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Biomarkers in Acutely Decompensated Heart Failure with Preserved or Reduced Ejection Fraction

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Abstract

Background—Acute decompensated heart failure (ADHF) occurs with preserved (HFpEF, EF ≥50%) or reduced (HFrEF, EF<50%) ejection fraction. Natriuretic peptide (NP) levels are lower in HFpEF than HFrEF. We hypothesized that lower NP levels in HFpEF may be associated with other differences in biomarkers; specifically, renin-angiotensin-aldosterone system (RAAS) activation, oxidative stress and a biomarker that reflects collagen synthesis.

Methods—In this pre-specified ancillary analysis of ADHF patients enrolled in the Diuretic Optimization Strategies Evaluation (DOSE) study, clinical features and NT-proBNP, cystatin C, plasma renin activity (PRA), aldosterone, oxidative stress (uric acid) and procollagen type III N-terminal peptide (PIIINP) were compared in HFpEF and HFrEF at enrollment and 60 day follow-up.

Results—Compared to HFrEF (n=219), HFpEF (n=81) patients were older, heavier, more commonly female, less treated with RAAS antagonists, but with similar NYHA class, jugular venous pressure and edema severity. NT-proBNP was lower and systolic blood pressure (BP) and cystatin C were higher in HFpEF. Despite higher systolic BP and less RAAS antagonist use in HFpEF, PRA and aldosterone levels were similar in HFpEF and HFrEF as were uric acid and PIIINP levels. Changes in biomarker levels from enrollment to 60 days were similar between HFrEF (n=149) and HFpEF (n=50).

Conclusion—Lower NP levels in decompensated HFpEF occur in association with similar ADHF severity, more impaired vascular and renal function but similar elevation of biomarkers that reflect RAAS activation, oxidative stress and collagen synthesis as in HFrEF.

Introduction

The heart failure (HF) syndrome can be associated with reduced (HFrEF) or preserved (HFpEF) ejection fraction (EF). A consistent finding has been lower natriuretic peptide (NP) levels in HFpEF as compared to HFrEF patients.¹⁻⁴ Lower NP levels in HFpEF have been variably attributed to less severe HF⁵, a higher prevalence of obesity in HFpEF with enhanced NP clearance by adipocytes^{6, 7} or reduced NP production due to obesity related differences in androgen status⁸ and lower LV wall stress (the stimulus for NP production) in HFpEF owing to the concentric vs. eccentric patterns of LV remodeling in HFpEF and HFrEF respectively.^{9, 10}

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Disclosures

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Subject Codes: Biomarkers, Diastolic Heart Failure, Systolic Heart Failure

The pathophysiologic implications of the lower NP levels in HFpEF are unclear. The endogenous NP system plays a key role in blood pressure and volume regulation and promotes renal vasodilatation and natriuresis, inhibits renin and aldosterone and opposes oxidative stress and fibrosis.¹¹⁻¹³ We hypothesized that limited ability to activate the endogenous NP system in HFpEF patients with ADHF may be associated with differences in other biomarkers, specifically, those reflecting RAAS activation, oxidative stress and collagen synthesis.

Accordingly, in a pre-specified ancillary analysis of patients with chronic HF hospitalized with ADHF and enrolled in the Diuretic Optimization Strategies Evaluation (DOSE) study, clinical features and multiple biomarkers including NT-proBNP, cystatin C, plasma renin activity (PRA), aldosterone and markers of oxidative stress (uric acid) and a biomarker that reflects collagen synthesis (Procollagen Type III N-terminal peptide, PIIINP) were measured at enrollment (within 24 hours of admission) and at 60 days post-discharge and compared between HFpEF and HFrEF.

Methods

DOSE study was a prospective, randomized, double-blind, controlled trial conducted by the Heart Failure Clinical Research Network (HFCRN) examining responses to different diuretic intensification (1.0 and 2.5 times outpatient dose) and administration (intravenous bolus or continuous infusion) strategies. The data coordinating center (Duke Clinical Research Institute) was responsible for data management and statistical analysis. The study was approved by the institutional review board at each site, and all patients provided written informed consent. The DOSE trial design and its primary findings have been reported.^{14, 15}

Participants

DOSE enrolled ADHF patients within 24 hours of admission. Additional entry criteria were a history of chronic HF, therapy with an oral loop diuretic at a furosemide equivalent dose between 80 mg and 240 mg daily and a serum creatinine ≤ 3.0 mg/dL. Participants with EF assessment (echocardiography, radionuclide or contrast ventriculogram or magnetic resonance imaging) performed for clinical reasons within one-year prior to enrollment were included in this biomarker substudy with patients designated as HFrEF (EF $<50\%$) or HFpEF (EF $\geq 50\%$).

Biomarkers

All plasma samples were collected without pre-specified postural, dietary, pharmacologic or temporal restrictions but were generally collected during the daylight hours in bed-ridden ADHF patients at baseline and in ambulatory outpatients in the seated position at 60 days. Samples were stored at -80°C until analysis by the HFCRN Biomarker Core Laboratory (University of Vermont, Colchester, VT) with methodologies and normal values outlined in supplemental material.

Statistical Analysis

Medians and interquartile range (IQR) or number and frequency are presented for continuous and nominal variables respectively. A p-value < 0.05 was considered statistically significant. Analysis was performed using validated SAS software (SAS Institute, Inc, Cary, NC) at the HFCRN data coordinating center (Duke Clinical Research Institute). If biomarker data were missing, the patient was excluded from that particular analysis. The Wilcoxon rank sum test, chi-square, or Fisher's tests were used to compare variables between HFrEF and HFpEF groups as appropriate. The Wilcoxon signed-rank test was used to evaluate change in continuous variables from baseline to 60 days. A general linear model was used to

adjust for pertinent covariates. Variables were log transformed before inclusion in linear models if distributions were skewed (NT-pro-BNP, Cystatin C, PRA, Aldosterone and NT-procollagen).

Results

Clinical characteristics in HFrEF and HFpEF with ADHF (Table 1)

A total of 308 patients were enrolled in the DOSE trial. LVEF assessment within one year (median of 1.3 months, IQR of 0 to 5.9 months) was available in 300 patients (echocardiogram (n=287), radionuclide (n=3) or contrast ventriculogram (n=6) or other (n=4)). There were 219 (73%) patients with HFrEF (median LVEF 24%, IQR, 20-32%) and 81 (27%) patients with HFpEF (median LVEF 57%, IQR 55-64%). Consistent with previous reports, HFpEF patients were older, heavier, more likely to be female, less likely to have recognized ischemic heart disease, and more likely to have atrial fibrillation or flutter. Systolic arterial and pulse pressure were higher and diastolic pressure was lower in HFpEF vs HFrEF. The NYHA class, jugular venous pressure (JVP) and edema severity were similar in the two groups, but HFpEF patients had more extensive pulmonary rales, higher serum sodium, lower estimated GFR and lower hemoglobin. HFpEF patients were more likely to be taking calcium channel blockers and alpha-adrenergic receptor blocking agents and less likely to be taking angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), aldosterone antagonists, beta-blockers or digoxin.

Biomarker profile in HFpEF and HFrEF at admission with ADHF (Figure 1)

A subset of HFrEF (n=214, 98%) and HFpEF (n=78, 96%) had biomarker data at admission. NT-proBNP levels were elevated in both groups but were lower in HFpEF compared to HFrEF. This difference remained significant after adjustment for age, sex, NYHA class, cystatin C and BMI (p=0.008).

Cystatin C levels were elevated above the normal range in both HFrEF and HFpEF but cystatin C was higher in HFpEF compared to HFrEF. This difference was no longer statistically significant when adjusted for age and sex.

PRA and aldosterone levels were elevated in both HFpEF and HFrEF. While patients with HFpEF had higher systolic blood pressure (mitigating PRA activation) and were less often taking medications that result in elevations of PRA (ACE inhibitors or ARBs), PRA levels did not differ between HFpEF and HFrEF. Similarly, while patients with HFpEF were less often taking medications that may decrease (ACE inhibitors or ARBs) or increase (aldosterone receptor antagonists) aldosterone levels, aldosterone levels did not differ between HFpEF and HFrEF.

Uric acid and PIIINP were similarly increased above the normal range in both groups. Uric acid was still similar after adjustment for the differences in cystatin C (p=0.92).

Biomarker Profile subsequent to the ADHF episode in HFpEF and HFrEF

A subset of HFrEF (n=149, 68%) and HFpEF (n=50, 62%) patients had biomarker data available at admission and 60 days. Incomplete data was due to death (n=29), inability to return or incomplete data collection. Baseline diuretic dose and aldosterone levels were higher in participants without 60 days follow-up, but the remaining baseline clinical characteristics and biomarker levels were not different between those with or without 60 days follow-up data (supplementary tables 1-3).

At 60 days follow-up, there were significant and similar decreases in weight, JVP, peripheral edema and NYHA functional class in HFrEF and HFpEF (Table 2). Systolic arterial and pulse pressures remained higher in HFpEF than HFrEF patients at 60 days.

NT-proBNP decreased in both groups but the change was not statistically significant in HFpEF (Table 3). The change in NT-proBNP did not differ between the two groups. NT-proBNP levels at 60 days were numerically, but not significantly lower in HFpEF than HFrEF.

Cystatin C increased in HFrEF but not HFpEF (Table 3). However, the change in cystatin C did not differ between groups. Cystatin C tended ($p=0.06$) to be higher in HFpEF at 60 days.

PRA and aldosterone both increased post-discharge in HFrEF and HFpEF (Table 3). Neither the change in PRA or aldosterone nor levels at 60 days differed in the two groups.

Uric acid and PIIINP levels did not change significantly in either group and there were no differences in uric acid and PIIINP levels at 60 days between groups (Table 3).

Discussion

In this well characterized, prospectively enrolled cohort of patients with ADHF, NT-proBNP levels were lower in HFpEF than HFrEF despite similar severity of ADHF. HFpEF was characterized by higher systolic blood pressure, more severe renal dysfunction but similar biomarkers of RAAS activation, oxidative stress as well as the serum peptide, PIIINP, which reflects collagen synthesis. Further, changes in all biomarkers at follow-up were directionally and quantitatively similar between the two types of HF with decreases in NT-proBNP, increases in cystatin-C, PRA and aldosterone and no change in uric acid and PIIINP despite evidence of clinical stabilization at 60 days. These findings provide insight into the pathophysiology of ADHF in HFpEF.

Natriuretic Peptides in HFpEF

Several studies have reported lower NP levels in HFpEF than in HFrEF.¹⁻⁴ Pharmacologic antagonism or surgically induced limitation of NP activation in experimental systolic HF was associated with vasoconstriction, renin and aldosterone activation, sodium retention and renal dysfunction.¹³ These observations, as well as studies in murine models of NP or NP receptor ablation have established the role of the endogenous NP system in blood pressure and volume control and as a compensatory system to maintain hemodynamic, humoral and renal function, and oppose myocardial remodeling under cardiac stress.¹² Thus, while NP levels in HFpEF are elevated as compared to normal individuals, the lower values in HFpEF as compared to HFrEF - despite a similar severity of clinical HF and adjusting for age, sex and body size - may indicate a “relative” NP deficiency in HFpEF, which could be associated with differences in other biomarkers reflective of RAAS activation, oxidative stress or collagen synthesis. However, in our study, other than more impaired vascular and renal function, no other differences in the biomarker profile of ADHF were seen in HFpEF vs HFrEF patients.

Blood pressure and renal dysfunction in HFpEF

As observed here, larger observational and registry studies of patients with ADHF also report that systolic blood pressure is higher in ADHF patients with preserved EF.¹⁶⁻¹⁹ HFpEF in our cohort was characterized by higher systolic and pulse pressures while diastolic blood pressure was lower confirming reports from large registries of acute HF hospitalization.^{17, 19} The elevated pulse pressure observed in HFpEF underscores the importance of impaired vascular compliance in HFpEF.

Cystatin C levels are thought to be independent of age, sex, muscle mass, protein intake or race and elevated levels are predictive of poor outcomes in ADHF.²⁰⁻²⁶ Higher cystatin C in HFpEF suggests that worse renal function may have contributed more prominently to decompensation in HFpEF. While cystatin C was higher in our HFpEF cohort, following adjustment for age and sex, this difference was no longer statistically significant suggesting potential confounding by differences in age and sex between HFpEF and HFrEF groups. Larger observational and registry studies in ADHF have reported similar or lower levels of creatinine in HFpEF patients as compared to HFrEF patients but have not utilized the more precise measure of renal function (cystatin C) used here.^{16-19, 27}

Renin angiotensin aldosterone system (RAAS) in HFpEF

In DOSE, PRA did not differ between HFpEF and HFrEF despite higher systolic blood pressure, similar diuretic dose and less use of confounding medications (ACE Inhibitor / ARB) in HFpEF patients. This raises the possibility of relatively greater activation of PRA in HFpEF but the power to ascertain the relative level of PRA activation, accounting for differences in blood pressure and medication use, is limited by the sample size in this study. Likewise, aldosterone levels did not differ between the two groups despite less frequent use of medications, which could affect aldosterone levels in HFpEF. These findings are concordant with a previous HF registry study that noted similar levels of aldosterone in HFpEF and HFrEF.² While trials of RAAS antagonists in HFpEF have not shown a benefit on clinical outcomes in HFpEF,²⁸ the current findings suggest that this can not be attributed to less severe RAAS activation in HFpEF - at least as assessed by circulating levels of PRA and aldosterone during ADHF. Notably, despite clinical stabilization, PRA and aldosterone increased post-discharge suggesting that the adverse neurohumoral activation during ADHF persists in the early post-discharge state, consistent with high risk for adverse events noted in DOSE, where over 40% of patients died or were readmitted within 60 days.¹⁴

Oxidative stress and collagen synthesis

The average level of uric acid in this ADHF cohort was higher than that observed in most HF studies²⁹ and did not decrease during follow up. These observations may reflect the severity of HF, high diuretic doses and worsening renal function observed over follow up. While uric acid levels in the two types of HF has not been previously studied, uric acid was found to be an independent predictor of prognosis in the “Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure” (SENIORS) trial which included patients with HFrEF and HFpEF.³⁰ While diuretic dose and renal function could modulate uric acid levels in HFpEF, adjustment for renal dysfunction did not reveal differences and diuretic dose was similar in HFpEF and HFrEF, suggesting that the high uric acid levels in HFpEF are similarly reflective of oxidative stress in the two types of HF.

Consistent with our findings, PIIINP was also noted to be similar in stable outpatients with HFpEF and HFrEF.³¹ Notably, in the advanced ADHF cohort in DOSE, PIIINP levels were significantly higher than reported in the outpatient study³¹ or other studies in HF, ADHF or hypertensive populations³²⁻³⁴. Importantly, PIIINP did not improve on outpatient follow-up, which may reflect persistently increased collagen synthesis post clinical stabilization.

Limitations

Assessment of biomarkers was carried out at enrollment and administration of diuretics prior to enrollment may have influenced our findings. The DOSE trial did not mandate EF measurement during the hospitalization. However, the median time since EF evaluation was 1.3 months and the characteristics of HFpEF patients were similar to those described in

other studies. The smaller number of subjects with paired data at 60 days limited power to detect differences and patients who were sicker may not have returned for follow up and thus, the follow up data may be biased. Assessment of oxidative stress was limited to uric acid and utilization of more comprehensive assessment of oxidative stress may have revealed differences. While we used PIIINP as a biomarker that reflects collagen synthesis, the release of PIIINP into serum during collagen degradation, its post-translational modification and variability in rate of hepatic clearance reduce our ability to use it as a direct measure of collagen synthesis or fibrosis.^{35, 36} Finally, inclusion in DOSE required a daily diuretic dose equivalent to 80-240 mg which may bias towards recruitment of subjects with more severe HF limiting our ability to generalize our study findings to all patients with ADHF.

Conclusion

In this contemporary, prospectively enrolled cohort of patients with ADHF, patients with HFpEF had similar HF severity as patients with HFrEF. However, as compared to HFrEF, HFpEF patients had lower NT-proBNP, higher systolic blood pressure and more severe renal dysfunction with similar levels of RAAS activation, oxidative stress and a marker that reflects collagen synthesis. These findings underscore the importance of similarly altered biomarkers of neurohumoral activation, oxidative stress and collagen synthesis in ADHF among patients with HFpEF and HFrEF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Biomarkers of neurohumoral activation, oxidative stress and collagen synthesis in ADHF with reduced (HFrEF) or preserved (HFpEF) ejection fraction

The median and IQR are presented for biomarkers. The upper limit for each biomarker (higher of expected value for men or women) are shown by the red dashed line. *p < 0.05 vs HFrEF.

Table 1
Clinical characteristics of HFrEF and HFpEF at enrollment

	HFrEF n=219	HFpEF n=81	P-value
Demographics			
Age, years	66.0 (54.0, 75.0)	74.0 (67.0, 80.0)	<0.001
Gender, male, %(n)	79.9% (175)	58.0% (47)	0.0002
Past Medical History, %(n)			
Ischemic heart disease	62.6% (137)	45.7% (37)	0.009
Hypertension	79.5% (174)	84.0% (68)	0.37
Atrial fibrillation/flutter	47.9% (105)	69.1% (56)	0.0009
Diabetes	53.0% (116)	46.9% (38)	0.35
Current NYHA Classification			
III	64.4% (132)	63.1% (41)	
IV	31.2% (64)	33.8% (22)	
Physical Examination			
Heart rate, bpm	77.0 (69.0, 87.0)	74.0 (67.0, 81.0)	0.05
Systolic blood pressure, mmHg	113.0 (103.0, 130.0)	120.0 (110.0, 136.0)	0.008
Diastolic blood pressure, mmHg	68.0 (60.0, 80.0)	62.0 (54.0, 74.0)	0.005
Pulse pressure, mmHg	45 (35.0, 55.0)	57 (46.0, 67.0)	<0.001
BMI, kg/m ²	30.8 (25.8, 35.6)	34.1 (28.1, 39.2)	0.01
JVP, %(n)			
< 8cm	9.6% (20)	5.3% (4)	0.16
8-12 cm	34.9% (73)	25.0% (19)	
13-16 cm	27.3% (57)	31.6% (24)	
> 16 cm	28.2% (59)	38.2% (29)	
Rales, %(n)			
None	44.5% (97)	31.3% (25)	0.007
<1/3	45.4% (99)	46.3% (37)	
1/3-2/3	8.7% (19)	22.5% (18)	
>2/3	1.4% (3)	0.0% (0)	
S3 auscultation, %(n)	23.4% (50)	12.8% (10)	0.04
Peripheral edema, %(n)			
None	5.9% (13)	1.2% (1)	0.06
Trace	18.3% (40)	12.3% (10)	
Moderate	48.9% (107)	48.1% (39)	
Severe	26.9% (59)	38.3% (31)	
Laboratory Tests (Site Local Lab)			
Sodium, mEq/L	138.0 (136.0, 140.0)	140.0 (137.0, 141.0)	0.005
Potassium, mEq/L	3.9 (3.5, 4.2)	4.1 (3.5, 4.3)	0.21
Creatinine, mg/dL	1.46 (1.16, 1.90)	1.55 (1.10, 1.92)	0.52
GFR, mL/min/1.73m ²	51.9 (37.7, 69.5)	44.5 (34.2, 57.5)	0.01
Albumin, g/dL	3.5 (3.1, 3.9)	3.4 (3.1, 3.8)	0.75

	HFrEF n=219	HFpEF n=81	P-value
Hemoglobin, g/dL	11.9 (10.5, 13.2)	10.4 (9.6, 12.3)	<0.001
Medications %(n)			
Baseline furosemide dose, mg	120.0 (80.0, 160.0)	120.0 (80.0, 160.0)	>0.99
ACE-I/ARB	71.2% (156)	44.4% (36)	<0.001
Beta-blocker	85.8% (188)	75.3% (61)	0.04
Aldosterone antagonist	32.0% (70)	19.8% (16)	0.03
Alpha blocker	5.9% (13)	14.8% (12)	0.02
Digoxin	36.5% (80)	13.6% (11)	<0.001
Calcium channel blocker	12.8% (28)	27.2% (22)	0.004

Table 2

Clinical characteristics at enrollment and 60 days in HFrEF and HFpEF

Clinical Characteristic, Median (IQR)	HFpEF (n=168)			HFpEF (n=58)			HFpEF vs HFrEF	
	Enrollment	60 Days	P-value*	Enrollment	60 Days	P-value§	P-value [†] , Change	P-value [‡] , 60 days
Heart rate, bpm	78 (69.0, 90.0)	78 (68.0, 87.0)	0.24	72 (64.0, 79.0)	74 (65.0, 80.0)	0.89	0.31	0.04
Systolic blood pressure, mmHg	112 (103.0, 128.0)	111.5 (100.5, 124.0)	0.59	120 (112.0, 132.0)	118 (101.0, 133.0)	0.27	0.46	0.046
Diastolic blood pressure, mmHg	68.5 (60.0, 80.0)	67 (60.0, 78.5)	0.07	65 (51.0, 74.0)	60 (54.0, 70.0)	0.29	0.95	0.002
Mean arterial pressure, mmHg	83.3 (76.7, 93.8)	82.7 (74.3, 91.2)	0.09	83 (73.3, 94.7)	80.7 (73.3, 89.3)	0.43	0.79	0.32
Pulse pressure, mmHg,	44 (35.0, 54.0)	41.5 (35.5, 54.5)	0.28	55 (47.0, 67.0)	56 (45.0, 70.0)	0.58	0.64	<0.001
Weight, lbs	202.5 (175.4, 241.7)	191.7 (163.8, 234.2)	<0.001	214.1 (180.5, 249.0)	206.9 (167.5, 237.2)	<0.001	0.95	0.32
JVP	14 (10.0, 20.0)	8 (8.0, 10.0)	<0.001	14 (10.0, 20.0)	10 (8.0, 14.0)	<0.001	0.68	0.28
Peripheral edema grade	2 (2.0, 3.0)	1 (0.0, 2.0)	<0.001	2 (2.0, 3.0)	2 (1.0, 2.0)	<0.001	0.28	0.01
NYHA classification	3 (3.0, 4.0)	3 (2.0, 3.0)	<0.001	3 (3.0, 4.0)	3 (2.0, 3.0)	<0.001	0.22	0.78

JVP < 8cm = 8, 8-12 cm = 10, 13-16 cm = 14, > 16 cm = 20; Edema grade: None = 0, Trace = 1, Moderate = 2, Severe = 3

* p-value for variable change within in each group

† change in variable between groups

‡ value at 60 days between groups are shown.

Table 3

Biomarkers at enrollment and 60 days in HFREF and HFpEF

Biomarkers, Median (IQR)	HFREF (n=149)				HFpEF (n=50)				HFpEF vs HFREF	
	Enrollment	60 Days	Change	P-value*	Enrollment	60 Days	Change	P-value*	P-value†, Change	P-value‡, 60 days
NT-pro-BNP, ng/L	4701 (2429, 11664)	3535 (1804, 9035)	-953.6 (-2845, 352.0)	<0.001	3373 (2391, 7160)	2854 (1503, 5286)	-642 (-1965, 390.0)	0.09	0.38	0.18
Cystatin C, mg/L	1.4 (1.08, 1.83)	1.58 (1.10, 2.14)	0.09 (-0.05, 0.33)	<0.001	1.78 (1.38, 2.03)	1.8 (1.43, 2.20)	0.09 (-0.10, 0.38)	0.19	0.66	0.06
Plasma Renin Activity, ng/mL/hr	4.2 (0.7, 15.8)	6.4 (1.2, 20.7)	0.3 (-1.2, 8.2)	0.01	2.2 (0.9, 11.8)	4.7 (1.9, 16.2)	0.9 (-0.4, 7.4)	0.01	0.44	0.68
Aldosterone, pg/mL	189.6 (104.5, 346.8)	245.2 (143.2, 409.2)	54.3 (-45.5, 163.5)	<0.001	153.4 (107.6, 259.2)	282.1 (163.5, 392.2)	59.6 (-21.5, 188.8)	0.007	0.44	0.74
Uric Acid, mg/dL	9.6 (7.9, 11.4)	9.1 (7.0, 11.2)	-0.3 (-1.4, 1.2)	0.2	9.5 (8.2, 11.3)	9.9 (8.2, 11.6)	-0.2 (-1.5, 1.2)	0.78	0.99	0.19
NT-procollagen III, µg/L	9.7 (7.4, 12.1)	9.8 (7.3, 12.3)	-0.3 (-1.9, 1.5)	0.43	10.3 (8.3, 12.2)	9.5 (7.8, 12.3)	-0.4 (-2.1, 1.7)	0.14	0.71	0.76

* p-value for variable change within in each group

† change in variable between groups

‡ value at 60 days between groups are shown