria	2.56	1.76–3.73	<0.001	1.95	1.24–3.08	0.004	0.70
Macroalbuminuria	2.75	1.65–4.57	<0.001	3.31	1.83–6.00	<0.001	0.26
	LVEF ≥50%			LVEF <50%			
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.87	1.19–2.94	0.007	1.71	1.13–2.58	0.010	0.14
Microalbuminuria	2.31	1.51–3.55	<0.001	2.31	1.57–3.41	<0.001	0.33
Macroalbuminuria	2.57	1.48–4.47	0.001	2.66	1.55–4.56	<0.001	0.04
	(+) Hypertension			(–) Hypertension			
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.69	1.20–2.38	0.003	1.97	1.01–3.85	0.040	0.66
Microalbuminuria	2.37	1.72–3.26	<0.001	1.70	0.86–3.36	0.140	0.47
Macroalbuminuria	2.52	1.65–3.86	<0.001	5.41	2.30–12.69	<0.001	0.22
	(+) Diabetes			(–) Diabetes			
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.81	1.07–3.07	0.030	1.70	1.17–2.47	0.005	0.78
Microalbuminuria	2.30	1.42–3.73	0.001	2.13	1.48–3.07	<0.001	0.78
Macroalbuminuria	2.26	1.26–4.06	0.006	3.09	1.82–5.23	<0.001	0.17
	(+) β-blocker			(–) β-blocker			
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.98	1.31–2.97	0.001	1.57	0.98–2.50	0.120	0.61
Microalbuminuria	2.39	1.63–3.49	<0.001	1.98	1.28–3.07	0.002	0.87
Macroalbuminuria	2.78	1.66–4.64	<0.001	2.50	1.41–4.43	0.002	0.93
	(+) RAS inhibitor			(–) RAS inhibitor			
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.90	1.32–2.71	0.006	1.49	0.83–2.69	0.180	0.45
Microalbuminuria	2.57	1.83–3.59	<0.001	1.40	0.78–2.54	0.260	0.32
Macroalbuminuria	2.96	1.90–4.62	<0.001	1.62	0.75–3.50	0.220	0.18
	(+) Statin			(–) Statin			
Normoalbuminuria (Reference)	1.00			1.00			
Subclinical microalbuminuria	1.77	1.04–3.01	0.030	1.78	1.23–2.58	0.002	0.76
Microalbuminuria	2.25	1.37–3.70	0.001	2.29	1.61–3.25	<0.001	0.46
Macroalbuminuria	2.52	1.37–4.64	0.003	2.85	1.74–4.68	<0.001	0.56

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

hemodynamics, and hemoglobin, BUN, eGFR and BNP. The patients with subclinical microalbuminuria and microalbuminuria, however, were characterized by lower prevalence of male gender, whereas LV function was similar among the 4 groups (Table 1).

Prognostic Impact of Clinical and Subclinical Microalbuminuria

During the median follow-up period of 2.69 years (IQR, 1.63–3.63 years), composite endpoints occurred in 506 patients (24.8%). Figure 3A shows the estimated curves for composite endpoints. As compared with the patients with normoalbuminuria, those with macroalbuminuria, microalbuminuria and subclinical microalbuminuria had poorer prognosis. As compared with the patients with normoalbuminuria, those with subclinical microalbuminuria had significantly increased incidence of cardiovascular death, non-cardiovascular death, and HF admission, but had similar incidence of acute myocardial infarction and stroke (Figure 4). Importantly, the patients with subclinical microalbuminuria and preserved eGFR or mildly reduced eGFR had significantly poorer prognosis compared with those with normoalbuminuria (Figures 3B,C). Furthermore, in patients with mildly reduced eGFR, there was no difference in the occurrence of the composite endpoints regard-

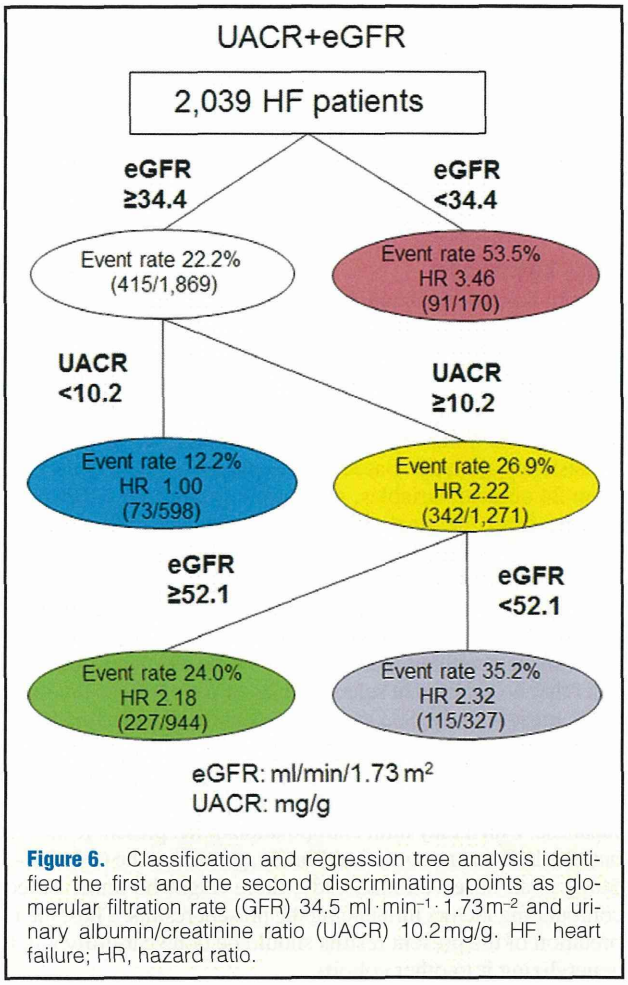

Figure 6. Classification and regression tree analysis identified the first and the second discriminating points as glomerular filtration rate (GFR) 34.5 ml·min^{-1}·1.73m^{-2} and urinary albumin/creatinine ratio (UACR) 10.2mg/g. HF, heart failure; HR, hazard ratio.

less of microalbuminuria, microalbuminuria or macroalbuminuria (Figure 3C). There was no difference in composite endpoints in patients with severely reduced GFR among the 4 groups (Figure 3D).

Figure 5 shows the results of non-adjusted and adjusted Cox proportional hazard regression models for composite endpoints. As compared with patients with normoalbuminuria (reference), multivariate adjusted Cox models showed that the patients with subclinical microalbuminuria, microalbuminuria and macroalbuminuria had 1.70-, 2.39- and 2.49-fold higher risk for composite endpoints, respectively (all P<0.001). In the patients with preserved GFR, the adjusted hazard ratio (HR) and 95%CI for composite endpoints was 1.90 (1.23–2.92), 2.50 (1.64–3.80) and 3.15 (1.71–5.81) for subclinical microalbuminuria, microalbuminuria and macroalbuminuria, respectively. Similarly, in patients with mildly reduced GFR, the adjusted HR (95% CI) was 2.29 (1.45–3.62), 2.24 (1.43–3.49) and 2.40 (1.36–4.24) in patients with subclinical microalbuminuria, microalbuminuria and macroalbuminuria, respectively. On subgroup analysis for composite endpoints, subclinical microalbuminuria was significantly associated with poor prognosis regardless of age, LVEF, hypertension or diabetes (Table 2). There was no significant interaction regarding sex and medications on subclinical microalbuminuria for mortality (Table 2). In a model using both eGFR and UACR, CART analysis showed that the first discriminating points for composite endpoints was eGFR=34.5 ml·min^{-1}·1.73 m^{-2} and the next split point was UACR=10.2mg/g (Figure 6).

Discussion

The novel findings of the present study are the follows. First, among the patients with stage C/D CHF, CART analysis showed that UACR=27.4mg/g and 10.2mg/g were the first and the second discriminating points to stratify risk for composite endpoints, respectively, suggesting the clinical importance of subclinical microalbuminuria in addition to microalbuminuria and macroalbuminuria. Second, approximately one-quarter of the CHF patients had subclinical microalbuminuria, which was associated with poor prognosis regardless of renal function. Importantly, subclinical microalbuminuria had a similar prognostic impact to microalbuminuria and macroalbuminuria in CHF patients with mildly impaired renal function. To the best of our knowledge, the present study is the first to demonstrate the clinical importance of subclinical microalbuminuria in the management of CHF patients in real-world practice.

UACR for Risk Stratification in CHF

Microalbuminuria has been traditionally defined as 30–300mg/g UACR in the previous studies and the current guidelines,[1] but this definition was originally derived from previous studies with small sample size that focused on determining the level of albuminuria to predict progression to overt proteinuria.[29,30] In the present study, we thus investigated UACR level to discriminate prognostic levels in the general practice of CHF patients. As a result, on CART analysis 27.4mg/g and 10.2mg/g were identified as the first and the second cut-off points of UACR, respectively, to discriminate cardiovascular risk of CHF patients. Especially, it is clinically important that we were able to identify UACR=27.4mg/g as the primary cut-off point to determine prognosis in CHF patients, given that the primary cut-off point for the definition of microalbuminuria is around 30mg/g in general practice. Furthermore, it is also important that we were able to identify UACR=10.2mg/g as the secondary discriminating point, suggesting the prognostic impact of subclinical microalbuminuria in CHF patients in general practice.

Subclinical Microalbuminuria and Microalbuminuria in CHF

The present study is the first to demonstrate the prevalence of subclinical microalbuminuria in association with renal function. In the present study, the prevalence of normoalbuminuria (UACR ≤10.2md/g) was decreased as eGFR increased. Of note, more than half of the patients with preserved or mildly reduced GFR had subclinical microalbuminuria or microalbuminuria associated with worse prognosis. It has been reported that the prevalence of microalbuminuria (UACR >30mg/g) was 5% in apparently healthy individuals, 16% in patients with hypertension, and almost 30% in those with diabetes mellitus or CHF.[5,6] In the present study, the prevalence of microalbuminuria was approximately 30% overall in the CHF patients regardless of renal function, while that of subclinical microalbuminuria was approximately 20% in CHF patients with preserved or mildly reduced GFR, but <10% in those with reduced GFR (Figure 2).

UACR and CHF

The present study primarily showed that CHF patients with microalbuminuria had worse prognosis than those without it, a consistent finding of the previous studies that reported that subjects with microalbuminuria, traditionally defined as UACR 30–300mg/g, had poorer prognosis regardless of diabetes, hypertension or renal function.[15–17] As reported in patients with

hypertension or diabetes,[2–4] microalbuminuria is also important in CHF patients[6,31] because the disorder is likely to be associated with increased intravascular volume with resultant edema,[7] RAS activation and/or inflammation.[16] In addition, several studies reported that subclinical microalbuminuria (UACR <30 mg/g) was associated with cardiovascular events and HF in the general population and in patients with hypertension, diabetes and CVD.[5,8–14,32] For example, it was reported that the risk of cardiovascular death in patients with diabetes increased almost 10-fold when albuminuria rose from 10 to 30 mg/g,[32] and that this is also the case in the general population.[5] Although the underlying pathophysiology remains to be fully elucidated, subclinical microalbuminuria is considered to be associated with inflammation and hypertriglyceridemia,[5] LV hypertrophy,[7] and progression of atherosclerosis.[33] It was also reported that the mean or median UACR in the general population was around 10 mg/g.[5–7] Thus, it is reasonable to consider that subclinical microalbuminuria above the normal range is associated with poor prognosis.

In the present study, subclinical microalbuminuria was also associated with non-cardiovascular death. Although the underlying mechanisms remain to be elucidated, there are 2 possible explanations. First, it was reported that patients with advanced malignant tumor have a significantly higher urinary albumin excretion rate than those with localized disease.[34] Second, reduced eGFR and albuminuria are associated with increased risk for infection-related mortality.[35] Thus, it is conceivable that subclinical microalbuminuria was associated with non-cardiovascular death, at least in part, as a reflection of severer general condition in CHF patients in the present study.

To our knowledge, only 2 studies previously examined the association between CVD and increasing microalbuminuria in CHF patients.[18,19] Although these studies examined the impact of microalbuminuria, they did not specifically examine that of subclinical albuminuria in detail. The present study is the first to show that UACR=10.2 mg/g and 27.4 mg/g is useful for risk stratification of cardiovascular events in a large-scale observational cohort of CHF patients. In the present study, subclinical microalbuminuria was noted in approximately one-quarter of CHF patients with preserved or mildly reduced GFR (**Figure 2**), and the prognostic impact of subclinical microalbuminuria was similar to that of microalbuminuria and macroalbuminuria. Thus, the clinical importance of subclinical microalbuminuria should be further emphasized in real-world CHF management.

Microalbuminuria and CKD

According to the current classification of CKD, microalbuminuria is defined as a risk factor even though GFR was preserved.[12] In the present study, we were able to show for the first time that not only microalbuminuria (UACR ≥27.4 mg/g) but also subclinical microalbuminuria (UACR 10.2–27.3 mg/g) are significantly associated with poorer prognosis as compared with normoalbuminuria (UACR <10.2 mg/g), particularly in those with preserved or mildly reduced GFR. In the present study, on CART analysis both eGFR (34.5 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) and UACR were useful as the first discriminating point for the composite endpoints, indicating that the prognostic impact of eGFR <34.5 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ outweighed any classification with UACR (**Figure 6**). Interestingly, however, CART analysis also showed that UACR=10.2 mg/g was the next discriminating point to stratify risk for composite endpoints (**Figure 6**), suggesting the superiority of UACR ≥10.2 mg/g to stratify risk in those without severe renal dysfunction (eGFR ≥34.5 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$). Among the patients with eGFR ≥34.5 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$, those with UACR ≥10.2 mg/g had increased incidence of cardiovascular events as compared with those without it (HR, 2.22; P<0.001; **Figure 6**). These results indicate that subclinical microalbuminuria is a therapeutic target in patients with preserved or mildly reduced GFR. Thus, we should pay more attention to subclinical microalbuminuria especially in patients with preserved or mildly reduced GFR, including those who are not classified as having CKD according to the current guidelines.

Study Limitations

Several limitations should be mentioned for the present study. First, in the present study, the patients with UACR data accounted for only approximately 50% of the total cohort. Patient background was considerably different between the patients with UACR measurement and those without it (**Table S1**). To minimize the influence of this selection bias, we performed a consistency analysis. Based on the propensity scores derived from 24 clinical variables, we randomly selected 1,440 individuals from the final subject group whose characteristics were similar to those of 2,591 patients excluded from the present study because of lack of UACR measurement. There were no difference in patient background or prognosis between the selected 1,440 patients with UACR measurement and excluded 2,591 patents without it (**Figure S1**; **Table S1**). Thus, we consider that no significant selection bias of patients was involved in the present study. Second, the present results were analyzed using data collected at study entry and we did not take into consideration the possible changes in UACR during the follow-up period. Third, all subjects in the CHART-2 Study were Japanese, which may limit extrapolation of the present results to patients in Western countries. Finally, given that the CHART-2 Study is an observational study, there might be unmeasured confounding factors influencing the present results. Thus, interpretation of the present results should be done carefully when generalizing it to other cohorts.

Conclusions

UACR=27.4 mg/g and 10.2 mg/g are the first and the second discriminating points to stratify risk in CHF patients regardless of renal function. Thus, the clinical importance of subclinical microalbuminuria should be underlined in the management of CHF patients in real-world practice, although studies are needed to further confirm the present results.

Acknowledgments

We thank all members of the Tohoku Heart Failure Society and the staff of the Departments of Cardiovascular Medicine and Evidence-Based Cardiovascular Medicine for their kind contributions (**Appendix S1**). This study was supported in part by Grants-in-Aid from the Ministry of Health, Labour, and Welfare and the Ministry of Education, Culture, Sports, Science, and Technology, Japan. The Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, is supported in part by unrestricted research grants from Daiichi Sankyo (Tokyo, Japan), Bayer Yakuhin (Osaka, Japan), Kyowa Hakko Kirin (Tokyo, Japan), Kowa Pharmaceutical (Tokyo, Japan), Novartis Pharma (Tokyo, Japan), Dainippon Sumitomo Pharma (Osaka, Japan), and Nippon Boehringer Ingelheim (Tokyo, Japan). H.S. has received lecture fees from Bayer Yakuhin (Osaka, Japan), Daiichi Sankyo (Tokyo, Japan) and Novartis Pharma (Tokyo, Japan).

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Supplementary Files

Supplementary File 1

Table S1. Baseline patient characteristics vs. presence of UACR measurement

Figure S1. Prognostic impact of subclinical microalbuminuria in the matched patients with urinary albumin/creatinine ratio measurement.

Appendix S1. Organization of the CHART-2 Study

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-14-0787

Relationship between the Seismic Scale of the 2011 Northeast Japan Earthquake and the Incidence of Acute Myocardial Infarction: A Population Based Study

Fumitaka Tanaka, MD,* Shinji Makita, MD,* Tomonori Ito, MD,* Toshiyuki Onoda, MD, PhD,† Kiyomi Sakata, MD, PhD,† Motoyuki Nakamura, MD*

From the *Department of Internal Medicine, Iwate Medical University, Morioka, Japan; †Department of Hygiene and Preventive Medicine, Iwate Medical University, Morioka, Japan.

Correspondence to Fumitaka Tanaka, MD, Department of Internal Medicine, Iwate Medical University, 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan. E-mail ftanaka@iwate-med.ac.jp

The total word count of the manuscript: 4,579

Running title: Population-based Study of the Incidence of AMI after Earthquakes

Abstract

Background: Previous studies have reported a relationship between large earthquakes and acute coronary events, but have yielded conflicting results. On 11 March 2011, a massive magnitude 9.0 earthquake hit the northeastern coast of Japan and generated repeated aftershocks. The aim of this study is to clarify the influence of this earthquake on the risk of acute myocardial infarction (AMI) including sudden cardiac death on the basis of data from a population based analysis.

Methods: The study subject was residents in the northeast of Iwate prefecture, Japan. Cases corresponding to the definition of AMI according to the criteria of the World Health Organization MONICA project were registered from four weeks before to eight weeks after the disaster and in the corresponding periods in 2009 and 2010.

Results: The relative risk of AMI was 2.03 (95% confidential interval 1.55 to 2.66) for the four week period after the disaster compared to the corresponding periods in the preceding years. The number of events peaked within the first week after the earthquake, decreased to levels seen in the preceding years, and then increased again following high magnitude aftershocks. The incidence of AMI was positively correlated with the seismic scale of the earthquake ($r = 0.75$, $p < 0.01$).

Conclusions: This population based study suggests that the increase in AMI events after a major earthquake varies depending on the seismic scale of the initial shock and each aftershock.

Keywords: myocardial infarction, population, epidemiology, stress, women

Introduction

Previous studies have reported a relationship between large earthquakes and acute coronary events [1-7], but have yielded conflicting results. After significant disasters, an increase in cardiac mortality based on death certificate review has been observed in several countries. [1-4] However, other studies have reported weak evidence of increased risk of acute myocardial infarction (AMI) and coronary death after earthquakes. [5,6] In the 1994 Northridge earthquake, [3,7] an increase in cardiac death was observed on the day of the main shock only, in contrast to the first two weeks after the 1995 Hanshin-Awaji earthquake in Japan. [4] These disparate results may be due to differences in definition of end points, earthquake magnitude, and case identification methodology. Furthermore, previous reports based on either review of death certificates or hospital admissions may not necessarily represent the real incidence of earthquake related coronary events. Therefore, a study based on both review of death certificates and hospital admissions should clarify the relationship between disasters and cardiac events.

On March 11, 2011, a massive magnitude 9.0 earthquake occurred off Japan's Pacific coast and hit the northeast of the country. The earthquake caused huge damage, including 15,883 deaths, 2,651 missing persons, and approximately 400,000 destroyed houses throughout the whole country. [8] Aftershocks of strong seismic intensity (SI) were generated repeatedly for four weeks after the main shock. Damage to electricity, water and gas supplies and failure of the supply of daily commodities such as food and fuel due to traffic cutoff continued for days, weeks or even several months in some areas. In coastal regions a tsunami caused huge damage and forced many people to be evacuated to temporary accommodation. The Iwate prefecture was one of the areas with the largest amount of damage and number of victims.

We have studied the incidence of AMI according to the criteria of the World Health Organization (WHO) MONICA project [9] in the community of Iwate prefecture. The aim of this study is to clarify the influence of the 2011 northeast Japan earthquake on the risk of AMI events including sudden cardiac death (SCD) on the basis of data from this population based analysis.