**Table 1**
Baseline clinical characteristics.

| | All patients ($n$ = 313) | HF-PEF ($n$ = 151) | HF-REF ($n$ = 162) | $p$-Value |
|---|---|---|---|---|
| Age, years | 67 ± 13 | 69 ± 12 | 67 ± 13 | 0.088 |
| Female, $n$ (%) | 127 (41) | 71 (47) | 56 (35) | 0.025 |
| NYHA functional class, I/II/III | 42/162/109 | 22/89/40 | 20/73/69 | 0.011 |
| Etiology, $n$ (%) | | | | <0.001 |
| Dilated cardiomyopathy | 81 (26) | 0 | 81 (50) | |
| Hypertensive heart disease | 80 (26) | 70 (46) | 10 (6) | |
| Ischemic heart disease | 60 (19) | 22 (15) | 38 (24) | |
| Valvular heart disease | 45 (14) | 29 (19) | 16 (10) | |
| Tachycardia-induced heart failure | 26 (8) | 18 (12) | 8 (5) | |
| Other | 21 (7) | 12 (8) | 9 (5) | |
| Atrial fibrillation, $n$ (%) | 108 (35) | 54 (36) | 54 (33) | 0.710 |
| Diabetes mellitus, $n$ (%) | 84 (27) | 37 (25) | 47 (29) | 0.334 |
| Dyslipidemia, $n$ (%) | 78 (25) | 35 (23) | 43 (27) | 0.452 |
| Current smoker, $n$ (%) | 83 (27) | 34 (23) | 49 (30) | 0.079 |
| Presentation profile | | | | |
| Systolic pressure, mm Hg | 117 ± 20 | 117 ± 21 | 118 ± 17 | 0.838 |
| Heart rate, bpm | 70 ± 14 | 71 ± 14 | 69 ± 14 | 0.351 |
| Body mass index, kg/m$^2$ | 22.7 ± 3.5 | 23.1 ± 3.3 | 22.5 ± 3.7 | 0.149 |
| eGFR, mL/min/1.73 m$^2$ | 66 ± 22 | 67 ± 21 | 64 ± 23 | 0.284 |
| Blood biomarkers | | | | |
| BNP, pg/mL (IQR) | 186 (76–584) | 124 (51–332) | 328 (126–846) | <0.001 |
| Troponin T, ng/mL (IQR) | 0.01 (0.01–0.02) | 0.01 (0.01–0.02) | 0.01 (0.01–0.03) | 0.261 |
| H-FABP, ng/mL (IQR) | 4.3 (2.9–6.6) | 3.8 (2.8–6.1) | 5.0 (3.1–7.8) | 0.005 |
| High sensitive CRP, mg/dL (IQR) | 0.18 (0.09–0.519) | 0.12 (0.06–0.40) | 0.20 (0.10–0.60) | 0.001 |
| Echocardiographic data | | | | |
| LA diameter, mm | 43.7 ± 7.8 | 43.7 ± 8.4 | 43.8 ± 7.2 | 0.878 |
| LV end-diastolic diameter, mm | 54.1 ± 9.9 | 49.3 ± 8.8 | 58.6 ± 8.7 | <0.001 |
| LV ejection fraction, % | 49.1 ± 18.4 | 65.4 ± 9.2 | 33.8 ± 9.7 | <0.001 |
| LV mass index, g/m$^2$ | 190 ± 68 | 176 ± 60 | 203 ± 71 | <0.001 |
| E/A ratio | 1.14 ± 0.84 | 0.95 ± 0.54 | 1.29 ± 1.01 | 0.005 |
| Medications, $n$ (%) | | | | |
| ACE inhibitors and/or ARBs | 216 (69) | 97 (64) | 119 (73) | 0.078 |
| β Blockers | 124 (40) | 51 (34) | 73 (45) | 0.041 |
| Ca channel blockers | 62 (20) | 42 (28) | 20 (12) | <0.001 |

Data are presented as mean ± SD or % unless otherwise indicated. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HF, heart failure; H-FABP, heart-type fatty acid-binding protein; IQR, interquartile range; LA, left atrial; LV, left ventricular; NYHA, New York Heart Association; PEF, preserved ejection fraction; REF, reduced ejection fraction.

plasma levels ranged from 6 to 1920 pg/mL (median 124 pg/mL) (Table 1). In patients with HF-REF, serum levels of H-FABP ranged from 0.1 to 31 ng/mL (median 5.0 ng/mL), serum levels of troponin T ranged from <0.01 to 1.45 ng/mL (median 0.01 ng/mL), and plasma levels of BNP ranged from 6 to 2000 pg/mL (median 328 pg/mL) (Table 1).

Serum H-FABP levels increased with advancing NYHA functional class, both in patients with HF-PEF and in those with HF-REF. However, serum levels of H-FABP did not differ between each NYHA functional class (Fig. 1).

*Clinical features of patients with ongoing myocardial damage*

The cut-off values used in this analysis were 4.3 ng/mL for H-FABP, and 0.01 ng/mL for troponin T. Myocardial membrane injury, as defined by elevated H-FABP levels (>4.3 ng/mL), was more frequently observed than myofibrillar injury, as defined by elevated troponin T levels (>0.01 ng/mL), in patients with HF-PEF (41% vs. 26% of patients, $p < 0.05$). When either H-FABP or troponin T levels were above the cut-off values, patients with HF were considered to have ongoing myocardial damage [12]. There were 62 HF patients with elevated serum H-FABP levels (Table 2), and 39 HF patients with elevated serum troponin T levels (Table 3). Patients with ongoing myocardial damage were older, were in a more severe NYHA functional class, had a lower mean BMI, worse renal function, higher levels of BNP, troponin T, H-FABP, and hs-CRP, and were treated with β blockers more frequently than those without myocardial damage. The etiology of HF did not differ between patients with or without ongoing myocardial damage. Echocardiographic findings, LV end-diastolic diameter, LVEF, and LV mass index did not differ between the two groups. Although the prevalence of atrial fibrillation, LA diameter, and E/A ratio were significantly greater in patients with high H-FABP levels than in those with low H-FABP levels (Table 2), these differences were not

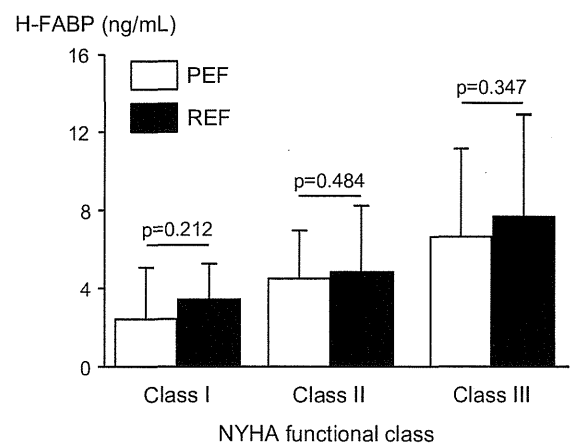


**Fig. 1.** Serum levels of heart-type fatty acid binding protein (H-FABP) in patients with heart failure and preserved ejection fraction (PEF) or reduced ejection fraction (REF). H-FABP levels did not differ between patients in different New York Heart Association (NYHA) functional classes.

**Table 2**
Clinical characteristics of the patients with heart failure, preserved ejection fraction and high or low heart-type fatty acid binding protein levels.

| | High H-FABP ($n=62$) | Low H-FABP ($n=89$) | $p$-Value |
|---|---|---|---|
| Age, years | 74±8 | 64±13 | <0.001 |
| Female, $n$ (%) | 32 (52) | 39 (44) | 0.345 |
| NYHA functional class, I/II/III | 1/35/26 | 21/54/14 | <0.001 |
| Etiology, $n$ (%) | | | 0.228 |
| Hypertensive heart disease | 29 (46) | 41 (46) | |
| Valvular heart disease | 10 (16) | 19 (21) | |
| Ischemic heart disease | 6 (10) | 16 (18) | |
| Tachycardia-induced heart failure | 11 (18) | 7 (8) | |
| Other | 6 (10) | 6 (7) | |
| Atrial fibrillation, $n$ (%) | 29 (47) | 25 (28) | 0.018 |
| Diabetes mellitus, $n$ (%) | 13 (21) | 24 (27) | 0.392 |
| Dyslipidemia, $n$ (%) | 13 (21) | 22 (25) | 0.591 |
| Current smoker, $n$ (%) | 14 (23) | 20 (22) | 0.987 |
| Presentation profile | | | |
| Systolic pressure, mm Hg | 115±22 | 118±22 | 0.430 |
| Heart rate, bpm | 71±13 | 71±14 | 0.975 |
| Body mass index, kg/m$^2$ | 22.3±3.7 | 23.7±2.9 | 0.009 |
| eGFR, mL/min/1.73 m$^2$ | 58±18 | 73±20 | <0.001 |
| Blood biomarkers | | | |
| BNP, pg/mL (IQR) | 235 (89–593) | 90 (38–210) | <0.001 |
| Troponin T, ng/mL (IQR) | 0.01 (0.01–0.05) | 0.01 (0.01–0.01) | 0.012 |
| H-FABP, ng/mL (IQR) | 6.6 (5.2–8.4) | 2.9 (2.2–3.5) | <0.001 |
| High sensitive CRP, mg/dL (IQR) | 0.29 (0.08–0.67) | 0.10 (0.05–0.29) | <0.001 |
| Echocardiographic data | | | |
| LA diameter, mm | 45.8±10.2 | 42.1±6.4 | 0.009 |
| LV end-diastolic diameter, mm | 48.4±7.5 | 49.9±9.7 | 0.326 |
| LV ejection fraction, % | 65.1±9.7 | 65.6±8.9 | 0.737 |
| LV mass index, g/m$^2$ | 181±59 | 172±61 | 0.409 |
| E/A ratio | 1.19±0.69 | 0.82±0.38 | 0.002 |
| Medications, $n$ (%) | | | |
| ACE inhibitors and/or ARBs | 42 (68) | 55 (62) | 0.453 |
| β Blockers | 28 (45) | 23 (26) | 0.014 |
| Ca channel blockers | 13 (21) | 29 (33) | 0.117 |

Data are presented as mean±SD or % unless otherwise indicated. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; H-FABP, heart-type fatty acid-binding protein; IQR, interquartile range; LA, left atrial; LV, left ventricular; NYHA, New York Heart Association.

apparent in patients with high troponin T levels, compared to those with low troponin T levels (Table 3).

*Correlation between biomarkers and other variables measured*

The correlations between biomarker levels and other variables measured were assessed (Table 4). Serum H-FABP levels were weakly correlated with age ($r=0.371$, $p<0.001$) and eGFR ($r=-0.295$, $p<0.001$). Weak relationships were also observed between H-FABP levels and LA diameter ($r=0.326$, $p<0.001$) and E/A ratio ($r=0.273$, $p=0.01$). However, serum H-FABP levels were not correlated with LV parameters, including LV end-diastolic diameter, LVEF, or LV mass index. Serum troponin T levels were weakly correlated with eGFR ($r=-0.264$, $p=0.026$). However, troponin T levels were not correlated with echocardiographic findings. Plasma BNP levels were weakly correlated with age ($r=0.184$, $p=0.024$), eGFR ($r=-0.239$, $p=0.003$), LV mass index ($r=0.322$, $p<0.001$), and E/A ratio ($r=0.261$, $p=0.014$).

*Predictors of subsequent cardiovascular events*

During the follow-up period, cardiovascular events were observed in 42 of 151 patients (28%). These included 17 cardiovascular deaths (12 due to progression of HF, 3 due to myocardial infarction, 1 due to stroke, and 1 sudden death), and 25 rehospitalizations for worsening HF. By univariate Cox analysis, age, NYHA functional class, the presence of atrial fibrillation, plasma BNP levels, serum H-FABP levels, and LA diameter were significantly associated with cardiovascular events (Table 5). Multivariate Cox analysis revealed that only the serum H-FABP level was an independent predictor of cardiovascular events (Table 5). Kaplan–Meier survival curves showed that patients in the highest tertile of H-FABP had a significantly increased risk of adverse cardiovascular events (log-rank test $p<0.001$; Fig. 2). Patients in the third tertile of H-FABP (5.0–24 ng/mL) had a significantly increased risk of all cardiovascular events, compared with those in the lowest tertile of H-FABP (0.5–3.0 ng/mL) [hazard ratio 4.394, 95% confidence interval (CI) 1.967–9.815, $p<0.001$]. Patients in the third tertile of H-FABP were older, were in a more severe NYHA functional class,

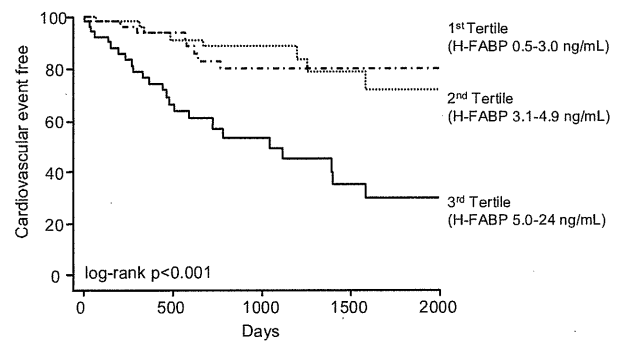


**Fig. 2.** Kaplan–Meier curves showing cardiac event-free survival in patients with heart failure and preserved ejection fraction, according to tertiles of heart-type fatty acid binding protein (H-FABP). All cardiac events at 5 years: 15.7% for patients in the first tertile of H-FABP (0.5–3.0 ng/mL), 16.0% for patients in the second tertile of H-FABP (3.1–4.9 ng/mL), and 47.0% for patients in the third tertile of H-FABP (5.0–24 ng/mL). Log rank $p<0.001$.

**Table 3**
Clinical characteristics of the patients with heart failure, preserved ejection fraction and high or low troponin T levels.

| | High troponin T ($n$ = 39) | Low troponin T ($n$ = 112) | $p$-Value |
|---|---|---|---|
| Age, years | 74 ± 10 | 67 ± 12 | 0.001 |
| Female, $n$ (%) | 20 (51) | 51 (46) | 0.395 |
| NYHA functional class, I/II/III | 0/21/18 | 22/68/22 | <0.001 |
| Etiology, $n$ (%) | | | 0.306 |
| Hypertensive heart disease | 20 (51) | 50 (45) | |
| Valvular heart disease | 6 (15) | 23 (21) | |
| Ischemic heart disease | 4 (10) | 18 (16) | |
| Tachycardia-induced heart failure | 7 (18) | 11 (10) | |
| Other | 2 (5) | 10 (9) | |
| Atrial fibrillation, $n$ (%) | 17 (44) | 37 (33) | 0.162 |
| Diabetes mellitus, $n$ (%) | 7 (18) | 30 (28) | 0.126 |
| Dyslipidemia, $n$ (%) | 7 (18) | 28 (25) | 0.196 |
| Current smoking, $n$ (%) | 7 (18) | 27 (24) | 0.240 |
| Presentation profile | | | |
| Systolic pressure, mm Hg | 116 ± 23 | 118 ± 21 | 0.690 |
| Heart rate, bpm | 70 ± 13 | 71 ± 14 | 0.530 |
| Body mass index, kg/m$^2$ | 22.0 ± 3.6 | 23.6 ± 3.1 | 0.006 |
| eGFR, mL/min/1.73 m$^2$ | 56 ± 19 | 72 ± 19 | <0.0001 |
| Blood biomarkers | | | |
| BNP, pg/mL (IQR) | 167 (83–584) | 112 (41–260) | 0.013 |
| Troponin T, ng/mL (IQR) | 0.06 (0.04–0.16) | 0.01 (0.01–0.01) | <0.001 |
| H-FABP, ng/mL (IQR) | 6.8 (5.3–8.4) | 3.1 (2.5–4.0) | <0.001 |
| High sensitive CRP, mg/dL (IQR) | 0.30 (0.10–0.68) | 0.10 (0.05–0.30) | 0.002 |
| Echocardiographic data | | | |
| LA diameter, mm | 45.3 ± 10.8 | 42.9 ± 7.0 | 0.114 |
| LV end-diastolic diameter, mm | 47.6 ± 6.7 | 50.0 ± 9.6 | 0.120 |
| LV ejection fraction, % | 65.4 ± 9.3 | 65.4 ± 9.1 | 0.995 |
| LV mass index, g/m$^2$ | 186 ± 54 | 171 ± 63 | 0.163 |
| E/A ratio | 1.11 ± 0.56 | 0.89 ± 0.52 | 0.079 |
| Medications, $n$ (%) | | | |
| ACE inhibitors and/or ARBs | 29 (74) | 68 (61) | 0.060 |
| β Blockers | 18 (46) | 33 (29) | 0.032 |
| Ca channel blockers | 7 (18) | 35 (31) | 0.090 |

Data are presented as mean ± SD or % unless otherwise indicated. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; H-FABP, heart-type fatty acid-binding protein; IQR, interquartile range; LA, left atrial; LV, left ventricular; NYHA, New York Heart Association.

had worse renal function, higher levels of BNP, troponin T, H-FABP, and hs-CRP, and were treated with β blockers more frequently than those in the lower tertile of H-FABP. Echocardiographic findings showed that patients in the highest tertile of H-FABP had higher E/A ratios than in those with lower H-FABP levels (Table 6).

## Discussion

### *Main findings*

The findings from this study were as follows: (1) Latent myocardial injury was frequently observed in patients with HF-PEF. Myocardial membrane injury was more frequently observed than myofibrillar injury. (2) The serum level of H-FABP was an independent predictor of subsequent cardiovascular events.

### *Ongoing myocardial damage in patients with HF-PEF*

Although many large cohort studies have shown that HF-PEF predominantly afflicts elderly, hypertensive patients [1–5], the pathophysiological differences between HF-PEF and HF-REF remain poorly elucidated. The current understanding of the progression of HF-REF invokes progressive ventricular remodeling in response to myocardial injury [15,16]. Several factors, including ischemic myocardial damage, activation of sympathetic nerve function, inflammatory processes, and autophagic degeneration, have been implicated in myocyte injury and death. All these pathways converge on myocardial damage and death by progressive necrosis or apoptosis [15–17].

Importantly, the results clearly show that latent myocardial injury was frequently observed in patients with HF-PEF. These results imply that myocardial injury is important in HF-PEF.

**Table 4**
Relationships between clinical parameters and biomarkers in patients with heart failure and preserved ejection fraction.

| | H-FABP | | Troponin T | | BNP | |
|---|---|---|---|---|---|---|
| | $r$ | $p$-Value | $r$ | $p$-Value | $r$ | $p$-Value |
| Age | 0.371 | <0.001 | 0.019 | 0.878 | 0.184 | 0.024 |
| eGFR | −0.295 | <0.001 | −0.264 | 0.026 | −0.239 | 0.003 |
| Echocardiographic data | | | | | | |
| LA diameter | 0.326 | <0.001 | 0.060 | 0.622 | 0.108 | 0.206 |
| LV end-diastolic diameter | −0.039 | 0.639 | −0.068 | 0.571 | 0.012 | 0.889 |
| LV ejection fraction | −0.010 | 0.906 | 0.002 | 0.985 | 0.005 | 0.952 |
| LV mass index | 0.082 | 0.334 | 0.170 | 0.160 | 0.322 | <0.001 |
| E/A ratio | 0.273 | 0.010 | 0.165 | 0.280 | 0.261 | 0.014 |

BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; H-FABP, heart-type fatty acid-binding protein; LA, left atrial; LV, left ventricular.

**Table 5**
Univariate and multivariate analyses of factors predicting cardiovascular events in patients with heart failure and preserved ejection fraction.

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI of HR | *p*-Value | HR | 95% CI of HR | *p*-Value |
| Age, per 10-year increase | 1.616 | 1.015–1.086 | 0.005 | 1.296 | 0.983–1.072 | 0.239 |
| Female gender | 1.254 | 0.674–2.333 | 0.476 | 1.142 | 0.474–2.753 | 0.767 |
| NYHA functional class III | 3.752 | 1.995–7.057 | <0.001 | 2.103 | 0.749–5.903 | 0.158 |
| Presence of | | | | | | |
| Atrial fibrillation | 2.132 | 1.142–3.982 | 0.018 | 0.971 | 0.357–2.642 | 0.955 |
| Diabetes mellitus | 1.445 | 0.733–2.847 | 0.288 | | | |
| Dyslipidemia | 1.089 | 0.532–2.230 | 0.815 | | | |
| Presentation profile | | | | | | |
| Systolic pressure, per SD increase | 0.887 | 0.981–1.006 | 0.328 | | | |
| Heart rate, per SD increase | 1.251 | 0.992–1.041 | 0.205 | | | |
| Body mass index, per SD increase | 0.900 | 0.867–1.081 | 0.568 | 0.903 | 0.850–1.107 | 0.649 |
| eGFR, per SD increase | 0.803 | 0.973–1.007 | 0.233 | 1.013 | 0.977–1.023 | 0.996 |
| Blood biomarkers | | | | | | |
| BNP, per 100 pg/mL increase | 1.105 | 1.000–1.001 | 0.011 | 1.030 | 0.999–1.001 | 0.552 |
| Troponin T, per 0.01 ng/mL increase | 1.990 | 0.849–4.665 | 0.113 | | | |
| H-FABP, per 1 ng/mL increase | 1.198 | 1.122–1.279 | <0.001 | 1.165 | 1.034–1.314 | 0.012 |
| High sensitive CRP, per 0.1 mg/dL increase | 1.029 | 0.914–1.921 | 0.137 | | | |
| Echocardiographic data | | | | | | |
| LA diameter, per SD increase | 1.641 | 1.002–1.122 | 0.041 | 1.244 | 0.957–1.101 | 0.461 |
| LV end-diastolic diameter, per SD increase | 0.817 | 0.941–1.014 | 0.218 | | | |
| LV ejection fraction, per SD increase | 1.191 | 0.986–1.053 | 0.262 | | | |
| LV mass index, per SD increase | 1.197 | 0.998–1.008 | 0.285 | | | |
| E/A ratio, per SD increase | 1.376 | 0.915–3.561 | 0.088 | | | |
| Medications | | | | | | |
| ACE inhibitors and/or ARBs | 1.036 | 0.534–1.992 | 0.915 | | | |
| β Blockers | 1.159 | 0.604–2.221 | 0.657 | | | |
| Ca channel blockers | 0.895 | 0.454–1.764 | 0.749 | | | |

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; H-FABP, heart-type fatty acid-binding protein; HR, hazard ratio; LA, left atrial; LV, left ventricular; NYHA, New York Heart Association; SD, standard deviation.

**Table 6**
Clinical characteristics by tertile of heart-type fatty acid binding protein levels in patients with heart failure and preserved ejection fraction.

| | 1st tertile H-FABP 0.5–3.0 ng/mL ($n=50$) | 2nd tertile H-FABP 3.1–4.9 ng/mL ($n=50$) | 3rd tertile H-FABP 5.0–24 ng/mL ($n=51$) | *p*-Value |
|---|---|---|---|---|
| Age, years | 61 ± 14 | 71 ± 8 | 73 ± 8 | <0.001 |
| Female, *n* (%) | 24 (48) | 22 (44) | 25 (49) | 0.868 |
| NYHA functional class, I/II/III | 20/23/7 | 1/39/10 | 1/27/23 | <0.001 |
| Etiology, *n* (%) | | | | 0.214 |
| Hypertensive heart disease | 21 (42) | 24 (48) | 25 (49) | |
| Ischemic heart disease | 8 (16) | 9 (18) | 5 (10) | |
| Valvular heart disease | 15 (30) | 7 (14) | 7 (14) | |
| Tachycardia-induced heart failure | 2 (4) | 7 (14) | 9 (18) | |
| Other | 4 (8) | 3 (6) | 5 (10) | |
| Atrial fibrillation, *n* (%) | 15 (30) | 19 (38) | 20 (39) | 0.578 |
| Diabetes mellitus, *n* (%) | 11 (22) | 15 (30) | 11 (22) | 0.542 |
| Dyslipidemia, *n* (%) | 13 (26) | 13 (26) | 9 (18) | 0.516 |
| Current smoker, *n* (%) | 13 (26) | 11 (22) | 10 (20) | 0.079 |
| Presentation profile | | | | |
| Systolic pressure, mm Hg | 114 ± 23 | 123 ± 18 | 114 ± 23 | 0.073 |
| Heart rate, bpm | 69 ± 13 | 74 ± 14 | 70 ± 13 | 0.154 |
| Body mass index, kg/m$^2$ | 23.4 ± 2.5 | 23.7 ± 3.2 | 22.2 ± 3.8 | 0.054 |
| eGFR, mL/min/1.73 m$^2$ | 79 ± 19 | 63 ± 18 | 58 ± 19 | <0.001 |
| Blood biomarkers | | | | |
| BNP, pg/mL (IQR) | 112 (38–253) | 93 (43–215) | 250 (86–589) | 0.006 |
| Troponin T, ng/mL (IQR) | 0.01 (0.01–0.01) | 0.01 (0.01–0.01) | 0.05 (0.02–0.16) | <0.001 |
| H-FABP, ng/mL (IQR) | 2.4 (1.8–2.8) | 3.8 (3.4–4.3) | 6.9 (6.1–9.1) | <0.001 |
| High sensitive CRP, mg/dL (IQR) | 0.10 (0.04–0.27) | 0.10 (0.05–0.24) | 0.32 (0.12–0.79) | <0.001 |
| Echocardiographic data | | | | |
| LA diameter, mm | 42.6 ± 6.5 | 42.5 ± 6.4 | 45.8 ± 11.1 | 0.094 |
| LV end-diastolic diameter, mm | 51.8 ± 9.6 | 47.1 ± 8.9 | 49.0 ± 7.5 | 0.127 |
| LV ejection fraction, % | 65.1 ± 9.6 | 67.0 ± 7.6 | 64.3 ± 10.1 | 0.315 |
| LV mass index, g/m$^2$ | 181 ± 66 | 160 ± 53 | 187 ± 59 | 0.069 |
| E/A ratio | 0.90 ± 0.43 | 0.74 ± 0.32 | 1.21 ± 0.69 | 0.002 |
| Medications, *n* (%) | | | | |
| ACE inhibitors and/or ARBs | 28 (56) | 33 (66) | 36 (71) | 0.295 |
| β Blockers | 14 (28) | 13 (26) | 24 (47) | 0.047 |
| Ca channel blockers | 13 (26) | 17 (34) | 12 (24) | 0.472 |

Data are presented as mean ± SD or % unless otherwise indicated. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; H-FABP, heart-type fatty acid-binding protein; IQR, interquartile range; LA, left atrial; LV, left ventricular; NYHA, New York Heart Association.

Unfortunately, the detailed processes involved in myocardial cell death in patients with HF-PEF have not been fully clarified. However, at least in the present study, ischemic myocardial injury was not associated with myocardial damage. A large number of patients with ischemic heart disease were included among those without ongoing myocardial damage. In agreement with previous reports [9–13], age, being in NYHA functional class III, renal function, and plasma BNP levels were associated with ongoing myocardial damage. The present findings, therefore, confirmed the close relationship between advanced HF and latent myocardial damage in patients with HF-PEF.

*Ongoing myocardial damage and LV function*

Progressive loss of myocytes is recognized as one of the pathophysiological mechanisms in the evolution of cardiac dysfunction in HF [15–17]. Latent loss of cardiomyocytes was detected clinically as increased serum levels of H-FABP and cardiac troponins. Previous studies confirmed a significant correlation between serum troponin levels and LV function [18,19]. However, in the present study, serum troponin T levels were not correlated with any echocardiographic parameters. One explanation for these different findings may be that troponin T levels were only measured once during the study period. Indeed, LVEF decreased by 5.9% in patients with high troponin T levels compared to those with normal troponin T levels, during a follow-up period of 20.8 ± 11.2 months [20]. Follow-up measurements of troponin T and echocardiographic findings may provide additional information on cardiac function.

The association between H-FABP and LV function has not been clarified. Serum H-FABP levels were also not correlated with LVEF, LV end-diastolic diameter, or LV mass index in patients with HF-PEF. Conversely, weak correlations were observed between serum H-FABP levels and LA diameter, and E/A ratio. There was a significant association between circulating H-FABP levels and LV diastolic function. As well as measuring cardiac troponin, additional measurements of H-FABP may be necessary to accurately assess the relationship between serum H-FABP levels and cardiac function.

*Prognostic value of H-FABP in patients with HF-PEF*

This study confirmed the superior sensitivity of H-FABP compared with that of troponin T, as demonstrated in this and earlier studies [12,21,22]. Basic and clinical research, using rats and human autopsy cases, revealed that leakage of H-FABP occurred despite the absence of myocyte necrosis [21]. H-FABP is a low molecular weight protein that is confined to the cytoplasm, and is released into the circulation through the porous membranes of damaged myocardial cells [22].

An association between BNP and outcomes in patients with HF-PEF has been reported previously [23,24]. Conversely, BNP did not independently predict cardiovascular events in the present study. Possible explanations for these different findings may be that H-FABP is not only just a marker of myocardial damage, but may also be a biomarker for several clinical characteristics. Consistent with our results, a large community-based population study demonstrated that serum H-FABP levels were associated with age, gender, and renal function [25]. In addition, circulating H-FABP levels were significantly correlated with cardiac sympathetic dysfunction [26]. Moreover, serum H-FABP levels were weakly correlated with LA diameter and E/A ratio, which are indicators of LV diastolic dysfunction. On the other hand, neither troponin T nor BNP levels were correlated with LA diameter. A persistent increase in LA filling pressure leads to dilation of the chamber and stretching of the atrial myocardium. Increased LA size is a more sensitive prognostic indicator than BNP levels in HF patients [27]. Several clinical indicators that provide prognostic information were significantly associated with serum levels of H-FABP. Therefore, H-FABP may be a more sensitive prognostic indicator than troponin T and BNP levels in patients with HF-PEF.

H-FABP levels were categorized into tertiles because the normal range for H-FABP in patients with HF-PEF has not been established. Although, in the adjusted model, there was no difference between patients in the first and second tertiles of H-FABP, patients in the highest tertile had a 4.4-fold increased risk of cardiac events. In this regard, awareness of latent myocardial damage is important during long-term follow-up of patients with HF-PEF, especially in patients with H-FABP levels >5.0 ng/mL.

*Study limitations*

First, this single-center study included a population of referred HF patients. Therefore, the characteristics of these patients with HF-PEF differed from those of patients enrolled in community-based studies. This study population showed a relatively high proportion of patients with valvular heart disease and tachycardia-induced cardiomyopathy. This study did not include patients with congenital heart disease and moderate or severe valvular heart disease. Second, the present findings in patients with HF-PEF may not be applicable to patients with severe HF. Consistent with previous research, the circulating level of H-FABP, but not BNP, was a predictor of cardiovascular events in patients with early stage HF [11]. However, BNP may also have better prognostic accuracy in other clinical settings. Third, detailed echocardiographic assessments were not performed in the present study. Patients with myocardial damage had higher E/A ratios than those without myocardial damage. This is referred to as the pseudonormalized mitral flow filling pattern, and may represent a moderate stage of diastolic dysfunction in patients with high levels of H-FABP. Advanced echocardiography may help to clarify the relationship between ongoing myocardial damage and LV diastolic function in patients with HF-PEF. Finally, serum H-FABP levels were measured once on the day of admission. Although patients with acute decompensated HF were excluded, serum H-FABP levels in patients in NYHA functional class III may be correlated with volume overload/wall stress in the setting of acute heart failure. Additional measurements of H-FABP may provide useful information during follow-up.

## Conclusions

Ongoing myocardial injury was frequently observed in patients with HF-PEF. Circulating H-FABP level was a significant predictor for increased risk of cardiovascular events in patients with HF-PEF. H-FABP may be a novel, useful biomarker for identifying patients with HF-PEF, who are at increased risk of death and re-hospitalization.

## Acknowledgments

This work was supported, in part, by a grant-in-aid for Scientific Research (No. 22790683, 21790700 and 21590923) from the Ministry of Education Culture, Sport, Science, and Technology and a grant-in-aid from the Global Century Center of Excellence (COE) program of the Japan Society for the Promotion of Science.

## References

[1] Satomura H, Wada H, Sakakura K, Kubo N, Ikeda N, Sugawara Y, Ako J, Momomura S. Congestive heart failure in the elderly: comparison between reduced ejection fraction and preserved ejection fraction. J Cardiol 2012;59:215–9.
[2] Goda A, Yamashita T, Suzuki S, Ohtsuka T, Uejima T, Oikawa Y, Yajima J, Koike A, Nagashima K, Kirigaya H, Sagara K, Ogasawara K, Isobe M, Sawada H, Aizawa T.

Heart failure with preserved versus reduced left ventricular systolic function: a prospective cohort of Shinken Database 2004–2005. J Cardiol 2010;55:108–16.
[3] Shah RV, Desai AS, Givertz MM. The effect of renin-angiotensin system inhibitors on mortality and heart failure hospitalization in patients with heart failure and preserved ejection fraction: a systematic review and meta-analysis. J Card Fail 2010;16:260–7.
[4] Yamamoto K, Sakata Y, Ohtani T, Takeda Y, Mano T. Heart failure with preserved ejection fraction. Circ J 2009;73:404–10.
[5] Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. New Engl J Med 2006;355:260–9.
[6] Kociol RD, Horton JR, Fonarow GC, Reyes EM, Shaw LK, O'Connor CM, Felker GM, Hernandez AF. Admission, discharge, or change in B-type natriuretic peptide and long-term outcomes: data from organized program to initiate lifesaving treatment in hospitalized patients with heart failure (OPTIMIZE-HF) linked to Medicare claims. Circ Heart Fail 2011;4:628–36.
[7] Kusumoto A, Miyata M, Kubozono T, Ikeda Y, Shinsato T, Kuwahata S, Fujita S, Takasaki K, Yuasa T, Hamasaki S, Tei C. Highly sensitive cardiac troponin T in heart failure: comparison with echocardiographic parameters and natriuretic peptides. J Cardiol 2012;59:202–8.
[8] Setsuta K, Seino Y, Ogawa T, Arao M, Miyatake Y, Takano T. Use of cytosolic and myofibril markers in the detection of ongoing myocardial damage in patients with chronic heart failure. Am J Med 2002;113:717–22.
[9] Arimoto T, Takeishi Y, Shiga R, Fukui A, Tachibana H, Nozaki N, Hirono O, Nitobe J, Miyamoto T, Hoit BD, Kubota I. Prognostic value of elevated circulating heart-type fatty acid binding protein in patients with congestive heart failure. J Card Fail 2005;11:56–60.
[10] Niizeki T, Takeishi Y, Arimoto T, Takahashi T, Okuyama H, Takabatake N, Nozaki N, Hirono O, Tsunoda Y, Shishido T, Takahashi H, Koyama Y, Fukao A, Kubota I. Combination of heart-type fatty acid binding protein and brain natriuretic peptide can reliably risk stratify patients hospitalized for chronic heart failure. Circ J 2005;69:922–7.
[11] Arimoto T, Takeishi Y, Niizeki T, Nozaki N, Hirono O, Watanabe T, Nitobe J, Tsunoda Y, Suzuki S, Koyama Y, Kitahara T, Okada A, Takahashi K, Kubota I. Cardiac sympathetic denervation and ongoing myocardial damage for prognosis in early stages of heart failure. J Card Fail 2007;13:34–41.
[12] Niizeki T, Takeishi Y, Arimoto T, Takabatake N, Nozaki N, Hirono O, Watanabe T, Nitobe J, Harada M, Suzuki S, Koyama Y, Kitahara T, Sasaki T, Kubota I. Heart-type fatty acid-binding protein is more sensitive than troponin T to detect the ongoing myocardial damage in chronic heart failure patients. J Card Fail 2007;13:120–7.
[13] Niizeki T, Takeishi Y, Arimoto T, Nozaki N, Hirono O, Watanabe T, Nitobe J, Miyashita T, Miyamoto T, Koyama Y, Kitahara T, Suzuki S, Sasaki T, Kubota I. Persistently increased serum concentration of heart-type fatty acid-binding protein predicts adverse clinical outcomes in patients with chronic heart failure. Circ J 2008;72:109–14.
[14] Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982–92.
[15] Olivetti G, Abbi R, Quaini F, Kajstura J, Cheng W, Nitahara JA, Quaini E, Di Loreto C, Beltrami CA, Krajewski S, Reed JC, Anversa P. Apoptosis in the failing human heart. New Engl J Med 1997;336:1131–41.
[16] Anversa P, Kajstura J. Myocyte cell death in the diseased heart. Circ Res 1998;82:1231–3.
[17] Kostin S, Pool L, Elsässer A, Hein S, Drexler HC, Arnon E, Hayakawa Y, Zimmermann R, Bauer E, Klövekorn WP, Schaper J. Myocytes die by multiple mechanisms in failing human hearts. Circ Res 2003;92:715–24.
[18] Logeart D, Beyne P, Cusson C, Tokmakova M, Leban M, Guiti C, Bourgoin P, Solal AC. Evidence of cardiac myolysis in severe nonischemic heart failure and the potential role of increased wall strain. Am Heart J 2001;141:247–53.
[19] Horwich TB, Patel J, MacLellan WR, Fonarow GC. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. Circulation 2003;108:833–8.
[20] Sato Y, Yamada T, Taniguchi R, Nagai K, Makiyama T, Okada H, Kataoka K, Ito H, Matsumori A, Sasayama S, Takatsu Y. Persistently increased serum concentrations of cardiac troponin T in patients with idiopathic dilated cardiomyopathy are predictive of adverse outcomes. Circulation 2001;103:369–74.
[21] Meng X, Ming M, Wang E. Heart fatty acid binding protein as a marker for postmortem detection of early myocardial damage. Forensic Sci Int 2006;160:11–6.
[22] Viswanathan K, Kilcullen N, Morrell C, Thistlethwaite SJ, Sivananthan MU, Hassan TB, Barth JH, Hall AS. Heart-type fatty acid-binding protein predicts long-term mortality and re-infarction in consecutive patients with suspected acute coronary syndrome who are troponin-negative. J Am Coll Cardiol 2010;55:2590–8.
[23] Valle R, Aspromonte N, Feola M, Milli M, Canali C, Giovinazzo P, Carbonieri E, Ceci V, Cerisano S, Barro S, Milani L. B-type natriuretic peptide can predict the medium-term risk in patients with acute heart failure and preserved systolic function. J Card Fail 2005;11:498–503.
[24] Grewal J, McKelvie RS, Persson H, Tait P, Carlsson J, Swedberg K, Ostergren J, Lonn E. Usefulness of N-terminal pro-brain natriuretic peptide and brain natriuretic peptide to predict cardiovascular outcomes in patients with heart failure and preserved left ventricular ejection fraction. Am J Cardiol 2008;102:733–7.
[25] Niizeki T, Takeishi Y, Takabatake N, Shibata Y, Konta T, Kato T, Kawata S, Kubota I. Circulating levels of heart-type fatty acid-binding protein in a general Japanese population: effects of age, gender, and physiologic characteristics. Circ J 2007;71:1452–7.
[26] Arimoto T, Takeishi Y, Niizeki T, Koyama Y, Okuyama H, Nozaki N, Hirono O, Tsunoda Y, Miyashita T, Shishido T, Okada A, Takahashi K, Kubota I. Ongoing myocardial damage relates to cardiac sympathetic nervous disintegrity in patients with heart failure. Ann Nucl Med 2005;19:535–40.
[27] Tamura H, Watanabe T, Nishiyama S, Sasaki S, Arimoto T, Takahashi H, Shishido T, Miyashita T, Miyamoto T, Nitobe J, Hirono O, Kubota I. Increased left atrial volume index predicts a poor prognosis in patients with heart failure. J Card Fail 2011;17:210–6.

European Journal of Heart Failure (2012) **14**, 367–376
doi:10.1093/eurjhf/hfs001

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

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*Received 1 November 2011; revised 12 December 2011; accepted 13 December 2011; online publish-ahead-of-print 31 January 2012*

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

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

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

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

## Introduction

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

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

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

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

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

# Methods

## Population and inclusion criteria

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

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

## Measurements of albuminuria

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

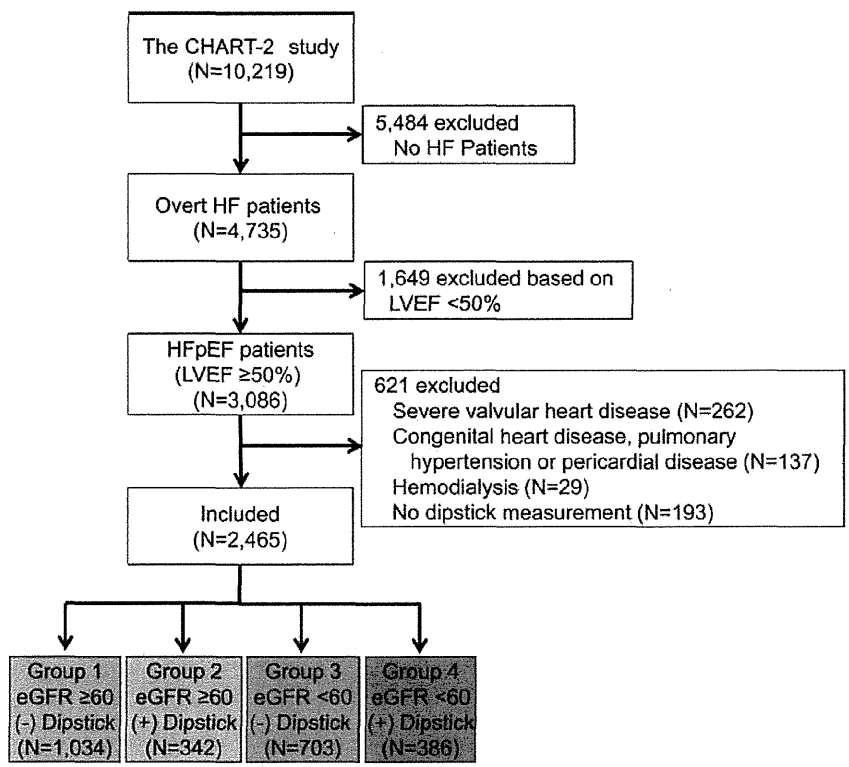


**Figure 1** Study flow diagram. eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction.

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

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

### Renal function

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

### Follow-up survey and study outcomes

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

### Statistical analysis

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

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

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

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

## Results

### Baseline characteristics (*Table 1*)

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

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

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

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

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

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

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

Analysis of variance (ANOVA) with reduced eGFR and positive urine dipstick test (UDT) as factors, including a test for interaction, was used to identify variables that were associated with reduced eGFR and/or positive urine dipstick test. Numerical data are shown as mean ± standard deviation.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate; HF, heart failure; NYHA, New York Heart Association; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

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

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

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

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

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

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

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

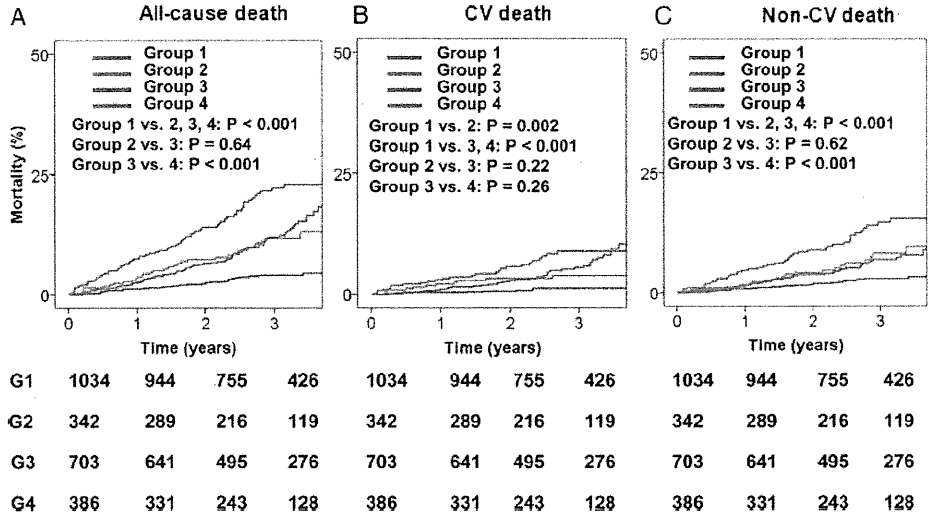


**Figure 2** Kaplan–Meier survival curves for all-cause death (*A*), cardiovascular (CV) death (*B*), and non-CV death (*C*). The four groups were categorized based on the estmated glomerular filtration rate (eGFR) and urine dipstick test (UDT): group 1 (G1) (eGFR ≥60, negative UDT), G2 (eGFR ≥60, positive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

# Discussion

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

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

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

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

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

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

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

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

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

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

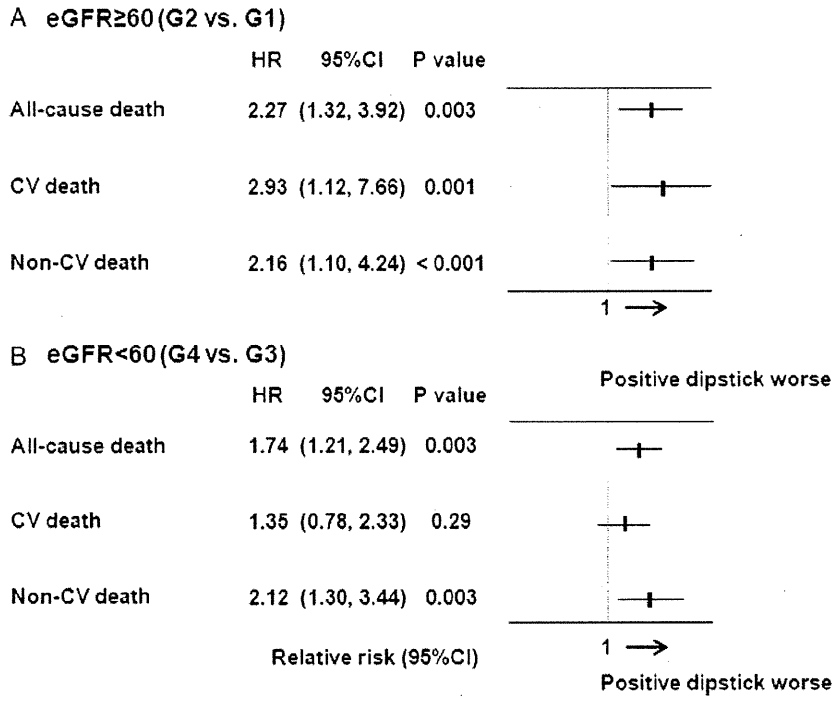


**Figure 3** Hazard ratios (HRs) for all-cause death, cardiovascular (CV) death, and non-CV death after adjustment by multiple covariates including estimated glomerular filtration rate (eGFR). (*A*) eGFR ≥60 (G2 vs. G1), (*B*) eGFR <60 (G4 vs. G3). 95%CI, 95% confidence interval.

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

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

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

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

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

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

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

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

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

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

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

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

## Study limitations

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

# Conclusions

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

## Acknowledgments

We thank all members of the Tohoku Heart Failure Society and staff of the department of evidence-based cardiovascular medicine for their kind contributions.

## Funding

The Ministry of Health, Labour, and Welfare (Grants-in-Aid from a Research Grant to H.S. and N.S.); the Ministry of Education, Culture, Sports, Science, and Technology of Japan (Research Grant to N.S.).

**Conflict of interest:** none declared.

## References


1. Meta-analysis Global Group in Chronic Heart Failure. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J* 2011;in press.
2. Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. *Circulation* 2000;**101**:2118–2121.
3. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J* 2011;**32**:670–679.
4. Paulus WJ, van Ballegoij JJ. Treatment of heart failure with normal ejection fraction: an inconvenient truth! *J Am Coll Cardiol* 2010;**55**:526–537.
5. Edelmann F, Stahrenberg R, Gelbrich G, Durstewitz K, Angermann CE, Düngen HD, Scheffold T, Zugck C, Maisch B, Regitz-Zagrosek V, Hasenfuß G, Pieske BM, Wachter R. Contribution of comorbidities to functional impairment is higher in heart failure with preserved than with reduced ejection fraction. *Clin Res Cardiol* 2011;**100**:755–764
6. Longhini C, Molino C, Fabbian F. Cardiorenal syndrome: still not a defined entity. *Clin Exp Nephrol* 2010;**14**:12–21.
7. Ahmed A, Rich MW, Sanders PW, Perry GJ, Bakris GL, Zile MR, Love TE, Aban IB, Shlipak MG. Chronic kidney disease associated mortality in diastolic versus systolic heart failure: a propensity matched study. *Am J Cardiol* 2007;**99**:393–398.
8. Arnlöv J, Evans JC, Meigs JB, Wang TJ, Fox CS, Levy D, Benjamin EJ, D'Agostino RB, Vasan RS. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. *Circulation* 2005;**112**:969–975.
9. Wachtell K, Ibsen H, Olsen MH, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlöf B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristianson K, Lederballe-Pedersen O, Nieminen MS, Okin PM, Omvik P, Oparil S, Wedel H, Snapinn SM, Aurup P. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. *Ann Intern Med* 2003;**139**:901–906.
10. Deckert T, Yokoyama H, Mathiesen E, Rønn B, Jensen T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen JS. Cohort study of predictive value of urinary albumin excretion for atherosclerotic vascular disease in patients with insulin dependent diabetes. *BMJ* 1996;**312**:871–874.
11. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation classification and stratification. *Am J Kidney Dis* 2002; **39**:S1–S266.
12. van de Wal RM, Asselbergs FW, Plokker HW, Smilde TD, Lok D, van Veldhuisen DJ, van Gilst WH, Voors AA. High prevalence of microalbuminuria in chronic heart failure patients. *J Card Fail* 2005;**11**:602–606.
13. Jackson CE, Solomon SD, Gerstein HC, Zetterstrand S, Olofsson B, Michelson EL, Granger CB, Swedberg K, Pfeffer MA, Yusuf S, McMurray JJ, CHARM Investigators and Committees. Albuminuria in chronic heart failure: prevalence and prognostic importance. *Lancet* 2009;**374**:543–550.
14. Anand IS, Bishu K, Rector TS, Ishani A, Kuskowski MA, Cohn JN. Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure. *Circulation* 2009;**120**:1577–1584.
15. Masson S, Latini R, Milani V, Moretti L, Rossi MG, Carbonieri E, Frisinghelli A, Minneci C, Valisi M, Maggioni AP, Marchioli R, Tognoni G, Tavazzi L. GISSI-HF Investigators. Prevalence and prognostic value of elevated urinary albumin excretion in patients with chronic heart failure: data from the GISSI-Heart Failure trial. *Circ Heart Fail* 2010;**3**:65–72.
16. Jackson CE, MacDonald MR, Petrie MC, Solomon SD, Pitt B, Latini R, Maggioni AP, Smith BA, Prescott MF, Lewsey J, McMurray JJ; ALiskiren Observation of heart Failure Treatment (ALOFT) investigators. Associations of albuminuria in patients with chronic heart failure: findings in the ALiskiren Observation of heart Failure Treatment study. *Eur J Heart Fail* 2011;**13**:746–754.
17. Shiba N, Nochioka K, Miura M, Kohno H, Shimokawa H. rend for westernization of etiology and clinical characteristics of heart failure patients in Japan. *Circ J* 2011; **75**:823–833.
18. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults. A Report of the ACC/AHA Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol* 2009;**14**:53:e1–e90.
19. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971;**285**:1441–1446.
20. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. *Circulation*2008;**118**:e523–e661.
21. Konta T, Hao Z, Takasaki S, Abiko H, Ishikawa M, Takahashi T, Ikeda A, Ichikawa K, Kato T, Kawata S, Kubota I. Clinical utility of trace proteinuria for microalbuminuria screening in the general population. *Clin Exp Nephrol* 2007;**11**: 51–55.
22. White SL, Yu R, Craig JC, Polkinghorne KR, Atkins RC, Chadban SJ. Diagnostic accuracy of urine dipsticks for detection of albuminuria in the general community. *Am J Kidney Dis* 2011;**58**:19–28.
23. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, Ura N, Kiyohara Y, Hirakata H, Watanabe T, Moriyama T, Ando Y, Inaguma D, Narita I, Iso H, Wakai K, Yasuda Y, Tsukamoto Y, Ito S, Makino H, Hishida A, Matsuo S. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. *Clin Exp Nephrol* 2007;**11**:41–50.
24. Tribouilloy C, Rusinaru D, Mahjoub H, Soulière V, Lévy F, Peltier M, Slama M, Massy Z. Prognosis of heart failure with preserved ejection fraction: a 5-year prospective population-based study. *Eur Heart J* 2008;**29**:339–347.
25. Kapoor JR, Heidenreich PA. Heart rate predicts mortality in patients with heart failure and preserved systolic function. *J Card Fail* 2010;**16**:806–811.
26. Scrutinio D, Passantino A, Santoro D, Catanzaro R. The cardiorenal anaemia syndrome in systolic heart failure: prevalence, clinical correlates, and long-term survival. *Eur J Heart Fail* 2011;**13**:61–67.
27. Shah RV, Desai AS, Givertz MM. The effect of renin–angiotensin system inhibitors on mortality and heart failure hospitalization in patients with heart failure and preserved ejection fraction: a systematic review and meta-analysis. *J Card Fail* 2010;**16**: 260–267.
28. Wegria R, Capeci NE, Blumenthal MR, Kornfeld P, Hays DR, Elias RA, Hilton JG. The pathogenesis of proteinuria in the acutely congested kidney. *J Clin Invest* 1955; **34**:737–743.
29. Wilcox CS. New insights into diuretic use in patients with chronic renal disease. *J Am Soc Nephrol* 2002;**13**:798–805.
30. Zile MR, Gaasch WH, Anand IS, Haass M, Little WC, Miller AB, Lopez-Sendon J, Teerlink JR, White M, McMurray JJ, Komajda M, McKelvie R, Ptaszynska A, Hetzel SJ, Massie BM, Carson PE; I-Preserve Investigators. Mode of death in patients with heart failure and a preserved ejection fraction: Results from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study Trial. *Circulation* 2010;**121**:1393–1405.
31. Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, Gans RO, Janssen WM, Grobbee DE, de Jong PE; Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002;**106**:1777–1782.
32. Perkins BA, Ficociello LH, Ostrander BE, Silva KH, Weinberg J, Warram JH, Krolewski AS. Microalbuminuria and the risk for early progressive renal function decline in type 1 diabetes. *J Am Soc Nephrol* 2007;**18**:1353–1361.
33. Pedersen LM, Terslev L, Stˆrensen PG, Stokholm KH. Urinary albumin excretion and transcapillary escape rate of albumin in malignancies. *Med Oncol* 2000;**17**: 117–122.
34. Asselbergs FW, Diercks GF, Hillege HL, van Boven AJ, Janssen WM, Voors AA, de Zeeuw D, de Jong PE, van Veldhuisen DJ, van Gilst WH; Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) Investigators. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation* 2004;**110**:2809–2816.
35. Jafar TH, Schmid CH, Landa M, Giatras I, Toto R, Remuzzi G, Maschio G, Brenner BM, Kamper A, Zucchelli P, Becker G, Himmelmann A, Bannister K, Landais P, Shahinfar S, de Jong PE, de Zeeuw D, Lau J, Levey AS. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Intern Med* 2001;**135**:73–87.
36. Ito S. Usefulness of RAS inhibition depends on baseline albuminuria. *Nat Rev Nephrol* 2010;**6**:10–11.

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Heart Failure

# Intrathoracic Impedance Monitoring in Patients With Heart Failure

## – Correlation With Dehydration and Bleeding Events –

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*Background:* Cardiac resynchronization therapy/defibrillators (CRTD) and implantable cardioverter defibrillators (ICD) with continuous intrathoracic impedance monitoring might provide an early warning of thoracic fluid retention. In contrast, volume loss events such as dehydration and bleeding are also common events in heart failure patients treated with diuretics and anticoagulants. The correlation between intrathoracic impedance and a volume loss event is not known.

*Methods and Results:* This study evaluated the association between intrathoracic impedance and volume loss events in 36 patients with chronic heart failure (New York Heart Association [NYHA] II, III and IV) who had received CRTD/ICD implantation. Elevation of thoracic impedance above the reference line was defined as a positive deviation of thoracic impedance (PDI). This study recorded 249 PDIs including 60 spike PDIs defined as over 5ohms elevation from the reference line and 17 large PDIs as over 5ohms elevation and continuing for at least 4 days. Clinically, 96 dehydration events and 2 bleeding events were observed over a 1-year period. The sensitivity and positive predictive value (PPV) for spike PDI was 31.6% and 51.7%, respectively, while those for large PDI were 17.3% and 100%, respectively.

*Conclusions:* A large PDI reflected dehydration and bleeding events with a high PPV in severe heart failure patients. The large PDI criteria might therefore be useful for predicting volume loss events in chronic heart failure patients. (*Circ J* 2012; **76:** 2592–2598)

**Key Words:** Cardiac resynchronization therapy; Heart failure; Implantable cardioverter defibrillator

Heart failure is a life-threatening and costly disease.[1–3] Repeated hospitalization due to heart failure increases medical costs and is also associated with the prognosis of these patients.[4] Early identification of heart failure-associated problems and early intervention before hospitalization would relieve some of this burden.[5] Fluid retention is the most common cause of heart failure-associated hospitalization.[6,7] The fluid retention detection algorithm (Fluid index in OptiVol, Medtronic Inc, Minneapolis, MN, USA) was designed to detect this common cause of heart failure-associated events. However, volume loss events such as low output syndrome due to dehydration as a result of excessive diuresis and gastrointestinal bleeding due to anticoagulation agents are often observed and are also severe problems.

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Thoracic impedance reflects not only fluid retention, but also fluid depletion. Actually, the feasibility of early detection of volume loss events has been shown in an animal model.[8] However, the clinical feasibility of a change in thoracic impedance to detect volume loss events associated with heart failure is not known.

The present study investigated the association between volume loss events and increased thoracic impedance in heart failure patients (New York Heart Association [NYHA] II, III and IV) with cardiac resynchronization therapy/defibrillators (CRTD) and implantable cardioverter defibrillators (ICD) with

Received February 13, 2012; revised manuscript received May 30, 2012; accepted June 20, 2012; released online July 14, 2012 Time for primary review: 20 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-12-0187

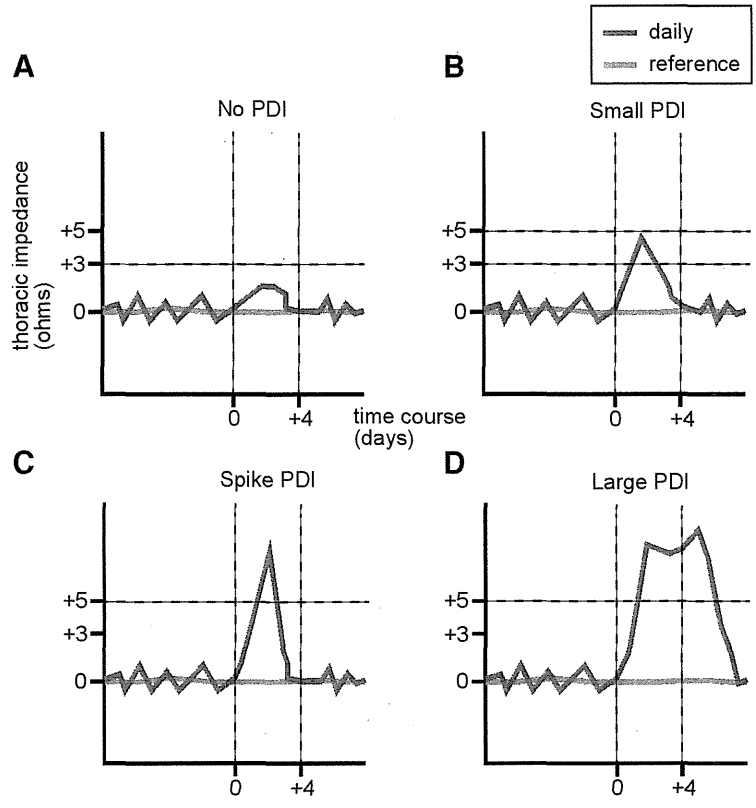


**Figure 1.** Definition of 4 criteria of positive deviation of thoracic impedance (PDI) for clinical use. Schematic diagrams illustrating the definition of positive deviation of thoracic impedance are shown (**A–D**). Impedance deviation within 3 ohms is counted as No PDI (**A**). Over 3 ohms to 5 ohms of impedance elevation above the reference line is defined as a small PDI (**B**). Over 5 ohms and less than 4 days' elevation is defined as a spike PDI (**C**). A large PDI is defined as over 5 ohms impedance and continuing for at least 4 days (**D**).

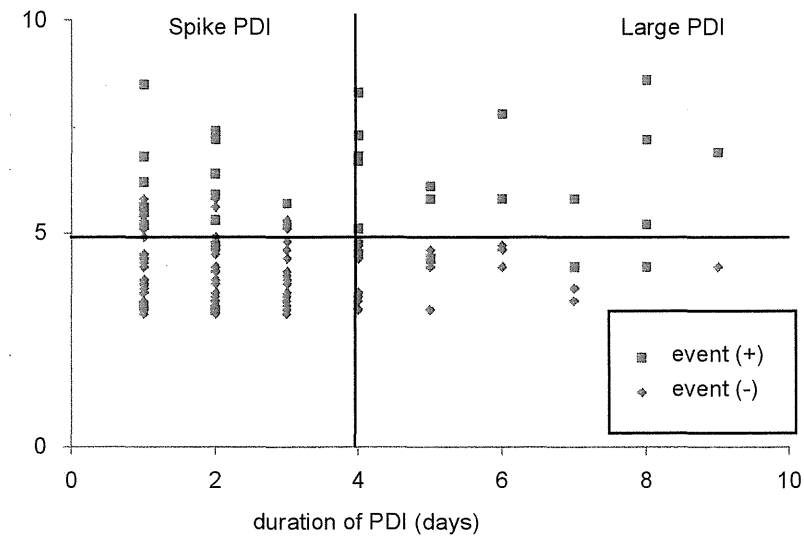


**Figure 2.** Distribution of the height and width of the positive deviation of thoracic impedances (PDIs). A dot plot of the peak level (ohms) in relation to the duration (days) of each PDI. The red closed squares indicate PDIs with dehydration or bleeding events. The blue closed diamonds indicate PDIs without dehydration or bleeding events. The solid lines show 5 ohms in the peak level and 4 days in the duration of the PDIs. The left upper area and right upper area indicate spike PDIs and large PDIs (also defined in **Figure 2**), respectively.

continuous intrathoracic impedance monitoring.

## Methods

This study retrospectively analyzed continuously monitored thoracic impedance for 18,615 days from 51 consecutive chronic heart failure patients (NYHA II, III and IV) undergoing CRTD or ICD implantation with the OptiVol Fluid Status Monitoring System (Medtronic Inc) between September 2009 and September 2011 at the University of Tokyo Hospital. Blood sampling performed once a month for the evaluation of volume loss or bleeding events was required for inclusion in this study. The most recent 1 year record of continuous thoracic impedance of each patient was analyzed. The analyzed period in-

**Table 1. Patients Characteristics (n=36)**

| | |
|---|---|
| **Age** | 59.6±15.0 |
| **Male** | 30 (83.3%) |
| **Cardiomyopathy** | |
| Ischemic | 11 (30.6%) |
| Non-ischemic | 25 (69.4%) |
| **NYHA** | |
| II | 8 (22.2%) |
| III | 19 (52.8%) |
| IV | 9 (25.0%) |
| **QRS** | 130±34 (ms) |
| **EF** | 38.6±19.3 (%) |
| **Cardiovascular disease** | |
| CAD | 14 (38.9%) |
| HT | 20 (55.6%) |
| DM | 10 (27.8%) |
| **Ventricular conduction disorders** | |
| LBBB | 15 (41.7%) |
| RBBB | 10 (27.8%) |
| Other | 3 (8.3%) |
| **Rhythm disorders** | |
| SSS | 10 (27.8%) |
| AF | |
| Paroxysmal | 7 (19.4%) |
| Persistent or Chronic | 10 (27.8%) |
| **HF medication** | |
| β-blocker | 27 (75.0%) |
| ACE inhibitor | 24 (66.7%) |
| Diuretics | 24 (66.7%) |
| Aldosterone antagonist | 19 (52.8%) |
| Digitalis | 3 (8.3%) |
| Anti-platelet drug | 14 (39.0%) |
| Anticoagulant | 18 (50.0%) |

Values are expressed as mean±SD
NYHA, New York Heart Association; QRS, QRS wiath; EF, ejection fraction; CAD, coronary artery disease; HT, hypertension; DM, diabetes mellitus; LBBB, left bundle branch block; RBBB, right bundle branch block; SSS, sick sinus syndrome; AF, atrial fibrillation; HF, heart failure; ACE, angiotensin converting enzyme.

**Table 2. Recorded PDIs From Continuous Intrathoracic Impedance Monitoring**

| Age | Event (–) | Event (+) |
|---|---|---|
| No PDI | ND | 12 |
| All PDI | 151 | 86 |
| Small PDI | 122 | 38 |
| Spike PDI | 29 | 31 |
| Large PDI | 0 | 17 |

PDI, positive deviation of thoracic impedance; ND, not done.

**Table 3. Sensitivity and PPV of PDIs for Volume Loss Events**

| Age | Sensitivity (%) | PPV (%) |
|---|---|---|
| All PDI | 87.8 | 34.8 |
| Small PDI | 38.8 | 22.1 |
| Spike PDI | 31.6 | 51.7 |
| Large PDI | 17.3 | 100.0 |

PDI, positive deviation of thoracic impedance; PPV, positive predictive value.

cluded the time from the pacemaker/defibrillator clinic visit until after over 1 year from device implantation in order to avoid non-specific thoracic impedance changes arising from inflammatory changes, fluid accumulation or infection around the generator. Upward deviation of thoracic impedance was defined as a positive deviation of thoracic impedance above the reference line (PDI). Small changes within 3 ohms for impedance change from the reference line was not counted as a PDI. Elevation impedance over 3 ohms up to 5 ohms above the reference was defined as a small PDI. Spike PDI was defined as elevation over 5 ohms over the reference line for a short time (within 4 days). A large PDI was defined as an elevation of the impedance over 5 ohms and continuing for at least 4 days. Three different types of PDI were defined by the degree of deviation and the duration of the deviated period from the reference line (Figure 1).

Volume loss events were analyzed using the following criteria: increases in blood urea nitrogen/serum creatinine ratio 2 times that observed on the prior blood test, the existence of clinical features of dehydration such as thirst, cutaneous dryness or low output syndrome that required clinical manipulation, including education regarding water intake, changing medications, rehydration therapy, blood infusions, catecholamine administration for low output syndrome and/or hospital admission.

A newly developed scale defined the clinical severity of the volume loss events as follows: 1 point, only education regarding water intake was required for recovery from dehydration; 2 points, adjustments to medications were required for recovery from dehydration or bleeding; 3 points, admission was required for recovery from dehydration, low output syndrome or bleeding; 4 points, catecholamine administration or blood infusion was required for recovery from dehydration, low output syndrome or bleeding.

The exclusion criteria were NYHA I patients at 1 year after device implantation, device-associated complications such as infection at the implanted site, lead troubles and the requirement of additional surgical manipulation after the first implantation. Those with right side implantation and device infection, thus leading to difficulties or hemodialysis, were also excluded from the study.

For each patient, blood tests were performed at least once a month to regularly evaluate dehydration and bleeding. If the interval between consecutive blood tests was more than 2 months, then the patient was excluded from this study.

The established protocol was in accordance with the Helsinki Declaration (2000 revision) and was approved by the institutional review board of the University of Tokyo Hospital. Written information consent was obtained from each patient before participation in the study.

### Statistical Analysis

All data are expressed as the mean±SD. The positive predictive values (PPVs) were calculated using Bayes' formula. Linear regression was used for the correlation analyses, which were expressed as Pearson correlation coefficients between thoracic impedance and the dehydration and bleeding event scale.

## Results

### Patients

There were a total of consecutive 51 chronic heart failure pa-

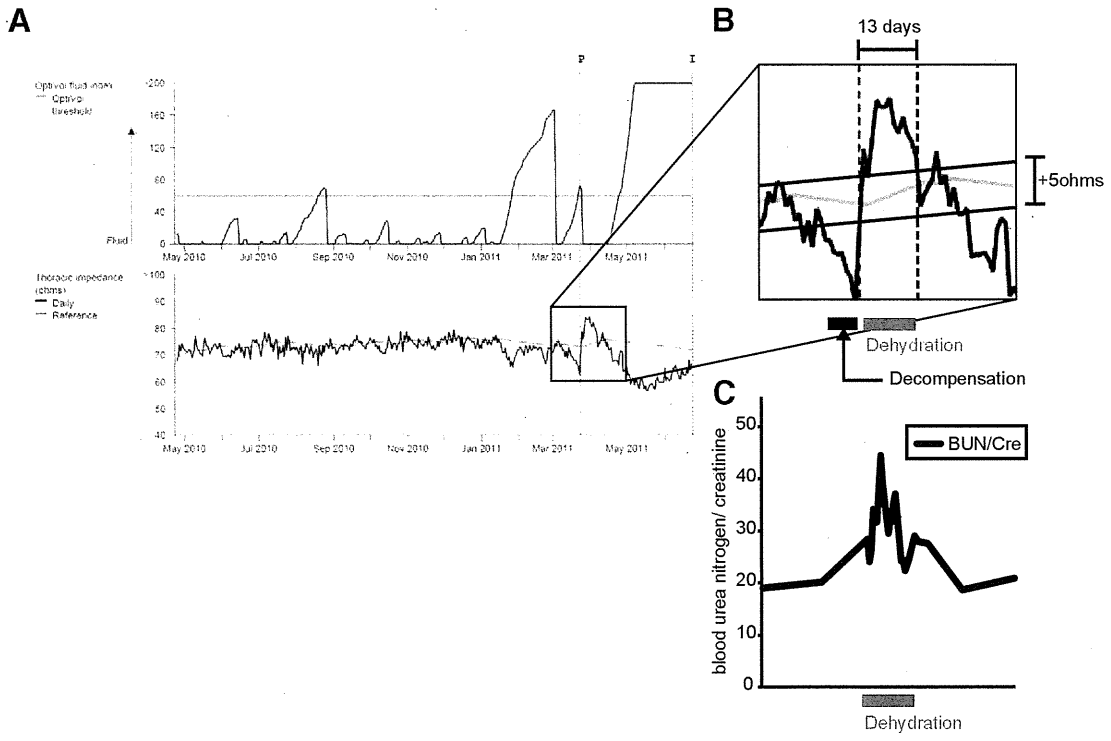


**Figure 3.** A typical large positive deviation of thoracic impedance (PDI) in intrathoracic impedance in the dehydration event during treatment of chronic heart failure patients. The OptiVol fluid trends report presents up to 14 months of rolling information on patient's OptiVol fluid index, average daily impedance and reference impedance (**A**,**B**). The time-course of intrathoracic impedance during acute decompensated heart failure (Decompensation: left closed box) and dehydration event (Dehydration: right closed box) after heart failure management including diuresis is shown (**A**,**B**). A large PDI was recorded and was consistent with the period of dehydration (**B**). The time-course of blood urea nitrogen/serum creatinine (BUN/Cr) ratio over the same periods in **Figure 2B** is shown. Thoracic impedance increased prior to BUN/Cr ratio elevation (**C**).

tients undergoing CRT/ICD implantation during the period of enrollment. Fifteen patients were excluded from the analysis based on the exclusion criteria (irregularity of blood sampling intervals (n=13) or hemodialysis (n=2)), thus a total of 36 adults patients (30 males, 6 females) were investigated (Table 1). Over 1 year passed after device implantation in all patients. The mean±SD age was 59.6±15.0 years. The causes of chronic heart failure were: ischemic cardiomyopathy (n=11) and non-ischemic cardiomyopathy (dilated cardiomyopathy) (n=25). All patients were of NYHA functional class II to IV at the time of implantation. In addition, 52.8% of patients were of NYHA class III and 25.0% were of class IV at the time of enrollment. The standard treatments were administered for chronic heart failure including renin-angiotensin inhibitors, $\beta$-blockers, diuretics, aldosterone antagonist, and anticoagulants.

## PDI Data Obtained During 1-Year Follow-up Periods

Two hundred and thirty-seven PDIs and 98 volume loss events, including 96 dehydrations and 2 bleedings, were recorded during the 1-year follow-up period, which was more than 1 year after device implantation (Table 2). All PDIs were analyzed for peak level and duration (Figure 1). This result suggests that PDIs with high peaks and long duration might reflect dehydration or bleeding events with high PPVs. For clinical convenience, 4 categories of PDI were defined, including spike PDI, large PDI, small PDI and no PDI (Figure 2). The PPVs for detecting dehydration and bleeding events were analyzed based on these criteria.

## Large PDIs Reflected Volume Loss Events With a High Positive Predictive Value

The sensitivity and PPV for a small PDI was 38.8% and 22.1%, respectively, for a spike PDI it was 31.6% and 51.7%, respectively, and for a large PDI it was 17.3% and 100%, respectively (Table 3). Although all PDI showed a high sensitivity, the PPV was low. In contrast, a spike PDI showed an intermediate high PPV for volume loss events. In addition, a large PDI showed a high PPV for volume loss events.

## Volume Loss Case 1: Dehydration Case

Figures 3A–C summarizes a case in which a patient with dilated cardiomyopathy was hospitalized due to volume retention. A CRT (Concerto C174AWK, Medtronic Inc) had been performed for repeated acute decompensated heart failure 2 years before this hospitalization. Intensive care was administered for congestive heart failure with diuretics and infusion of atrial natriuretic peptide to improve pulmonary congestion. However, excessive use of diuretics provoked significant dehydration after recovery from fluid retention. The time-course of thoracic impedance showed a dip below the reference line,