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ORIGINAL ARTICLE
Heart Failure

Novel Strain Rate Index of Contractility Loss Caused by Mechanical Dyssynchrony

– A Predictor of Response to Cardiac Resynchronization Therapy –

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Background: Time-delay indexes are limited in predicting the response to cardiac resynchronization therapy (CRT), partly because they do not reflect the residual left ventricular (LV) contractility. We computed a novel index of LV contractility loss due to dyssynchrony (the strain rate (SR) dispersion index: SRDI) by using the speckle-tracking SR and compared the efficacy of the SRDI, time-delay indexes, and strain delay index (SDI), the previously reported index of wasted energy due to dyssynchrony, for predicting the acute response to CRT.

Methods and Results: Echocardiography was performed in 19 heart failure patients (LV ejection fraction (EF) 25±6%) before and 2 weeks after CRT. The standard deviation of time to peak velocity, or strain, was calculated as time-delay indexes. The SRDI was calculated as the average of segmental peak systolic SR minus global peak systolic SR. Longitudinal SDI (L-SDI), longitudinal SRDI (L-SRDI), and circumferential SRDI (C-SRDI) significantly correlated with the change in global longitudinal strain (Δglobal LSt), whereas the time-delay indexes did not. Although the time-delay indexes were comparable between responders (Δglobal LSt ≥0.3%) and nonresponders, the L-SDI, L-SRDI, and C-SRDI were greater in responders. The area under the receiver operating characteristic curve of the L-SRDI, L-SDI, and C-SRDI for predicting responders was 0.89, 0.81, and 0.78, respectively.

Conclusions: The SRDI correlated fairly well with an improvement in global LV systolic function after CRT. (*Circ J* 2011; **75:** 2167–2175)

Key Words: Cardiac resynchronization therapy; Echocardiography; Heart failure; Left ventricular dyssynchrony; Left ventricular systolic function

Cardiac resynchronization therapy (CRT) has been shown to improve left ventricular (LV) function and mortality in patients with advanced heart failure.[1–5] However, 30–40% of the patients who meet the standard selection criteria of widened QRS complex and low LV ejection fraction (EF) do not respond to CRT.[2,6] Thus, it has been emphasized that LV mechanical dyssynchrony should be evaluated to predict the response to CRT, which has been estimated by time-delay indexes derived from the time-delay measurement of regional wall motion using velocity data acquired with tissue Doppler imaging (TDI).[7–9] However, in the multicenter Predictors of Responders to CRT (PROSPECT) trial, the time-delay indexes assessed by TDI could not accurately predict the responses to CRT.[10] One of the reasons for these disappointing results was thought to be the high variability of the time-delay indexes.[10] In addition, because conduction disturbance, such as left bundle branch block, causes redistribution of myocardial shortening and external work, resulting a reduction in LV global systolic function,[11–13] the amount of wasted contractility related to LV dyssynchrony should be taken into account in the prediction of CRT response.[14–17]

Lim et al proposed a strain delay index (SDI), using myocardial strain assessed by the 2-dimensional speckle tracking method (2DST), to estimate the potential for incremental contractility gain after CRT.[18] This index could reflect not only the time-delay of regional wall motion but also the amount of wasted energy related to LV dyssynchrony. In

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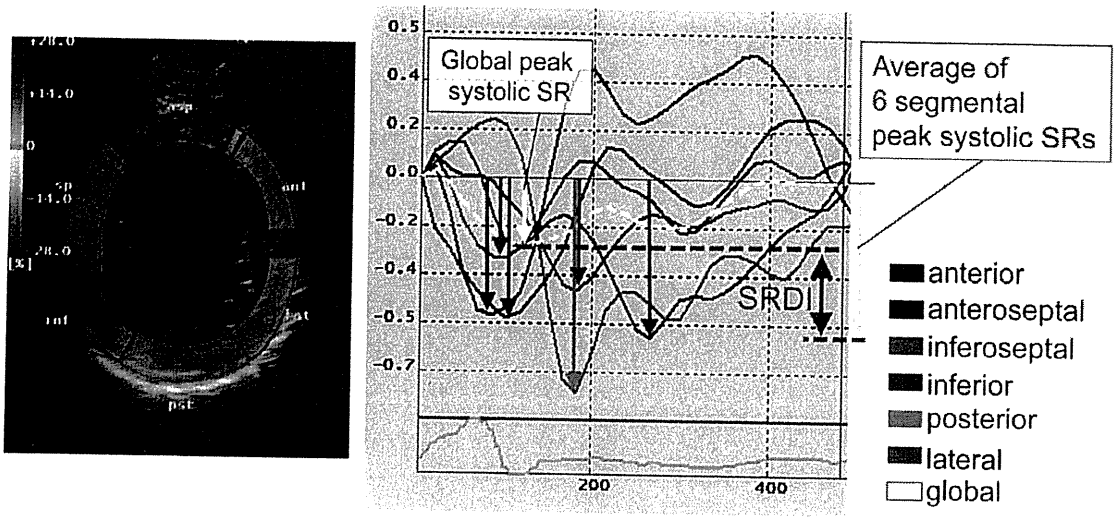

Figure 1. Demonstrable circumferential strain rate (SR) curves (**Right**) obtained from 6 segments (**Left**). The 6 colored curves indicate segmental SRs and the white, dashed curve indicates global SR. The strain rate dispersion index (SRDI) was calculated by subtracting the global peak systolic SR (white arrow) from the averaged segmental peak systolic SR (yellow arrow).

fact, they demonstrated that the SDI predicted LV reverse remodeling after CRT better than Doppler- or 2DST-derived time-delay indexes.[18] However, the myocardial strain rate (SR) may be more suitable for the evaluation of LV contractility because it is thought to be less load-dependent than strain.[19] We thus constructed an index to estimate the amount of LV contractility loss caused by dyssynchrony by using the 2DST-derived SR. The aim of the present study was to determine whether our new index, the SR dispersion index (SRDI), correlates better with the change in LV systolic function by CRT than either the time-delay indexes or the SDI.

Methods

Study Subjects and Protocol

Our study group comprised 26 consecutive patients with heart failure referred for CRT device implantation in Hokkaido University Hospital. The criteria for CRT were: (1) the presence of drug-refractory symptomatic heart failure (New York Heart Association (NYHA) functional class III or IV), (2) depressed LV systolic function defined as EF≤35%, and (3) prolonged QRS duration (≥120ms).[20] Transthoracic echocardiography including TDI and 2DST was performed before and 2 weeks after implantation of the CRT device. The study protocol was approved by the Ethics Committee of the Hokkaido University, and all patients gave informed consent before participation in the study.

CRT Device Implantation

The LV lead of the CRT device was inserted through the coronary sinus and positioned into the lateral or posterolateral cardiac vein with the help of a venogram. The right atrial and ventricular leads were positioned conventionally, and all leads were connected to the device. A dual-chamber biventricular implantable cardioverter-defibrillator (Concerto, Medtronic or Contak Renewal 4, Guidant Corporation) was implanted in all patients, except one in whom a CRT without defibrillator was implanted.

Echocardiography

All studies were performed with a commercially available ultrasound system (Aplio SSA-770A, Toshiba Medical Systems, Tochigi, Japan) with a 2.5-MHz phased array transducer. Digital 2D and color TDI cine loops were obtained in the apical 4-, 2-, and 3-chamber, and midventricular short-axis views. Care was taken to acquire the cine loops that have close intervals of the R to R wave for analysis of 2DST and TDI in patients with atrial fibrillation. The frame rates were 44–62/s (57±8) for 2D imaging used for 2DST, and 54–69/s (58±5) for TDI. The velocity range for TDI was ±15cm/s.

LV end-diastolic and end-systolic volumes were measured from the apical 4- and 2-chamber images using the biplane method of disks, and EF was calculated.[21] In patients with atrial fibrillation, LV volumes were measured over 5 consecutive beats, and these values were averaged. The mitral regurgitation was graded as severe when the volume measured by the proximal isovelocity surface area method was more than 60ml.[22]

TDI Analysis

The color TDI cine loops were analyzed off-line using commercial software (TDI-Q, Toshiba Medical Systems, Tochigi, Japan). Longitudinal tissue velocities of the LV wall were measured in the basal and mid segments in 3 apical views for a total of 12 segments. Time from the onset of QRS to peak systolic velocity during the ejection phase was measured in each segment. Next, the standard deviation of time to peak systolic velocity (TDI-SD) was calculated within the 12 segments.[8] The ejection phase was defined as the period from aortic valve opening to closure as determined by LV outflow using the pulsed Doppler method.

Speckle-Tracking Strain Analysis

Myocardial strain and SR were analyzed using 2DST software (Toshiba Medical Systems, Tochigi, Japan). The LV endocardial and epicardial borders were manually traced on an end-diastolic frame for the 3 apical views and on an end-

Table 1. Baseline Characteristics of the Study Patients

	All (n=19)	Responders (n=10)	Nonresponders (n=9)	P value
Age (year)	57±12	52±12	62±10	0.067
Male, n (%)	13 (84)	7 (70)	6 (67)	0.88
NYHA class, n (%)				
III	15 (79)	8 (80)	7 (78)	0.91
IV	4 (21)	2 (20)	2 (22)	0.91
Ischemic cardiomyopathy, n (%)	4 (21)	1 (10)	3 (33)	0.21
Electrocardiographic findings				
Atrial fibrillation, n (%)	2 (11)	0 (0)	2 (22)	0.13
QRS duration (ms)	164±24	167±27	161±22	0.63
Left bundle branch block, n (%)	11 (58)	6 (60)	5 (56)	0.84
Right ventricular pacing, n (%)	4 (21)	3 (30)	1 (11)	0.31
Echocardiographic findings				
LV end-diastolic volume (ml)	226±125	196±81	260±159	0.28
LV end-systolic volume (ml)	172±111	148±63	199±147	0.33
LV ejection fraction (%)	25±6	25±4	26±8	0.65
Global longitudinal strain (%)	−4.9±1.8	−4.6±1.9	−5.1±1.9	0.56
Severe MR, n (%)	6 (32)	2 (20)	4 (44)	0.25
Medication, n (%)				
ACEI or ARB	16 (84)	8 (80)	8 (89)	0.60
β-blocker	16 (84)	9 (90)	7 (78)	0.47
Diuretic	19 (100)	10 (100)	9 (100)	
Spironolactone	11 (58)	3 (30)	8 (89)	0.009
Amiodarone	9 (47)	5 (50)	4 (44)	0.81

P values are for comparison between responders and nonresponders.
NYHA, New York Heart Association; LV, left ventricular; MR, mitral regurgitation; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 2. Echocardiographic and Electrocardiographic Parameters at Baseline and After CRT

	Overall (n=19)		Responders (n=10)		Nonresponders (n=9)		P value
	Baseline	After CRT	Baseline	After CRT	Baseline	After CRT	
LV end-diastolic volume (ml)	226±125	212±116*	196±81	186±84	260±159	242±142	0.650
LV end-systolic volume (ml)	172±111	154±95†	148±63	130±61*	199±147	180±122	0.276
LV ejection fraction (%)	25±6	29±6‡	25±4	30±4‡	26±8	27±7	0.331
Global longitudinal strain (%)	−4.9±1.8	−5.3±1.9	−4.6±1.9	−6.0±1.8†	−5.1±1.9	−4.5±1.7*	0.555
Global longitudinal SR (s^{-1})	−0.24±0.09	−0.25±0.09	−0.24±0.10	−0.29±0.09*	−0.24±0.09	−0.22±0.73	0.996
Global circumferential SR (s^{-1})	−0.38±0.18	−0.43±0.22	−0.41±0.18	−0.52±0.25†	−0.34±0.19	−0.33±0.16	0.455
Global radial SR (s^{-1})	0.55±0.28	0.63±0.34	0.61±0.32	0.79±0.36	0.52±0.20	0.44±0.19	0.358
QRS duration (ms)	164±24	145±25†	167±27	147±24†	161±22	143±27	0.629
TDI-SD (ms)	48±10	38±13†	47±9	35±14†	48±11	41±13	0.832
LS-SD (ms)	125±51	103±30	128±53	105±32	123±51	100±30	0.819
CS-SD (ms)	91±42	75±38	80±43	61±28	102±41	89±43	0.261
RS-SD (ms)	142±54	85±47†	148±63	58±28†	135±42	132±48	0.693
L-SDI (%)	17.4±9.5	14.4±2.7	22.2±8.8	14.1±2.8*	12.2±7.6	14.7±2.7	0.017
C-SDI (%)	5.9±2.9	3.1±1.6†	6.9±3.2	2.9±1.9†	4.8±2.3	3.3±1.2	0.128
R-SDI (%)	15.7±7.8	9.2±4.7†	18.5±8.4	6.9±3.7†	12.2±6.4	12.1±4.4	0.100
L-SRDI (s^{-1})	0.19±0.09	0.17±0.05	0.25±0.08	0.16±0.05*	0.13±0.07	0.16±0.05	0.004
C-SRDI (s^{-1})	0.15±0.10	0.09±0.05†	0.19±0.10	0.10±0.05*	0.10±0.08	0.07±0.05	0.049
R-SRDI (s^{-1})	0.41±0.21	0.29±0.14	0.48±0.26	0.26±0.08*	0.32±0.10	0.34±0.19	0.130

P values are for comparison of responders and nonresponders at baseline. *P<0.05 vs. baseline, †P<0.01 vs. baseline, ‡P<0.001 vs. baseline.
CRT, cardiac resynchronization therapy; LV, left ventricular; SR, strain rate; TDI-SD, standard deviation of time to segmental peak velocities by tissue Doppler imaging; LS-SD, standard deviation of time to segmental peak longitudinal strain; CS-SD, standard deviation of time to segmental peak circumferential strain; RS-SD, standard deviation of time to segmental peak radial strain; L-SDI, longitudinal strain delay index; C-SDI, circumferential strain delay index; R-SDI, radial strain delay index; L-SRDI, longitudinal strain rate dispersion index; C-SRDI, circumferential strain rate dispersion index; R-SRDI, radial strain rate dispersion index.

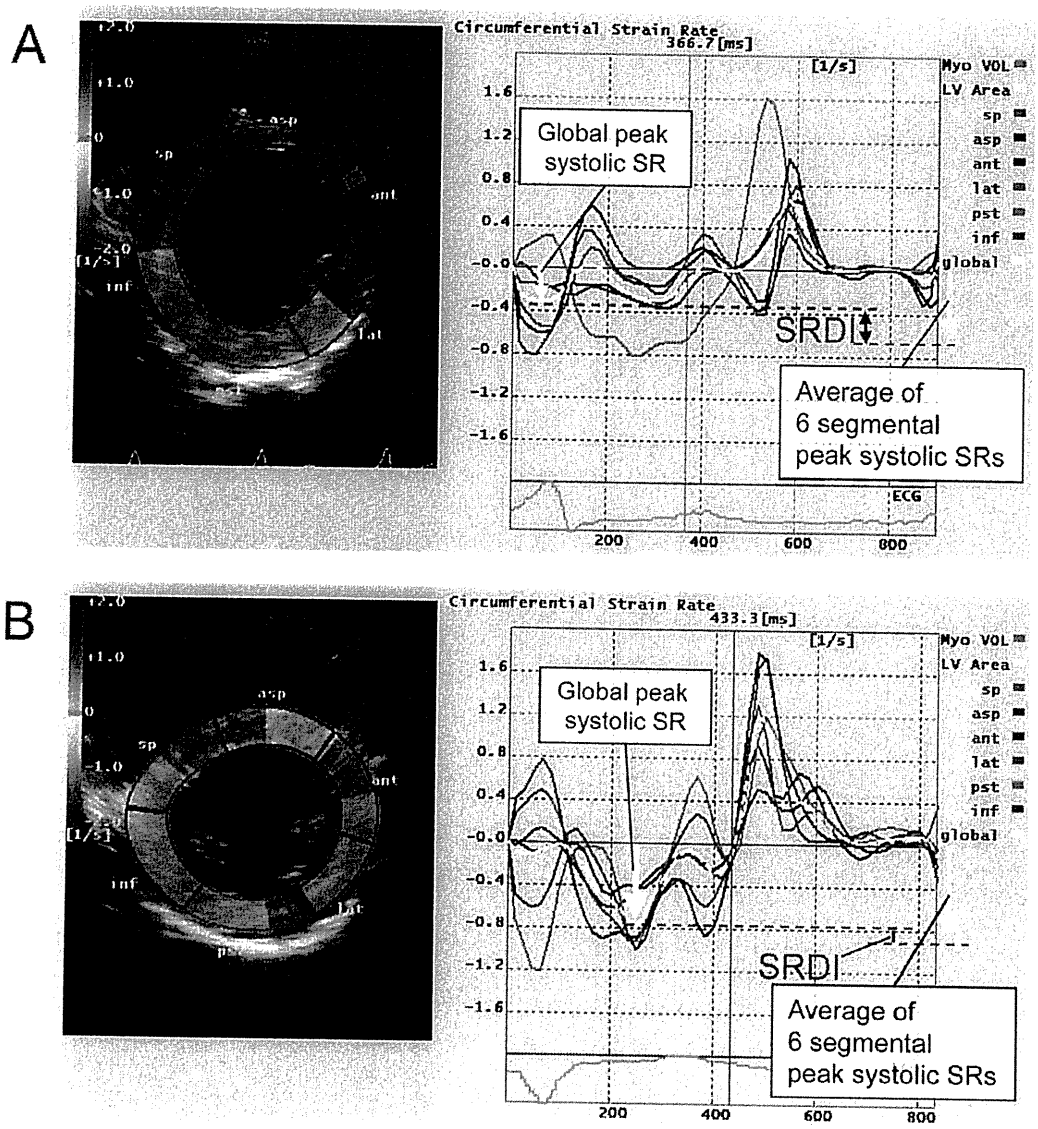

Figure 2. Time–circumferential strain rate curve obtained from a responder before (**A**) and 2 weeks after CRT (**B**). Note that the value of global peak systolic strain rate (white arrow in **B**) increased by CRT up to the level of average of 6 segmental peak systolic SRs at baseline (yellow arrow in **A**). SR, strain rate; SRDI, strain rate dispersion index.

systolic frame for the midventricular short-axis view. LV wall was divided into 6 segments within each view, and the time-strain and time–SR curves for each segment were extracted by automated tracking of the endocardial border for the longitudinal and circumferential indexes and that of both the endocardial and epicardial borders for the radial indexes. Longitudinal strain/SR curves were obtained from 3 apical views, and circumferential and radial strain/SR from the short-axis view. The standard deviation of time from the onset of QRS to segmental peak strain was calculated for the longitudinal, circumferential, and radial strains (LS-SD, CS-SD, and RS-SD, respectively).

The time-global strain curve was also extracted as reported by Lim et al, determining end-systole as the time point of peak global strain.[18] Briefly, to correct the differences of the R to R intervals among the apical images, strain values of all segments were averaged at every 2.5% of the R to R interval for the calculation of global longitudinal strain. Global circumferential and radial strains were obtained by averaging 6 segmental strains at each frame in the short-axis view. Peak strain (ε_{peak}) and strain at end-systole (ε_{ES}) were measured in each segment. Next, the longitudinal SDI (L-SDI) was measured as the sum of ($\varepsilon_{peak}-\varepsilon_{ES}$) from the 16 segments in the 3 apical views. The circumferential SDI (C-SDI) and radial SDI (R-SDI) were calculated from 6 segments in the short-axis view. In the segments that showed the strain in the stretching direction or biphasic strain with the absolute value of the stretching strain greater than the shortening strain, ($\varepsilon_{peak}-\varepsilon_{ES}$) were counted as zero.[18]

The SRDI was calculated as a new index of global LV

contractility loss caused by dyssynchrony. Peak systolic SRs were measured in all segments within each view. We also extracted the time–global SR curve by averaging all segmental SRs at every 2% of the R to R interval and measured global peak systolic SR. The SRDI was then calculated as the average of the segmental peak systolic SRs minus global peak systolic SR (Figure 1). The longitudinal SRDI (L-SRDI) was derived from the 3 apical views, and the circumferential SRDI (C-SRDI) and radial SRDI (R-SRDI) were derived from the short-axis view.

The accuracy of speckle tracking for each myocardial segment was visually judged by 2 independent observers. Patients who had 2 or more segments judged as having inadequate tracking quality in at least one view were excluded.

Estimation of LV Systolic Function

LV systolic function was estimated by global longitudinal strain and EF before and 2 weeks after CRT. Response to CRT were defined as an improvement of ≥0.3% in global longitudinal strain at follow-up.

Statistical Analysis

Continuous variables are expressed as mean±SD and compared with the 2-tailed Student's t-test for paired and unpaired data. Proportions were compared using chi-square analysis. Linear regression analysis was carried out for the detection of correlation between 2 continuous variables. Receiver-operating characteristic (ROC) curves were determined to evaluate the diagnostic performance of the time-delay indexes and indexes of LV contractility loss to detect responders to CRT. For all tests, $P<0.05$ was considered significant.

Results

Patients' Baseline Characteristics

Of the 26 patients, 7 were excluded because of inadequate tracking quality of 2DST. Thus, the final study group consisted of 19 patients, whose baseline characteristics are summarized in Table 1. All patients had heart failure symptoms (NYHA class III or IV) with severe LV dysfunction and wide QRS duration; 15 patients had left bundle branch block (58%) or right ventricular pacing rhythm (21%) and the other causes of prolonged QRS duration were intraventricular conduction disturbance in 3 patients and right bundle branch block in 1 patient. Etiology was ischemic for 21% of all patients. Medications were optimal for heart failure, including angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, β-blockers, diuretics, and spironolactone.

Acute Responses to CRT

A CRT device was successfully implanted in all patients without any complications. None of the patients died or underwent heart transplantation during the follow-up. Two weeks after the implantation of the CRT device, NYHA functional class was significantly reduced from 3.2±0.4 to 2.8±0.4 ($P<0.05$). The QRS duration decreased. EF significantly increased and global longitudinal strain tended to increase after CRT, but did not reach statistical significance (Table 2). Global longitudinal, circumferential, and radial SRs did not change after CRT in the overall patient group. There was a significant correlation between EF and global longitudinal strain ($R=-0.57$, $P<0.001$).

The time-delay indexes, such as TDI-SD and RS-SD, and indexes of LV contractility loss, including the C-SDI, R-SDI, and C-SRDI, significantly decreased from baseline values after CRT, whereas the LS-SD, CS-SD, L-SDI, L-SRDI, and R-SRDI did not change (Table 2).

Table 3. Correlation Between Echocardiographic Parameters and the Change in LV Systolic Function by CRT

	Δglobal longitudinal strain		ΔEF	
	R	P value	R	P value
QRS duration	−0.31	0.204	0.41	0.09
TDI-SD	−0.09	0.712	0.05	0.83
LS-SD	−0.40	0.090	0.27	0.26
CS-SD	−0.02	0.941	−0.09	0.73
RS-SD	−0.31	0.198	0.14	0.56
L-SDI	−0.59	0.008	0.64	0.003
C-SDI	−0.30	0.220	0.29	0.23
R-SDI	−0.26	0.279	0.23	0.34
L-SRDI	−0.69	0.001	0.76	<0.001
C-SRDI	−0.47	0.045	0.34	0.15
R-SRDI	−0.36	0.13	0.28	0.24

Abbreviations see in Tables 1,2.

Acute Responses in Responders vs. Nonresponders

Among the 19 patients, there were 10 acute responders (53%) defined as an increase in global longitudinal strain after CRT (Δglobal LSt) ≥0.3%. The remaining 9 patients (47%) were classified as nonresponders. Responders showed a significant increase in EF and a slightly but significant decrease in LV end-systolic volume (Table 2). In contrast, nonresponders showed no changes in either of these parameters. Moreover, responders showed significantly improved global longitudinal strain, global longitudinal SR, and global circumferential SR whereas nonresponders did not. Global radial SR tended to increase in responders, but did not reach statistical significance (Table 2). Among the responders, QRS duration decreased (Table 2). RS-SD significantly decreased with CRT in the responders but not LS-SD and CS-SD (Table 2). The L-SDI, C-SDI, R-SDI, L-SRDI, C-SRDI, and R-SRDI all decreased with CRT in the responders (Table 2, Figure 2). In contrast, none of these parameters changed in the nonresponders (Table 2).

Prediction of Response to CRT

Baseline clinical and echocardiographic parameters were comparable between responders and nonresponders, except for spironolactone use (Table 1). The L-SDI, L-SRDI and C-SRDI at baseline were significantly higher in responders than in nonresponders (Table 2).

Linear regression analyses showed that neither QRS duration nor the TDI-SD at baseline correlated with Δglobal LSt (Table 3). The LS-SD, CS-SD, RS-SD, C-SDI, R-SDI, and R-SRDI did not correlate with Δglobal LSt (Table 3, Figure 3). In contrast, the L-SDI, L-SRDI and C-SRDI significantly correlated with Δglobal LSt (Table 3, Figure 3). Similar trend was observed when LV systolic function was estimated by EF (Table 3).

ROC analyses for predicting the responders showed that, among these parameters, the L-SRDI had the largest area under the ROC curve. The L-SDI, L-SRDI, and C-SRDI could significantly discriminate between responders and nonresponders (Table 4).

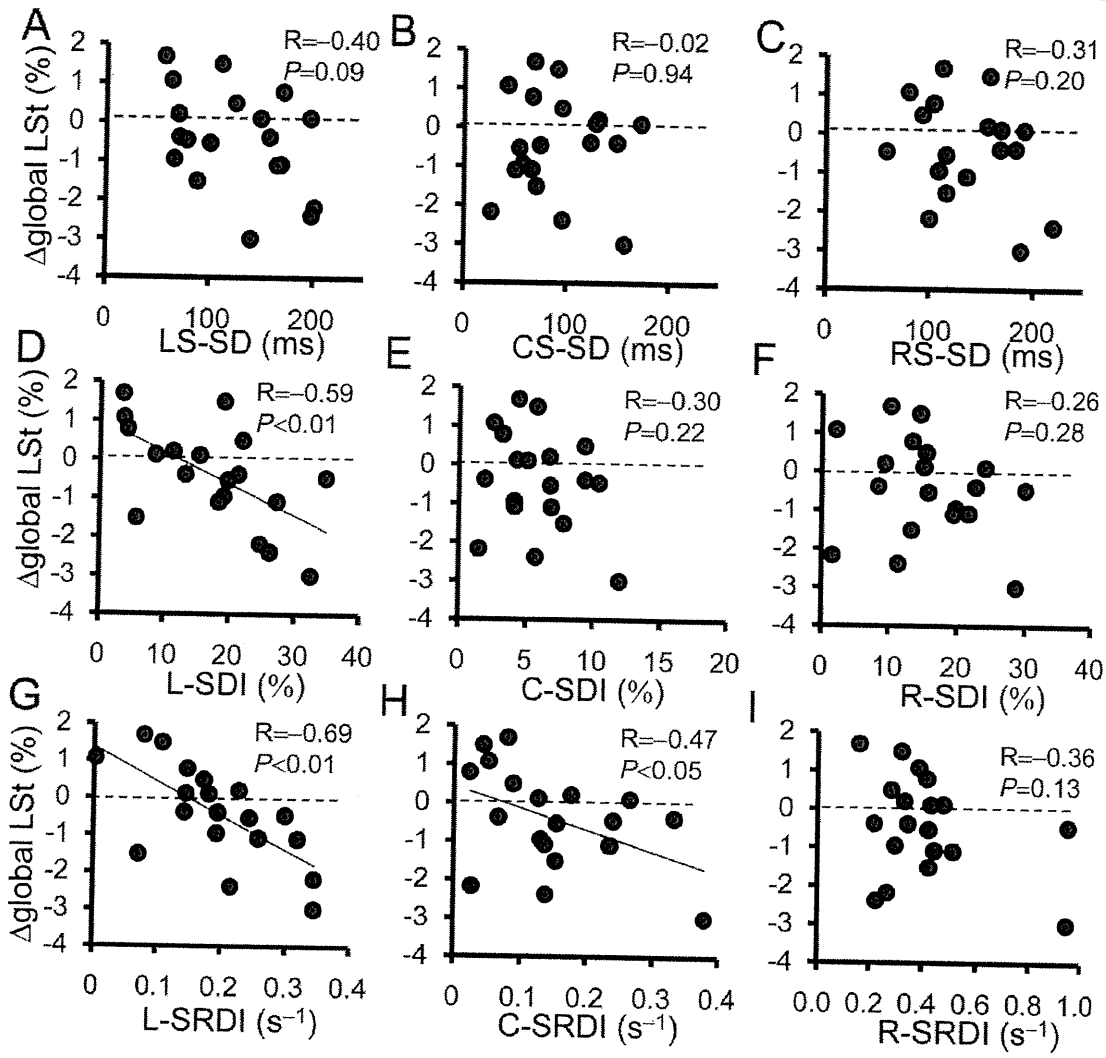

Figure 3. Correlations between Δglobal LSt and LS-SD (**A**), CS-SD (**B**), RS-SD (**C**), L-SDI (**D**), C-SDI (**E**), R-SDI (**F**), L-SRDI (**G**), C-SRDI (**H**), and R-SRDI (**I**). Δglobal LSt, changes in global longitudinal strain before and after CRT. LS-SD, standard deviation of time to peak longitudinal strain; CS-SD, standard deviation of time to peak circumferential strain; RS-SD, standard deviation of time to peak radial strain; L-SDI, longitudinal strain delay index; C-SDI, circumferential strain delay index; R-SDI, radial strain delay index; L-SRDI, longitudinal strain rate dispersion index, C-SRDI, circumferential strain rate dispersion index; R-SRDI, radial strain rate dispersion index.

Table 4. AUC for Predicting Responders to CRT

	AUC	95% CI	P value
TDI-SD	0.49	0.21–0.77	0.94
LS-SD	0.57	0.30–0.84	0.62
CS-SD	0.34	0.09–0.60	0.25
RS-SD	0.54	0.28–0.81	0.74
L-SDI	0.81	0.62–1.00	0.02
C-SDI	0.70	0.50–0.97	0.14
R-SDI	0.73	0.49–0.98	0.09
L-SRDI	0.89	0.70–1.00	0.006
C-SRDI	0.78	0.55–1.00	0.04
R-SRDI	0.68	0.43–0.92	0.19

P values are for AUCs vs. the null hypothesis of a true area of 0.5. AUC, area under the receiver-operating curve; CI, confidence interval. Other abbreviations see in Table 2.

Reproducibility

Intra- and interobserver variabilities of EF were both 7% in our laboratory. Reproducibility of strain and SR measurements were assessed in 10 randomly selected patients. Analyses of global longitudinal strain, LS-SD, CS-SD, RS-SD, L-SDI, C-SDI, R-SDI, L-SRDI, C-SRDI, and R-SRDI were performed by 2 independent observers using the same 2D cine loop and the same cardiac cycle. A single blinded observer repeated the analyses after an interval of 2 weeks. The respective intra- and interobserver variabilities were 0.5% (9%) and 0.5% (10%) for global longitudinal strain, 12 ms (10%) and 20 ms (16%) for LS-SD, 17 ms (18%) and 19 ms (19%) for CS-SD, 26 ms (20%) and 31 ms (24%) for RS-SD, 1.9% (12%) and 3.0% (17%) for L-SDI, 0.9% (16%) and 0.9% (17%) for C-SDI, 2.9% (19%) and 3.9% (25%) for R-SDI, 0.02 s^{-1} (10%) and 0.03 s^{-1} (17%) for L-SRDI, 0.02 s^{-1}

(13%) and 0.02 s^{-1} (15%) for C-SRDI, and 0.07 s^{-1} (18%) and 0.09 s^{-1} (22%) for R-SRDI.

Discussion

This is the first study to demonstrate that a novel index of LV contractility loss because of dyssynchrony, the SRDI, could predict acute responders to CRT. Furthermore, the SRDI correlated well with the improvement in LV systolic function.

CRT has been shown to improve LV function and survival in NYHA III–IV patients with severe LV dysfunction and a wide QRS.[1–5] However, more than 30% of patients selected on the basis of QRS duration do not respond to CRT,[2,6] suggesting that mechanical rather than electrical dyssynchrony can better predict the response to CRT. Measurement of regional peak-systolic velocities with TDI has been shown to be highly predictive for the response to CRT and prognosis.[7–9] However, limitations of the time-delay indexes measured by TDI to assess LV mechanical dyssynchrony for the prediction of response to CRT have been reported.[10,23] The limited accuracy of the TDI parameters to predict the response to CRT might have several reasons. First, the accuracy of measurement of regional myocardial velocities by TDI is limited by ultrasound angle dependency and tethering effects, which are especially prominent in the dilated LV commonly seen in patients with severe heart failure who require CRT.[24,25] Second and more importantly, the time-delay indexes do not take regional myocardial contractility into account. In the presence of a conduction disturbance, especially in left bundle branch block or right ventricular pacing, asynchronous electrical activation causes redistribution of myocardial shortening and external work, which is associated with a reduction in LV global systolic function.[11–13] CRT improves the heterogeneity of myocardial shortening by activation of the latest activated site, resulting in augmentation of global LV contractility.[26] Therefore, dyscoordination of contraction can more directly associate with the improvement of LV systolic function by CRT than the dispersion of the timing of regional contraction. In fact, the present study demonstrated that the time-delay indexes derived from TDI and 2DST could not predict the changes in LV systolic function (**Tables 3,4**).

The indexes of dyscoordination, which measure the amount of both myocardial stretch and shortening during systole, were recently reported to better correlate with the immediate[15] and chronic responses to CRT[14,16,17] than the time-delay indexes. The SDI, an index of wasted energy caused by dyssynchrony, has been also reported as a strong predictor of the response to CRT.[18] This index can account for the difference between ε_{peak} and ε_{ES}, which represents wasted energy caused by dyssynchrony per segment and sums these values in all LV segments. The SDI can be regarded as a dyscoordination index, but is somewhat different because it does not measure the amount of stretch. Therefore, we consider that our new index, the SRDI, is a logical extension of SDI. The concept of the SRDI is based on the idea that the wasted contractility from mechanical dyssynchrony can be the acute gain of contractility expected to be obtained by CRT. The average of the segmental peak systolic SR was estimated as global LV systolic function when the contraction is synchronized and global peak systolic SR was measured as the actual global LV systolic function in the presence of mechanical dyssynchrony. Therefore, the SRDI, the difference between the estimated and actual global LV systolic function, can estimate the increase of global LV systolic function by the correction of dyssynchrony. Indeed, the present results demonstrated that the SRDI correlated better than the time-delay indexes with the changes in LV systolic function by CRT.

The present results support previous findings that indexes of LV systolic function wasted by mechanical dyssynchrony correlate better with the CRT response than the time-delay indexes.[14–18] Our study, as well as that by Lim et al, demonstrated that both the SDI and SRDI correlated with the changes in LV systolic function after CRT. We thus consider that our index, the SRDI, is suitable for predicting the acute response to CRT for several reasons. First, although myocardial strain substantially depends on the afterload, the myocardial SR is less load-dependent.[19] Therefore, SR can more accurately reflect regional systolic function than strain. Second, the segment that shows biphasic strain with myocardial stretching, (ε_{peak}–ε_{ES}) is estimated as zero for the calculation of SDI, which is acceptable in a segment with predominantly scarred myocardium. On the contrary, in the segment with viable myocardium remaining, the SDI may underestimate regional systolic function. In contrast, the SRDI can detect the decreased contractility of residual viable myocardium by measuring segmental peak systolic SR. Third, for the calculation of the SDI, the strain values need to be measured at 2 time points for each segment, whereas the SRDI can be calculated by measuring only the peak SR for each segment and the peak SR on the global SR curve. In addition, the 2DST-software can automatically measure the peak SR on a time–SR curve. Hence, the SRDI is a simpler than the SDI and can be used more easily in routine clinical practice.

It is generally considered that the reproducibility of the SR is substantially lower than that of strain when derived from 2DST. In the present study, however, the reproducibilities of the SDI and SRDI were similar. The calculation of the SDI needs 2 time points to be measured for each segmental strain curve, whereas the SRDI can be calculated by measuring peak SR alone for each segment. This difference in the number of measurement points could be a reason why the reproducibility of the SRDI was not worse than that of the SDI. In addition, the image quality was relatively good in our study population, resulting in less noisy SR curves being obtained in most of the patients.

Study Limitations

First, the results were obtained from a relatively small number of patients in a single center. Therefore, we have to acknowledge that this study is preliminary and further study with a larger number of patients is necessary to confirm the efficacy of the SRDI. Second, the SRDI cannot be applied to the patients for whom optimal echocardiographic images are not available. We excluded 7 of the original 26 patients (27%) because of inadequate image quality, whichis is similar to the 30% excluded by Lim et al.[18] Third, we have to acknowledge that the follow-up period was short. We analyzed only the immediate changes in LV systolic function by CRT whereas the response to CRT is usually a combination of both immediate changes in systolic function and short-term reduction of LV volumes.[27] Thus, it must be determined whether the SRDI is effective in predicting the longer term beneficial response to CRT. In addition, we evaluated LV systolic function by global longitudinal strain, because it is generally considered to be a more sensitive marker of systolic function than EF. Even though the cut-off values of global longitudinal strain were somewhat arbitrary, it was significantly correlated with EF in our study patients.

Moreover, the parallel behavior between global strain and EF has been confirmed by the previous study by Brown et al.[28] Fourth, although the frame rates of 2DST were comparable to those used in a previous report of the 2DST-derived SR,[29] those of the TDI were considerably low, which could reduce the accuracy of the TDI-SD. Fifth, contrary to previously reported results,[16,30,31] none of the radial indexes correlated with the changes in LV systolic function after CRT in the present study. The automated tracking of both the endo- and epicardial borders obtained from the dilated LV, in which adequate images including the entire epicardium were difficult to obtain, might deteriorate the reproducibility of radial indexes. We consider this lead to the radial indexes being ineffective in predicting the response to CRT. Sixth, because the dispersion of the timing of the peak SRs was not analyzed, we could not demonstrate a uniform comparison of timing vs. amplitude parameters for both strain and SR in the present study. Seventh, the L-SDI and L-SRDI strongly correlated with the changes in LV systolic function after CRT in the present study, whereas the C-SDI and C-SRDI had a weak correlation. Lim et al also reported that longitudinal strain better reflected regional or global wall motion than circumferential or radial strain.[18] On the other hand, studies using magnetic resonance imaging reported the utility of circumferential strain for the evaluation of mechanical dyssynchrony.[32,33] Therefore, it remains to be determined which direction of strain/SR can better predict functional improvement after CRT and further investigations are needed to clarify this issue.

Conclusions

SRDI, a novel index of LV contractility loss because of mechanical dyssynchrony, correlated fairly well with an improvement of global LV systolic function after CRT. This new index is expected to be predictive of the long-term beneficial effects of CRT.

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Hyperuricemia predicts adverse outcomes in patients with heart failure

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ABSTRACT

Background: Hyperuricemia is associated with worse outcomes of patients with chronic heart failure (HF). However, it is unknown in an unselected HF patients encountered in routine clinical practice. We thus assessed the impact of hyperuricemia on long-term outcomes including mortality and rehospitalization among patients hospitalized with worsening HF.

Methods: The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) studied prospectively the characteristics and treatments in a broad sample of hospitalized HF patients and the outcomes were followed for 2.1 years after discharge. Study cohorts ($n=1869$) were divided into 2 groups according to serum uric acid (UA) at discharge; ≥7.4 mg/dL ($n=908$) and <7.4 mg/dL ($n=961$).

Results: Of the total cohort of HF patients, 56% had hyperuricemia defined as UA≥7.0 mg/dl. Patients with UA≥7.4 mg/dL had higher rates of all-cause death, cardiac death, rehospitalization, and all-cause death or rehospitalization due to worsening HF. After multivariable adjustment, higher UA levels were a significant and independent predictor for all-cause death (adjusted hazard ratio [HR] 1.413, 95% confidence interval [CI] 1.094–1.824, $P=0.008$) and cardiac death (adjusted HR 1.399, 95% CI 1.020–1.920, $P=0.037$).

Conclusions: Hyperuricemia was common in patients with HF encountered in clinical practice and higher UA was independently associated with long-term adverse outcomes in these patients.

1. Introduction

High serum uric acid (UA) or hyperuricemia has been well demonstrated to be associated with morbidity and mortality in general population [1–3] as well as in patients with coronary artery disease [4,5]. It is also associated with poor outcomes in patients with mild to severe heart failure (HF) [6–9]. Hyperuricemia in HF may be due to the upregulation of the xanthine oxidase (XO), a key enzyme in the generation of oxygen free radicals. Therefore, it may induce proinflammatory activation [10], impaired oxidative metabolism [11], vascular endothelial dysfunction [12], and exercise intolerance [13,14] in HF. These conditions may well explain the association between hyperuricemia and poor outcome in chronic [6,8] as well as acute HF [9]. However, previous studies enrolled small numbers of HF patients ($n=100$–500) and were performed in a single center [6,8,9]. The impact of hyperuricemia on outcomes has not been assessed in a broad cohort of HF patients. Therefore, the purpose of this study was to examine the prevalence of hyperuricemia in HF patients encountered in routine clinical practice and to determine whether it is independently associated with the long-term outcomes. We analyzed the data from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD), a prospective database of the clinical characteristics, treatments, and outcomes in a broad sample of patients hospitalized with worsening HF in Japan [15–19].

2. Materials and methods

2.1. Study patients

The details of the JCARE-CARD have been described previously [15]. Briefly, eligible patients were those hospitalized due to worsening HF as the primary cause of admission. The patients with acute HF were excluded. For each patient, baseline data obtained at discharge included (1) demography; (2) causes of HF; (3) precipitating causes; (4) comorbidities; (5) complications; (6) clinical status; (7) electrocardiographic and echocardiographic findings; (8) plasma brain-type natriuretic peptide (BNP); and (9) treatments including discharge medications. Histories of hypertension, diabetes mellitus, hyperlipidemia, prior stroke, chronic obstructive pulmonary disease (COPD), smoking, prior myocardial infarction, and sustained ventricular tachycardia/fibrillation (VT/VF) were recorded if they were documented at the discharge of index hospitalization. The definition of each comorbidity was described in our previous report [15]. The diagnosis of atrial fibrillation (AF) was based on a 12-lead standard electrocardiogram performed during the hospitalization.

The JCARE-CARD enrolled a total of 2675 patients hospitalized for HF at 164 participating hospitals. Individual participating hospitals entered the data using a web-based electronic data capture (EDC) system licensed by the JACRE-CARD (www.jcare-card.jp). 806 patients were excluded with missing data of serum uric acid, resulting in 1869 patients included in this analysis. They were divided into 2 groups according to serum UA levels at discharge; ≥7.4 mg/dL ($n=908$) and <7.4 mg/dL ($n=961$).

2.2. Outcomes

The status of all patients was surveyed after discharge and the following information was obtained: (1) survival, (2) causes of death, and (3) the rehospitalization due to an

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exacerbation of HF that required more than continuation of their usual therapy on prior admission. Only patients who survived the initial hospitalization were included in the follow-up analysis. Out of 1869 patients, 104 patients (5.6%) who died during the hospitalization and 145 patients (7.7%) who were missed during the follow-up were excluded from the follow-up analysis. Follow-up data were obtained in 1620 out of 1869 patients (86.7%). Mean post-discharge follow-up was 777 ± 312 days (2.1 ± 0.9 years).

2.3. Statistical analysis

Patient characteristics and treatments were compared using Pearson chi-square test for categorical variables and Mann–Whitney *U* test for continuous variables. Multiple linear regression analysis was used to select those variables that were significantly associated with serum UA levels. The model was obtained by using a stepwise regression selection. Cumulative event-free rates during the follow-up were derived using the method of Kaplan and Meier. The relationship between the serum UA level at baseline and outcomes was evaluated among patients with multivariable adjustment. Baseline clinical variables, treatment factors, and the severity of HF at discharge were used in developing the post-discharge Cox proportional hazard models. A *P* value of <0.05 was used for criteria for variables to stay in the model. SPSS version 16.0 J for Windows was used for all statistical analyses.

3. Results

3.1. Patient characteristics

Fig. 1 shows the distribution of serum UA among 1869 patients. Mean serum UA level in the study subjects was 7.3 ± 2.4 mg/dL, ranging from 0.3 to 22.5 mg/dL. 1041 (55.7%) patients had hyperuricemia defined as serum UA ≥ 7.0 mg/dL.

The mean age of the total cohort was 71.1 ± 12.9 years and 60.0% was men (Table 1). The causes of HF were ischemic in 32.5%, valvular in 28.5%, hypertensive in 25.9%, and dilated cardiomyopathy in 17.7%. The mean echocardiographic left ventricular ejection fraction (LVEF) was 44.6 ± 16.4%.

Patients with serum UA ≥ 7.4 mg/dL were more often men and significantly higher body mass index (BMI) (Table 1). Causes of HF did not differ between groups. They were more likely to be smoker and have chronic atrial fibrillation and coronary artery bypass grafting (CABG). Serum creatinine and plasma BNP levels were significantly higher and estimated glomerular filtration rate (eGFR) was lower in patients with serum UA ≥ 7.4 mg/dL. They had greater LV end-diastolic and end-systolic diameters and lower LVEF. The implantations of ICD, CRT, and CRT-D were not significantly different between 2 groups.

Patients with serum UA ≥ 7.4 mg/dL were prescribed more by diuretics, especially loop diuretics, and digitalis at discharge (Table 2). However, the use of other medications such as angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and β-blocker did not differ between groups.

3.2. Variables associated with serum UA levels

In a multiple linear regression analysis, younger age [standardized partial regression coefficients (β) 0.183, $P<0.001$], male gender (β 0.092, $P=0.013$), lower eGFR (β 0.405, $P<0.001$), higher hemoglobin concentration (β 0.120, $P=0.004$), and diuretics use (β 0.103, $P=0.003$) were significantly associated with serum UA levels. Low eGFR was the most important factor in this model. However, the multiple correlation coefficient (R^2) of the model entered these five variables was 0.190, indicating that the contribution of these variables to serum UA levels would be minor.

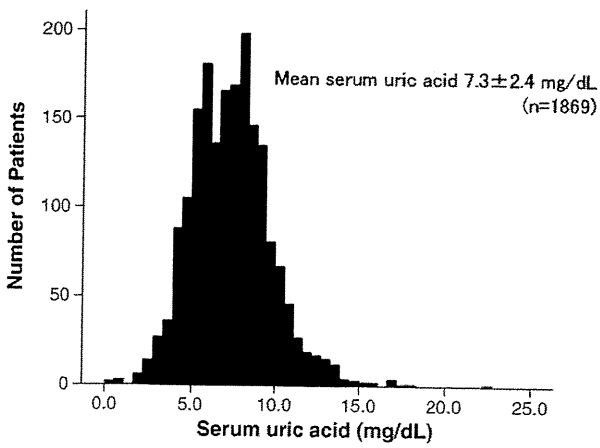

Fig. 1. The distribution of serum UA (mg/dL) at baseline among 1869 patients.

Table 1
Baseline patient characteristics.

Characteristics	Total ($n=1869$)	UA≥7.4 mg/dL ($n=908$)	UA<7.4 mg/dL ($n=961$)	*P* value
Demographics				
Age, yrs (mean ± SD)	71.1 ± 12.9	70.4 ± 14.0	71.8 ± 11.8	0.243
Male, %	60.0	67.4	53.0	<0.001
BMI, kg/m^2	22.3 ± 4.1	22.5 ± 4.1	22.1 ± 4.1	0.013
Causes of heart failure, %				
Ischemic	32.5	33.0	32.0	0.648
Valvular heart disease	28.5	28.7	28.3	0.833
Hypertensive	25.9	24.9	27.0	0.310
Dilated cardiomyopathy	17.7	18.5	17.0	0.383
Hypertrophic cardiomyopathy	1.9	2.1	1.7	0.496
Medical history, %				
Hypertension	53.4	54.4	52.4	0.395
Diabetes mellitus	31.5	32.0	31.1	0.702
Hyperlipidemia	25.0	25.8	24.2	0.436
Prior stroke	16.1	16.7	15.5	0.500
COPD	6.7	7.2	6.2	0.408
Smoking	38.2	43.7	32.9	<0.001
Prior myocardial infarction	27.5	28.2	26.8	0.502
Atrial fibrillation	35.5	38.1	33.0	0.022
Sustained VT/VF	6.5	6.5	6.5	0.968
Previous procedures, %				
PCI	18.5	18.0	19.0	0.590
CABG	9.1	10.6	7.7	0.030
Valvular surgery	7.0	7.1	6.9	0.906
ICD	2.2	2.2	2.2	0.972
CRT	1.6	1.7	1.5	0.830
CRT-D	0.2	0.1	0.2	0.611
Vital signs at discharge				
NYHA functional class	1.8 ± 0.7	1.8 ± 0.7	1.7 ± 0.7	0.006
NYHA classes 3 and 4, %	10.2	11.1	9.3	0.192
Heart rate, bpm	70.6 ± 12.3	70.2 ± 12.4	71.0 ± 12.1	0.156
SBP, mmHg	117.7 ± 19.2	117.1 ± 18.9	118.2 ± 19.4	0.260
DBP, mmHg	66.2 ± 11.9	66.1 ± 12.4	66.3 ± 11.4	0.938
Laboratory data at discharge				
Serum creatinine, mg/dl	1.4 ± 1.2	1.6 ± 1.3	1.2 ± 1.1	<0.001
eGFR, ml/min/1.73 m^2	51.1 ± 25.2	42.4 ± 20.9	58.5 ± 26.1	<0.001
Hemoglobin, g/dL	12.1 ± 2.6	12.0 ± 2.7	12.1 ± 2.6	0.289
Plasma BNP, pg/ml	403 ± 539	485 ± 643	327 ± 405	<0.001
Echocardiographic data at discharge				
LV EDD, mm	55.7 ± 10.3	57.1 ± 10.9	54.4 ± 9.5	<0.001
LV ESD, mm	43.0 ± 12.3	44.8 ± 12.8	41.4 ± 11.6	<0.001
LVEF, %	44.6 ± 16.4	42.8 ± 16.4	46.1 ± 16.3	0.002

BMI, body mass index; COPD, chronic obstructive pulmonary disease; VT/VF, ventricular tachycardia/fibrillation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy device with defibrillator; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; BNP, brain-type natriuretic peptide; LV, left ventricular; EDD, end-diastolic diameter; ESD, end-systolic diameter; EF, ejection fraction. Values are percent or means ± SD.

3.3. Outcomes

During the follow-up of 2.1 years after hospital discharge, the rates of adverse outcomes were as follows; all-cause death 21.0%, cardiac death 13.5%, rehospitalization due to the worsening HF 36.5%, and all-cause death or rehospitalization 43.9% (Fig. 2). These event rates were significantly higher in patients with serum UA ≥ 7.4 mg/dL.

On multivariate analysis with patients with serum UA < 7.4 mg/dL as the reference, patients with serum UA ≥ 7.4 mg/dL had adverse risk for all-cause death (adjusted hazard ratio [HR] 1.413, 95% confidence interval [CI] 1.094–

Table 2
Medication use at hospital discharge.

	Total (n = 1869)	UA ≥ 7.4 mg/dL (n = 908)	UA < 7.4 mg/dL (n = 961)	P value
ACE inhibitor, %	36.9	36.1	37.6	0.527
ARB, %	45.8	45.2	46.4	0.617
β blocker, %	48.3	47.9	48.6	0.785
Diuretics, %	88.6	91.4	85.9	<0.001
Loop diuretics, %	80.1	84.4	76.0	<0.001
Thiazide diuretics, %	3.6	4.1	3.2	0.275
Potassium sparing diuretics, %	41.6	41.2	42.0	0.719
Digitalis, %	31.5	34.0	29.2	0.030
Ca channel blocker, %	25.8	27.3	24.4	0.168
Nitrates, %	24.4	24.0	24.8	0.671
Antiarrhythmics, %	16.4	16.9	15.9	0.579
Aspirin, %	47.1	47.9	46.3	0.491
Warfarin, %	40.8	41.8	40.0	0.438
Statin, %	19.8	19.0	20.6	0.406

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

1.824, P = 0.008) and cardiac death (adjusted HR 1.399, 95% CI 1.020–1.920, P = 0.037) (Table 3). Therefore, serum UA levels were significantly associated with long-term adverse outcomes including all-cause death and cardiac death even after adjustment for all other covariates including eGFR and the use of diuretics. They were also associated with rehospitalization due to worsening HF (unadjusted HR 1.248, P = 0.040) and all-cause death or rehospitalization (unadjusted HR 1.322, P = 0.013), which, however, did not reach statistical significance after multivariable adjustment (adjusted HR 1.025, P = 0.801 and adjusted HR 1.089, P = 0.304) (Table 3). CABG was not significantly associated with any endpoints including all-cause death, cardiac death, rehospitalization, and all-cause death or rehospitalization. ICD implantation was significantly associated with rehospitalization (adjusted HR 2.094, 95% CI 1.340–3.273, P = 0.001) and all-cause death or rehospitalization (adjusted HR 1.844, 95% CI 1.186–2.868, P = 0.007). CRT implantation was associated with cardiac death (adjusted HR 2.668, 95% CI 1.164–6.114, P = 0.020), rehospitalization (adjusted HR 2.248, 95% CI 1.327–3.809, P = 0.003), and all-cause death or rehospitalization (adjusted HR 2.009, 95% CI 1.192–3.386, P = 0.009). In contrast, valvular surgery was associated with lower rates of all-cause death (adjusted HR 0.466, 95% CI 0.238–0.910, P = 0.025) and cardiac death (adjusted HR 0.419, 95% CI 0.184–0.951, P = 0.038). However, the inclusion of these procedures as covariates in the Cox regression model did not change our original results shown in Table 3.

The independent predictors associated with all-cause death among those entered into the Cox proportional hazard analysis were serum UA, BMI, eGFR, plasma BNP, age, and NYHA functional class (Table 4). There was 6.8% increase in all-cause death for each 1 mg/dL increase in serum UA level (P = 0.017).

4. Discussion

The present study demonstrated that hyperuricemia was seen in 56% of the patients hospitalized with HF. They had higher serum

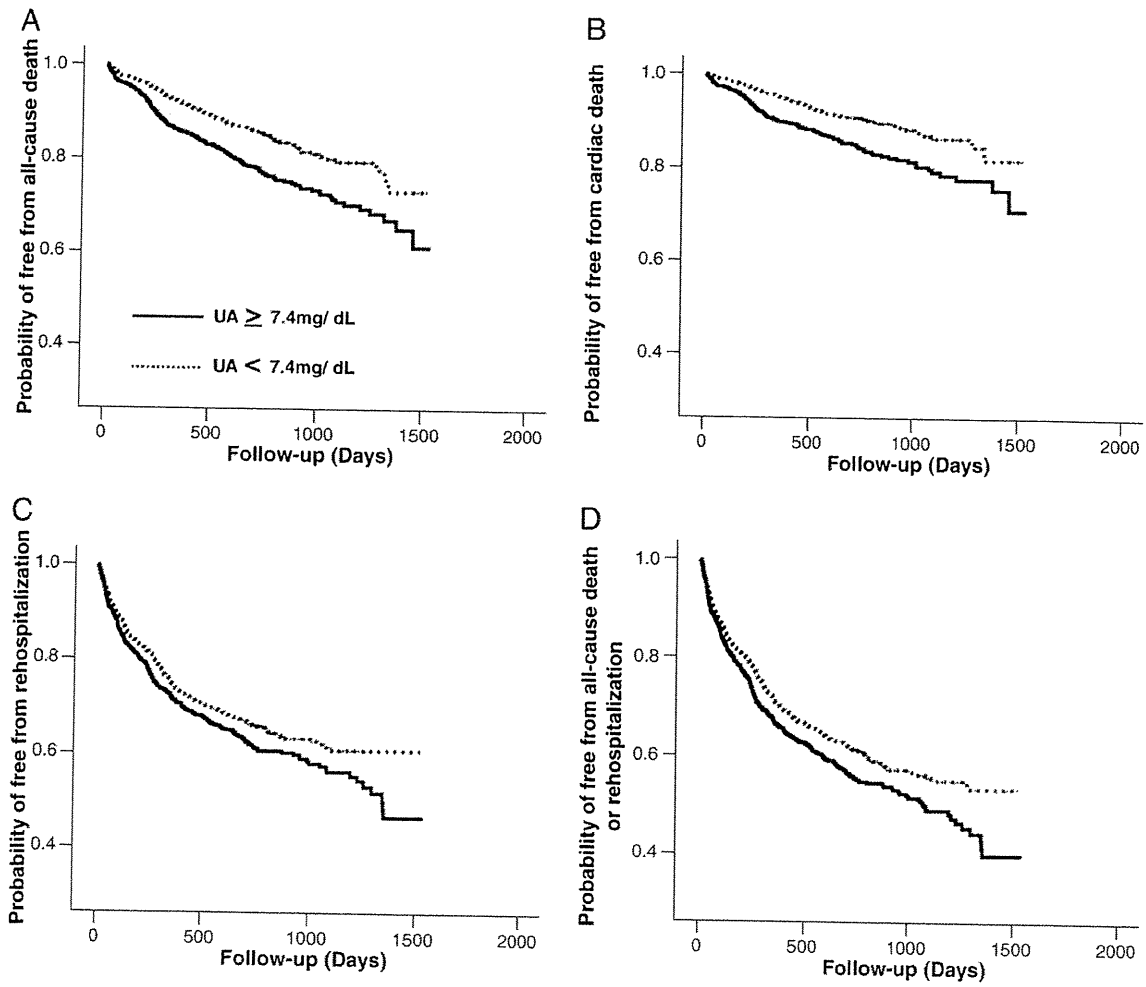

Fig. 2. Kaplan–Meier event-free curves free from all-cause death (A), cardiac death (B), rehospitalization due to worsening HF (C), and all-cause death or rehospitalization (D) comparing patients with serum UA ≥ 7.4 mg/dL (solid lines) and those with serum UA < 7.4 mg/dL (dashed lines).

Table 3
Cox analysis for hazard ratios of outcomes associated with the UA level.

Outcomes	Number (%)					
	UA≥7.4 mg/dl ($n=776$)	UA <7.4 mg/dl ($n=844$)	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
All-cause death	199 (25.6)	141 (16.7)	1.772 (1.388–2.261)	<0.001	1.413 (1.094–1.824)	0.008
Cardiac death	132 (17.0)	87 (10.3)	1.738 (1.285–2.350)	<0.001	1.399 (1.020–1.920)	0.037
Rehospitalization	303 (39.0)	289 (34.2)	1.248 (1.043–1.494)	0.040	1.025 (0.848–1.239)	0.801
All-cause death or rehospitalization	367 (47.3)	344 (40.8)	1.322 (1.120–1.560)	0.013	1.089 (0.914–1.298)	0.340

The Cox regression model used in the analysis was adjusted for the following covariates: demographics (age, sex, and BMI), medical history (smoking and chronic atrial fibrillation), CABG, NYHA functional class, eGFR, BNP, LVEF, and medication use (diuretics and digitalis). BNP and LVEF at discharge were entered into the model as the categorical variables; i.e. BNP at discharge ≥240 pg/ml or <240 pg/ml or unknown and LVEF at discharge<40% or ≥40% or unknown. HR, hazard ratio; CI, confidence interval.

creatinine, higher plasma BNP, and lower LVEF and were prescribed more by loop diuretics and digitalis. Importantly, the risk of adjusted long-term adverse outcomes including all-cause death and cardiac death were significantly higher in patients with UA≥7.4 mg/dl.

Even though the association between UA and cardiovascular diseases, including HF, has remained controversial [20,21], previous studies have demonstrated that UA is an independent risk factor for cardiovascular diseases [2,22,23]. Furthermore, experimental studies have identified mechanisms by which UA induces cardiovascular diseases [24,25]. The present results were consistent with these previous reports [6–9,26,27] and extended their prognostic value to a large, non-selected HF population encountered in routine clinical practice and, more importantly, during the long-term follow-up up to 2.1 years by analyzing the large registry data of hospitalized HF patients.

It should be noted that our results were adjusted with all covariates known to have prognostic value in HF and hyperuricemia was demonstrated to be associated with adverse clinical outcomes independent of renal function and diuretic use (Table 3). In the present study, patients with higher UA had more severe renal dysfunction (Table 1). Renal dysfunction causes hyperuricemia via decreased excretion of UA. Moreover, an elevation of UA level itself can lead to renal dysfunction [25,28–32]. In the present study, the multiple linear regression analysis demonstrated that renal function was the most important factor determining UA level. However, the contribution rate of renal function to serum UA levels was low and serum UA levels were independently associated with the adverse outcomes in HF (Tables 3 and 4). These findings have been also reported by other previous studies [10,11,33]. Therefore, even though serum UA levels can be affected by various factors such as age, gender, renal function, and diuretic use, the present study and other previous studies confirmed that hyperuricemia was independently associated with the adverse clinical outcomes in HF.

The normal UA values are usually higher in men than women. The patients with higher UA levels were more often men in the present study (Table 1). Therefore, the association between UA levels and adverse outcomes might be affected by their gender differences. However, the significant impact of serum UA levels on outcomes was consistently observed even after adjustment with gender (Tables 3 and 4). In addition, to exclude the contribution of gender differences of UA levels, we further analyzed by using the different definition of hyperuricemia based on the genders; >7 mg/dL for men and >6 mg/dL for women. Based on this definition, 1112 (59.5%) patients had hyperuricemia. The prevalence of male was the same between hyperuricemia and no hyperuricemia groups (60.3 vs 59.6%, $P=0.770$). However, even with the use of different definition of hyperuricemia according to the genders, the relationship between UA and outcomes was consistent with that in our original submission with the UA cut-off values of 7.4 mg/dL.

Table 4
Multivariate predictors of all-cause death by Cox proportional hazard models.

Variables	HR	95% CI	P value
BMI (per 1 kg/m^2 increase)	0.958	0.924–0.993	0.019
eGFR (per 1 ml/min/1.73 m^2 decrease)	1.016	1.010–1.023	<0.001
Serum uric acid (per 1 mg/dL increase)	1.068	1.012–1.127	0.017
Age (per 10 years increase)	1.368	1.214–1.542	<0.001
BNP at discharge ≥240 pg/ml	1.579	1.090–2.287	0.016
NYHA classes 3 and 4 at discharge	1.699	1.165–2.476	0.006

The Cox regression model used in the analysis was adjusted for the following covariates: demographics (age, sex, and BMI), medical history (smoking and chronic atrial fibrillation), CABG, NYHA functional class, eGFR, BNP, LVEF, and medication use (diuretics and digitalis). BNP, LVEF, and NYHA functional class at discharge were entered into the model as the categorical variables; i.e. BNP at discharge ≥240 pg/ml or <240 pg/ml or unknown, LVEF at discharge <40% or ≥40% or unknown, and NYHA classes 1 and 2 or 3 and 4. HR, hazard ratio; CI, confidence interval.

There are several mechanisms of hyperuricemia responsible for the increased mortality risk in HF. Serum UA levels may reflect the degree of XO activation in HF [34,35]. XO is one of the major sources of oxygen free radical production and its excess has been shown to be involved in the pathogenesis of HF [36–39]. XO is also shown to impair the regulation of vascular tone [12,33] and reduced vasodilator capacity could lead to exercise intolerance [13,40]. In addition, XO can induce the upregulation of inflammatory cytokines [10]. Hyperuricemia can also reflect an impairment of oxidative metabolism [11]. An inverse relationship between the anaerobic threshold and serum UA concentration has been shown to be present in HF [14]. Finally, hyperuricemia can be a result of renal dysfunction, which may decrease the clearance of UA. However, in the present study as well as other previous studies [11,33], the significant effect of hyperuricemia on outcomes was observed even after the adjustment for risk factors including renal dysfunction.

Several limitations inherent in the design of the registry should be considered. First, the documentation of serum UA levels at hospital discharge might not accurately reflect those after discharge or their changes over time. Second, the information regarding the use of hypouricemiant drugs was not collected in the present study. Similar to the previous studies which also did not collect such information [4–9,27], the critical analysis based on the subgroups with and without the use of hypouricemiant drugs could not be performed. Third, the present study is not a prospective randomized trial and, despite covariate adjustment, other measured and unmeasured factors might have influenced outcomes. For example, serum UA levels have been shown to be higher in patients with postmenopausal state, insulin resistance, elevated leptin level, obstructive sleep apnea, peripheral vascular disease, and movement from rural to urban communities [20]. These factors might be associated with adverse cardiovascular outcomes. Moreover, hyperuricemia is related to inflammation, free radicals and oxidative stress, including XO. However, this study did not collect these data. In addition, the data regarding an indication for surgical treatment were also not collected. However, in the subgroup of prior CABG or valvular surgery higher UA levels were not a significant risk of adverse outcomes either before or after multivariable adjustment. Forth, Cox proportional hazard model has proven to be a useful

approach for identifying the relationships of risk factors. However, such approaches must be interpreted with extreme caution when used to determine the covariates. The other hand, the Cox proportional hazard model for survival analysis has gained widespread use from medical researchers. This is mainly due to the fact that this model is quite well suited for the analysis of epidemiological cohort studies and clinical trials [41]. In fact, this has been used in the previous studies which assessed the relationship between variables including hyperuricemia and survival [8,27]. Fifth, although the present study demonstrated that low BMI values were significant predictors of all-cause death (Table 4), their values themselves were as low as 22 kg/m^2 compared to those in patients from Europe and United States. However, according to the International Study of Macro-Micro nutrients and Blood Pressure (INTERMAP) study [42], the mean BMI values of Japanese middle-aged men and women were 23.7 and 23.2 kg/m^2, respectively, which were much lower than those of 29.1 and 28.7 kg/m^2 in US population, indicating that the low BMI values in our study patients are a population issue of Japanese. Finally, data were dependent on the accuracy of documentation and abstraction by individual medical centers that participated in this study. However, it was not the objective of this study to restrict enrollment to the narrowly defined population of HF usually included in clinical trials but rather to include a broad range of patients reflecting the current reality of clinical practice. Even though we made an extensive effort to better address and focus the limitation of this study, some major limitation may be still present.

In conclusion, the present study demonstrated that hyperuricemia was common in patients hospitalized with worsening HF and independently associated with long-term adverse outcomes in these patients. Further studies are definitely needed to establish the role of serum UA levels as a potential biomarker for the future risk stratification and a therapeutic target for HF.

Acknowledgments

The JCARE-CARD investigators and participating cardiologists are listed in the Appendix of our previous publication [15]. This study could not have been carried out without the help, cooperation and support of the cardiologists in the survey institutions. We thank them for allowing us to obtain the data. The JCARE-CARD was supported by the Japanese Circulation Society and the Japanese Society of Heart Failure and by grants from Health Sciences Research Grants from the Japanese the Ministry of Health, Labor and Welfare (Comprehensive Research on Cardiovascular Diseases), the Japan Heart Foundation, and the Japan Arteriosclerosis Prevention Fund. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [43].

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ORIGINAL ARTICLE

Decreased glomerular filtration rate is a significant and independent risk for in-hospital mortality in Japanese patients with acute myocardial infarction: report from the Hokkaido acute myocardial infarction registry

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Renal dysfunction is a significant risk factor in the prognosis of patients with cardiovascular diseases. We sought to determine the relationship between estimated glomerular filtration rate (eGFR) values and in-hospital mortality in Japanese acute myocardial infarction (AMI) patients. A total of 2266 consecutive AMI patients admitted to 22 hospitals in Hokkaido were registered. The eGFR values were determined using the following equation: $eGFR=194\times(\text{serum creatinine})^{-1.094}\times(\text{age})^{-0.287}$ ($\times 0.739$ if female). Patients were classified into four groups according to their eGFR values: $\geqslant 60$ ($n=1304$), 30–59 ($n=810$), 15–29 ($n=87$) and <15 ml min^{-1} per 1.73 m^2 ($n=65$). A total of 110 patients (4.9%) died during hospitalization. The in-hospital mortality rate was significantly higher in patients with reduced eGFR values at 2.3, 5.4, 24.1 and 23.1% for eGFR values of $\geqslant 60$, 30–59, 15–29, and <15 ml min^{-1} per 1.73 m^2, respectively. The odds ratios for in-hospital all cause death were 8.26 (95% confidence interval (CI): 2.22–30.77) for eGFR <15 ml min^{-1} per 1.73 m^2 and 3.42 (95% CI: 1.01–11.61) for eGFR 15–29 ml min^{-1} per 1.73 m^2 compared with eGFR $\geqslant 60$ ml min^{-1} per 1.73 m^2. Similarly, the odds ratios for in-hospital cardiac death were 8.43 (95% CI: 1.82–39.05) for eGFR <15 ml min^{-1} per 1.73 m^2 and 5.47 (95% CI: 1.51–19.80) for eGFR 15–29 ml min^{-1} per 1.73 m^2. In conclusion, the eGFR of <30 ml min^{-1} per 1.73 m^2 was a significant and independent risk for in-hospital mortality in abroad cohort of Japanese patients with AMI.
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Keywords: acute myocardial infarction; chronic kidney disease; estimated glomerular filtration rate; mortality

INTRODUCTION

Chronic kidney disease (CKD) is increasingly becoming recognized as a global public health problem.[1] The National Kidney Foundation has published clinical guidelines on the evaluation, classification and risk stratification in patients with CKD.[2] Despite the recognized association between a reduced estimated glomerular filtration rate (eGFR) and poor prognosis, screening for CKD is frequently limited to the measurement of serum creatinine,[3,4] which does not accurately reflect the GFR. As a result, the management of this risk is often not optimized. The risks of CKD included not only the progression to end-stage renal failure but also the occurrence of adverse cardiovascular outcomes.[5–9] Previous studies have demonstrated that CKD is an independent risk factor for morbidity and mortality in the general population,[10] as well as in patients with cardiovascular diseases such as post acute myocardial infarction (AMI).[11] Anavekar *et al.*[11] reported that CKD was a common and significant independent risk factor for cardiovascular events in AMI patients based on data from the Valsartan in Acute Myocardial Infarction Trial (VALIANT). The risk was progressive, and each 10 unit reduction in the eGFR was significantly associated with a 10% increase in the relative risk of death or nonfatal cardiovascular complications.[11] However, the patients in the VALIANT study had heart failure, left ventricular dysfunction, or both as a complication of AMI, and patients with a baseline serum creatinine level >2.5 mg dl^{-1} were excluded. Therefore, the patients enrolled in the study by Anavekar *et al.*[11] were not representative of the general AMI population routinely encountered in clinical practice. It is critically important to determine the prognostic impact of CKD in the registry data of Japanese patients with AMI.

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The aim of the present study was to examine the prognostic significance of eGFR values on the in-hospital mortality in Japanese AMI patients in routine clinical practice.

METHODS

Patients

The study patients consisted of 2266 consecutive patients hospitalized because of AMI in 22 hospitals in Hokkaido from 2005 to 2007.

AMI was defined by the presence of at least two of the following criteria:[12–14] (1) a clinical history of chest pain persisting for ⩾30 min, (2) ischemic electrocardiographic changes and (3) a peak creatine kinase level equivalent to more than twice the upper limit of normal. All patients underwent coronary catheterization within 24 h after the onset of AMI. Body weight and height were measured in the morning after fasting. Body mass index was calculated as body weight (kg) divided by squared height (m). Smoking habits were determined using a self-reported questionnaire. Patients who had never smoked and ex-smokers were classified as 'nonsmokers'. Hypertension was defined as a history of systolic blood pressure ⩾140 mm Hg and/or diastolic blood pressure ⩾90 mm Hg or the use of oral antihypertensive drugs. Dyslipidemia was defined as a fasting total cholesterol ⩾220 mg per 100 ml or the use of anti-hypercholesterol drugs. Diabetes mellitus was defined as fasting plasma glucose ⩾126 mg per 100 ml or the use of oral hypoglycemic drugs or insulin. Patients who had suffered from myocardial infarction and stroke were defined as 'prior cardiovascular disease'. Blood samples were obtained after an overnight fast in the hospital. The creatine kinase values were measured every 4 h after admission to determine the peak value. The information regarding all cause death and cardiac death during hospitalization was obtained by physicians in the hospitals where the patients were admitted. Cardiac death was defined as a death due to heart failure, fatal arrhythmia, cardiac rupture or recurrent myocardial infarction. The patient data were registered in each hospital and reported to the data management office at Hokkaido University. Written informed consent was obtained from each patient or a family member. The study protocol was approved by the ethics committee at Hokkaido University School of Medicine.

Measurement of the eGFR

To calculate the eGFR, serum creatinine was measured using the compensated Jaffe creatinine method at the time of admission to the hospital. The eGFR was calculated using the equation for Japanese as follows:[15] eGFR=194×(serum creatinine)$^{-1.094}$×(age)$^{-0.287}$ (×0.739 if female) ml min^{-1} per 1.73 m^2.

Statistical analysis

The characteristics of the study subjects were expressed as means ± s.d. for continuous variables, median (and interquartile range) for skewed distribution variables, and percentages for categorical variables according to the eGFR values. The differences in variables among groups were examined by analysis of variance, Kruskal–Wallis test or chi-square test. The association between the risk factors and in-hospital deaths of AMI patients was assessed using multiple logistic regression analysis. The principal model included the following candidate variables: demographics (age, sex, body mass index, smoking, prior cardiovascular disease), medical history (hypertension, diabetes mellitus, dyslipidemia, Q wave myocardial infarction and peak creatine kinase), angiographic data (number of diseased vessels, Killip classification, thrombolysis in myocardial infarction flow grade 0 at admission and thrombolysis in myocardial infarction flow grade 3 after treatment) and procedural information (mechanical support and treatment). Variables that were regarded as significant ($P<0.05$) were included in subgroup multivariate analyses. A P-value of <0.05 indicated statistical significance. All statistical analyses were performed using the SPSS statistical package for Windows version 11.0 (Chicago, IL, USA).

RESULTS

Patient characteristics

Figure 1 shows the distribution of the eGFR in the study patients. The mean eGFR value was 64.4 ± 23.7 ml min^{-1} per 1.73 m^2, ranging from 3.3 to 171.2 ml min^{-1} per 1.73 m^2 for 2254 patients. In all, 12 patients under hemodialysis were included in the group of eGFR values

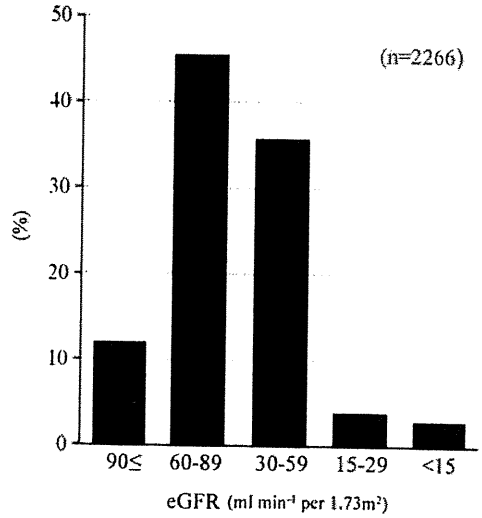

Figure 1 The distribution of the eGFR in the study patients.

<15 ml min^{-1} per 1.73 m^2. In all, 962 (42.5%) patients had an eGFR <60 ml min^{-1} per 1.73 m^2 or dialysis treatment.

Table 1 shows the baseline demographic and medical characteristics of the patients according to eGFR levels. The mean age of the patients was 66 ± 12 years and 72.0% were men. Patients with a reduced eGFR were older and more often women. They were more likely to have hypertension, diabetes mellitus, dyslipidemia and prior cardiovascular disease.

Table 2 shows the baseline angiographic and procedural characteristics of the patients according to eGFR levels. Patients with a reduced eGFR were more likely to have severe coronary artery stenosis, severe heart failure symptoms based on Killip classifications and higher use of mechanical supports such as intraaortic balloon pumping or percutaneous cardiopulmonary support. The prevalence of thrombolysis in myocardial infarction flow grade 0 at admission and thrombolysis in myocardial infarction flow grade 3 after treatment was lower with reduced eGFR levels. The performance of percutaneous coronary intervention by stent implantation was lower and that of thrombolysis, balloon angioplasty and coronary artery bypass grafting was higher with reduced eGFR levels.

Outcomes

A total of 110 (4.9%) patients died because of any causes and 84 (3.7%) patients died because of cardiac events during hospitalization during the follow-up period of 20 ± 17 (2–92) days.

Table 3 shows the odds ratios and 95% confidence interval (CI) for all cause and cardiac death according to eGFR levels. The rates of all cause death were 2.3, 5.4, 24.1 and 23.1% in patients with eGFR values ⩾60, 30–59, 15–29 and <15 ml min^{-1} per 1.73 m^2, respectively. The rates of cardiac death were 1.8, 4.1, 19.5 and 15.4% in subjects with eGFR values ⩾60, 30–59, 15–29 and <15 ml min^{-1} per 1.73 m^2, respectively. Decreases in the eGFR levels were associated with a significant progressive elevation of risk for all cause ($P<0.05$ for trend) and cardiac death ($P<0.01$ for trend). By multivariate analysis with an eGFR ⩾60 ml min^{-1} per 1.73 m^2 as the reference, patients with eGFR of 15–29 and <15 ml min^{-1}per 1.73 m^2 had a significantly elevated risk for all cause death (OR 3.42, 95% CI 1.01–11.61 and OR 8.26, 95% CI 2.22–30.77, respectively) and cardiac death (OR 5.47, 95% CI 1.51–19.80 and OR 8.43, 95% CI 1.82–39.05, respectively). By multiple logistic regression analysis, age, Killip classification ⩾II at admission, prior cardio-

Table 1 Demographic and medical characteristics of the patients according to eGFR levels

		eGFR				
	Total (n=2266)	*≥60 (n=1304)*	*30–59 (n=810)*	*15–29 (n=87)*	*<15 (n=65)*	*P-value*
Age (years)	66±12	63±12	71±11	77±9	78±11	<0.001
Male (%)	72.0	76.5	67.9	55.2	56.4	<0.001
Body mass index ($kg\,m^{-2}$)	24.4±3.7	24.5±3.6	24.3±3.5	23.5±4.4	24.2±6.5	0.15
Smoking (%)	50.5	57.3	41.8	30.8	48.3	<0.001
Hypertension (%)	44.6	36.1	53.0	69.4	76.2	<0.01
Diabetes mellitus (%)	22.7	19.5	23.8	38.8	50.0	<0.001
Dyslipidemia (%)	20.6	18.7	23.0	28.0	20.0	<0.05
Prior cardiovascular disease (%)	20.7	16.5	26.1	26.4	29.7	<0.01
Q wave myocardial infarction (%)	66.1	72.3	55.7	67.5	70.2	0.57
Peak creatine kinase (IU per 100 ml)	2559 (1441–4201)	2623 (1486–4275)	2492 (1440–4107)	2505 (1018–3692)	2604 (1112–4281)	0.26

Abbreviation: eGFR, estimated glomerular filtration rate.
Values are means±s.d., median (and interquartile range) and percentage.

Table 2 Angiographic and procedural characteristics of the patients according to eGFR levels

		eGFR				
	Total (n=2266)	*≥60 (n=1304)*	*30–59 (n=810)*	*15–29 (n=87)*	*<15 (n=65)*	*P-value*
Number of diseased vessels (%)						
LMT	4.3	2.8	5.1	9.2	16.9	<0.001
One vessel	55.1	59.6	50.9	47.8	29.2	<0.001
Two vessel	27.3	26.1	29.1	22.1	35.4	<0.01
Three vessel	13.3	11.5	14.9	20.9	18.5	<0.001
Killip classification ≥II						
At admission (%)	18.5	11.7	24.5	47.1	43.5	<0.01
Mechanical support (IABP/PCPS) (%)	13.7	10.8	15.6	26.4	30.8	<0.001
TIMI flow grade 0 at admission (%)	68.8	69.7	69.9	57.5	53.8	<0.01
TIMI flow grade 3 after treatment (%)	99.1	99.4	98.9	97.3	96.2	<0.05
Treatment (%)						
Thrombolysis	6.8	5.2	8.1	13.8	13.9	<0.001
Balloon angioplasty	6.6	6.6	6.3	5.8	12.3	<0.001
Coronay stent	85.9	87.5	85.1	79.3	72.3	<0.001
CABG	0.7	0.7	0.5	1.1	1.5	<0.001

Abbreviations: CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; IABP, intraaortic balloon pumping; LMT, left main trunk; PCPS, percutaneous cardiopulmonary support; TIMI, thrombolysis in myocardial infarction.

vascular disease, peak creatine kinase and eGFR values were significant and independent predictors for all cause death. Age, the use of mechanical support, peak creatine kinase and eGFR values were significant and independent predictors for cardiac death (Table 4).

Table 5 shows the results of subgroup analysis for all cause death according to eGFR levels stratified by sex, age (≥65 *vs.* <65 years) and comorbidities (hypertension *vs.* no hypertension and diabetes mellitus *vs.* no diabetes mellitus). The eGFR $<30\,ml\,min^{-1}$ per 1.73 m^2 was associated with poor outcomes in each subgroup, which is in agreement with the results of the primary analysis.

DISCUSSION

The present study demonstrated that the prevalence of AMI patients with an eGFR $<60\,ml\,min^{-1}$ per 1.73 m^2 was 42.5% based on a large-scale, multicenter trial. A reduced eGFR was a significant and independent risk for in-hospital all-cause and cardiac mortality. Moreover, AMI patients with eGFR values $<30\,ml\,min^{-1}$ per 1.73 m^2 had a significantly greater mortality risk than patients with values $\geq 60\,ml\,min^{-1}$ per 1.73 m^2.

Previous studies used serum creatinine levels rather than the eGFR to detect renal dysfunction.[3,4] However, the accuracy of serum creatinine levels is limited as a marker of renal function because significant kidney dysfunction can be present despite a normal serum creatinine concentration. Serum creatinine has a nonlinear association with eGFR according to age, sex and lean body mass.[16,17] The National Kidney Foundation[2] and Kidney Disease Improving Global Outcomes (KDIGO)[18] have recommended using an eGFR estimated by serum creatinine, and eGFR $<60\,ml\,min^{-1}$ per 1.73 m^2 is selected as the cutoff value for the diagnosis of CKD. The eGFR values were generally estimated by the modification of diet in renal disease or creatinine clearance. Imai *et al.*[19] reported that the modification of diet in renal disease equation might overestimate the GFR in Japanese populations compared with the GFR measured using insulin clearance. Matsuo *et al.*[15] demonstrated that the accuracy of the eGFR estimation was

Table 3 The odds ratios and 95% CI for all cause and cardiac death according to eGFR values

	eGFR				
	≥60 (n=1304)	*30–59 (n=810)*	*15–29 (n=87)*	*<15 (n=65)*	*P for trend*
All cause death					
n (%)	30 (2.3)	44 (5.4)	21 (24.1)	15 (23.1)	
Model 1, odds ratio (95% CI)	1.00	1.66 (1.01–2.73)	7.58 (3.95–14.53)	10.64 (5.31–21.30)	<0.001
Model 2, odds ratio (95% CI)	1.00	1.58 (0.99–2.81)	6.24 (3.03–12.85)	9.55 (4.39–20.77)	<0.001
Model 3, odds ratio (95% CI)	1.00	1.05 (0.47–2.36)	3.42 (1.01–11.61)	8.26 (2.22–30.77)	<0.05
Cardiac death					
n (%)	24 (1.8)	33 (4.1)	17 (19.5)	10 (15.4)	
Model 1, odds ratio (95% CI)	1.00	1.52 (0.87–2.67)	7.49 (3.67–15.29)	8.90 (4.01–20.00)	<0.001
Model 2, odds ratio (95% CI)	1.00	1.46 (0.85–2.52)	7.10 (3.31–15.20)	8.88 (3.74–21.04)	<0.001
Model 3, odds ratio (95% CI)	1.00	1.02 (0.41–2.53)	5.47 (1.51–19.80)	8.43 (1.82–39.05)	<0.01

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.
Model 1, adjusted for demographic (age and sex) variables.
Model 2, adjusted for demographic (age and sex) and medical (hypertension, diabetes mellitus and dyslipidemia) variables.
Model 3, adjusted for demographic (age and sex), medical (body mass index, smoking, hypertension, diabetes mellitus, dyslipidemia, prior cardiovascular disease, Q wave myocardial infarction and peak creatine kinase), angiographic (number of diseased vessles and killip classification ≥II) and procedural (mechanical support, TIMI (thrombolysis in myocardial infarction) flow grade 0 at admission and TIMI flow grade 3 after treatment) variables.

Table 4 Multivariate predictors of outcomes by multiple logistic regression analysis

	Odds ratio	*95% CI*	*P-value*
All cause death			
Age (per 1 year increase)	1.06	1.02–1.10	<0.01
Killip classification ≥II at admission	2.60	1.19–5.69	<0.05
Prior cardiovascular disease	2.21	1.02–4.79	<0.05
Peak creatine kinase (per 100 IU per 100 ml increase)	1.02	1.01–1.03	<0.01
eGFR (per 10 ml min^{-1} per 1.73 m^2 decrease)	1.36	1.14–1.62	<0.01
Cardiac death			
Age (per 1 year increase)	1.06	1.02–1.10	<0.01
Mecanical support (IABP/PCPS)	3.51	1.39–8.84	<0.01
Peak creatine kinase (per 100 IU per 100 ml increase)	1.01	1.01–1.02	<0.05
eGFR (per 10 ml min^{-1} per 1.73 m^2 decrease)	1.37	1.13–1.68	<0.01

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; IABP, intraaortic balloon pumping; PCPS, percutaneous cardiopulmonary support.
Adjusted for demographic (age and sex), medical (body mass index, smoking, hypertension, diabetes mellitus, dyslipidemia, prior cardiovascular disease, Q wave myocardial infarction, peak creatine kinase and eGFR), angiographic (number of diseased vessles and killip classification ≥II) and procedural (mechanical support, TIMI (thrombolysis in myocardial infarction) flow grade 0 at admission and TIMI flow grade 3 after treatment) variables.

more improved using the new Japanese equation rather than using the modification of diet in renal disease equation in Japanese populations. Therefore, the present study used the new Japanese equation to calculate the eGFR values.

Previous studies demonstrated that CKD is an independent risk factor for cardiovascular disease in the general population in Japan.[20,21] Anavekar *et al.*[11] showed that the prevalence of CKD patients suffering from AMI in Western countries was 33.5%, and Nakamura *et al.*[22] reported that it was 31.6% in Japanese patients with coronary artery disease. The prevalence of CKD in the present study was 42.4%, which is higher than the rates reported in previous studies.[11,22] These discrepancies may be partially explained by the differences in ethnicity and other risk factors such as age and obesity. More importantly, the registry used in this study enrolled all patients that were admitted to the hospital because of AMI and did not exclude those who had higher levels of serum creatinine or dialysis treatment. Thus, the patients in the present study had a high prevalence of renal dysfunction and were considered to be more reflective of current routine clinical practice.

The present study extended the previous studies and demonstrated the prognostic significance of reduced eGFR in patients with coronary artery disease.[3,10,20,21,23–28] The Atherosclerosis Risk in Communities (ARIC) study[23] and the Second National Health and Nutrition Examination Survey (NHANES II)[3] demonstrated that a mild reduction in eGFR was a significant risk factor for both coronary vascular disease and all-cause mortality. The present study confirmed the prior studies by Anavekar *et al.* in which reduced eGFR was independently associated with an increased risk of fatal and nonfatal adverse cardiovascular events after AMI.[11] However, in their study, the study patients were limited to have baseline serum creatinine levels $<2.5\ mg\ dl^{-1}$ and heart failure. In addition, only 20% of the patients were treated with percutaneous coronary intervention. Thus, the impact of CKD has not been elucidated in a representative cohort of patients receiving contemporary therapy for AMI. To examine the