Effects of topiroxostat administration on brain natriuretic peptide levels in heart failure patients with a preserved ejection fraction: A pilot study

Running title: Effect of topiroxostat on BNP in HFpEF

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Abstract

Background: Various optimal medical therapies have been established for the treatment of heart failure (HF) with a reduced ejection fraction (HFrEF). Like HFrEF, HF with a preserved ejection fraction (HFpEF) too is related to poor prognoses. We aimed to investigate the effect of topiroxostat, an oral xanthine oxidoreductase inhibitor, in HFpEF patients with hyperuricemia or gout.

Methods: In this non-randomized, open-label, single-arm trial, we administered topiroxostat (40–160 mg/day) to HFpEF patients with hyperuricemia or gout to achieve a target uric acid level of 6.0 mg/dl. The primary outcome was the rate of change in the log-transformed brain natriuretic peptide (BNP) levels from the baseline to 24 weeks after topiroxostat treatment. The secondary outcomes included the amount of change in the BNP levels, uric acid evaluation values, and oxidative stress marker levels after 24 weeks of topiroxostat treatment. Thirty-six patients were enrolled; three were excluded before study initiation.

Results: The log-transformed BNP levels decreased by $-3.4 \pm 8.9\%$ ($p = 0.043$) after 24 weeks of topiroxostat treatment. The rate of change in the BNP level decreased ($-18.0 [-57.7, 4.0]$ pg/ml, $p = 0.041$). The levels of uric acid and 8-hydroxy-2'-deoxyguanosine/creatinine, an oxidative stress marker, also significantly decreased (-2.8 ± 1.6 mg/dl, $p < 0.001$, -2.3 ± 3.7 ng/mgCr, $p = 0.009$, respectively).

Conclusions: The BNP levels were significantly lowered in HFpEF patients with hyperuricemia or gout after topiroxostat administration; however, the rate of decrease was low. Further trials are needed to confirm our findings.

Keywords: Topiroxostat, ejection fraction, heart failure, brain natriuretic peptide

Introduction

Accumulating evidence reveals that patients with heart failure (HF) and hyperuricemia have poor prognoses¹⁻⁴, and recent studies have evaluated the relationship between hyperuricemia and cardiovascular disease and demonstrated that impaired vascular endothelial function might be a contributing factor for HF⁵. Xanthine oxidoreductase (XOR), an enzyme that mediates uric acid (UA) production, promotes arteriosclerosis by modulating vascular endothelial cells through the production of UA⁶. In addition, XOR promotes cardiac remodeling by generating reactive oxygen species (ROS)^{7, 8}. Notably, topiroxostat, a novel non-purine selective XOR inhibitor, suppresses XOR activity and the subsequent UA production. Although HF with hyperuricemia is known to be associated with poorer prognoses than that without hyperuricemia⁹, it is unclear whether prognosis is improved by administration of UA-lowering drugs, such as topiroxostat.

HF with a preserved ejection fraction (HFpEF) is characterized by HF symptoms that result from diastolic dysfunction and has recently attracted significant attention¹⁰.

Pathologically, HFpEF is classified based on systemic inflammation, reductions in the level of nitric oxide bioavailability, and interstitial fibrosis, which promotes diastolic left ventricular dysfunction⁸. HFpEF patients and HF patients with a reduced ejection fraction (HFrEF) have the same mortality rate¹¹ and no effective treatment options are available for HFpEF. Therefore, establishment of appropriate treatment modalities is a critical and urgent issue in medical practice.

Brain natriuretic peptide (BNP) has been established as a surrogate marker for HF prognosis. For example, studies revealed that for each 100-pg/ml increase in the BNP

level, there is a 35% increase in the risk of death¹², and that topiroxostat effectively decreases the levels of BNP and high-sensitivity C-reactive protein in patients with multiple cardiovascular risks¹³. Additionally, topiroxostat lowers UA levels in patients with hyperuricemia who have a high risk of developing cardiovascular disease¹³ and strongly inhibits XOR activity compared to allopurinol, which is a purine analog XOR inhibitor^{14, 15}. However, no known studies have elucidated the effects of topiroxostat in HFpEF patients. Therefore, the purpose of this study was to examine the manner in which the administration of topiroxostat affects cardiac function in HFpEF patients with hyperuricemia; in particular, we sought to determine whether a decrease in plasma BNP levels is a surrogate marker for HF.

Materials and Methods

Study design and ethical considerations

The Suggestion of using topiroxostat for a group of hyperuricemic congestive heart failure patients with preserved ejection fraction for better treatment outcomes (SOUGHT) study was a pilot study conducted as a prospective, single-center, open-label, single-arm trial and included patients who were recruited between March 2017 and April 2018. The trial was registered with the University Hospital Medical Information Network (registration number, UMIN000024981). The study protocol was approved by the institutional ethics committee at the Nippon Medical School Hospital (ID: 228005). Based on a previous investigation¹³, this trial was designed to have 80% power to detect a reduction of 39% in log-transformed BNP levels at 24 weeks, with a type I error of 0.05 (two-sided). Therefore, we determined that the appropriate sample size was 32 patients¹³. Considering a 10% drop-out rate, we registered 36 patients in this trial. The investigation

conformed with the principles outlined in the Declaration of Helsinki. All enrolled patients provided written informed consent prior to the beginning of the study.

Patients

In this trial, we enrolled HFpEF patients with hyperuricemia or gout. The diagnostic criteria for HFpEF were based on the European Society of Cardiology guidelines¹⁶. Hyperuricemia was defined as a UA level ≥ 7.0 mg/dl. Patients who met all of the following inclusion criteria were included in this trial: aged between 20 and 90 years, had either hyperuricemia or gout, had not taken medication for hyperuricemia or gout within 4 weeks of the trial, a diagnosis of HFpEF, clinically stable HF, and were capable of giving their written consent. The exclusion criteria were as follows: allergy to either topiroxostat, febuxostat, or allopurinol; intake of mercaptopurine or azathioprine; having undergone coronary artery bypass grafting surgery or percutaneous coronary intervention within 6 months; malignancy; high alanine aminotransferase and aspartate aminotransferase levels; chronic hepatitis B or C; liver cirrhosis; severe renal dysfunction; or any other condition indicating that it was inappropriate for the patient to participate in the trial.

Study protocol

Eligible patients began taking oral topiroxostat within 8 weeks after providing written informed consent. We followed-up the patients every 6 weeks for a total of 24 weeks. We set the therapeutic level of UA at < 6.0 mg/dl based on the American College of Rheumatology guidelines¹⁷. Patients started taking 20 mg of topiroxostat every morning and night after meals. The dose of topiroxostat was increased every 6 weeks by 40 mg/day until the target dose of 120 mg/day was reached, unless the serum UA level

was < 3.0 mg/dl. Patients with a UA level of 6.0 mg/dl or lower were under continuous observation while taking topiroxostat at a dose of 120 mg/day. The dose was increased from 120 mg/day to 160 mg/day only when patients were unable to achieve a serum UA level < 6.0 mg/dl. If the patient showed gouty arthritis on the day on which topiroxostat treatment initiation or dose increase was planned, we did not increase the doses or start the drug treatment. If the serum UA level was below 3.0 mg/dl after initiating or increasing the dose of topiroxostat, the dosage was lowered.

Study outcomes

The primary outcome was the rate of change of plasma BNP levels, as a surrogate marker for HF, from baseline to 24 weeks after topiroxostat treatment. We evaluated the changes in log-transformed BNP levels, as plasma BNP levels are not normally distributed¹⁸. The secondary outcomes were the values and changes in the following items during each observation: 1) UA evaluation, including serum UA level, plasma XOR activity, and hypoxanthine and xanthine levels. Blood samples were collected using a blood collection tube coated with ethylenediaminetetraacetic acid-2K and were centrifuged at 2,000 g for 10 min at 4 °C for plasma separation. Plasma XOR activity was measured using liquid chromatography-triple quadrupole mass spectrometry (Nexera HLC, SHIMADZU, Japan/QTRAP 4500, SCIEX) to detect [¹³C2, ¹⁵N2] uric acid, with [¹³C2, ¹⁵N2] xanthine as a substrate, as previously reported¹⁹⁻²¹; 2) Cardiac function (the amount of change in the BNP and log-transformed BNP levels, troponin T, high-sensitivity C-reactive protein, and left ventricular ejection fraction [LVEF] assessed using the Teichholz or Modified Simpson method); 3) Left ventricular mass index; 4) Mitral E/E' ratio; 5) Mitral E/A ratio; 6) Left atrial dimension; 7) Tricuspid annular plane systolic excursion; 8) Tricuspid regurgitation peak gradient; and 9)

Peripheral vascular endothelial function, assessed using the reactive hyperemia index (RHI), which was evaluated by reactive hyperemia peripheral arterial tonometry with Endo-PAT2000® (Itamar Medical, Caesarea, Israel). Measurement of RHI using reactive hyperemia peripheral arterial tonometry is described in detail elsewhere²². In addition, oxidative stress markers (urinary 8-hydroxy-2'-deoxyguanosine [8-OHdG]), blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), as evaluated by the modified Modification of Diet in Renal Disease method with a new Japanese coefficient according to a three-variable Japanese equation ($\text{eGFR}[\text{mL}/\text{min}/1.73 \text{ m}^2] = 194 \times [\text{Scr}]^{-1.094} \times [\text{Age}]^{-0.287} \times [0.739 \text{ if female}]$), cystatin C, urinary liver type-fatty acid protein, and general health-related items (body weight, body mass index, blood pressure, and pulse) were also considered secondary outcomes. All safety analyses were performed in the safety population. We defined adverse events (AEs) as follows: cerebral infarction, myocardial infarction, and HF exacerbation. Topiroxostat administration was continued in patients who had mild AEs. We also evaluated the incidence rates of liver dysfunction and gouty arthritis.

Statistical analyses

The endpoints were primarily analyzed using the full analysis set, which included 33 patients. Safety analysis sets were evaluated using the safety population, which comprised all or some of the enrolled patients. Categorical variables are expressed as prevalence rates (%). Continuous variables are presented as means and standard deviations or medians and interquartile ranges, as appropriate. The paired t-test was used to compare the changes in log-transformed BNP levels from baseline to 24 weeks after topiroxostat treatment. The Wilcoxon signed-rank test was used to analyze

variables that were not normally distributed, such as plasma BNP levels. For data requiring multiple observations at multiple points after the start of the study, the paired t-test for within-group comparisons and longitudinal data analysis using the mixed-effect model for repeated measures were conducted. A two-sided p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute., Cary, NC, USA).

Results

Patient details

A total of 41 patients were eligible for this study. Five patients were excluded, as they declined to participate in the study; thus, 36 patients were registered. Three patients dropped out of the study before taking the initial dosage of topiroxostat. Therefore, 33 patients were included in the final analysis (Fig. 1).

Figure 1 Here

Patient characteristics

The patients' baseline characteristics are summarized in Table 1. Twelve patients (36%) were female and 21 (64%) were male. The mean patient age and body mass index were 72 ± 10 years and 24.3 ± 5.2 kg/m², respectively. The mean serum UA level at baseline was 8.0 ± 1.8 mg/dl. Only one patient had a prior history of gout. At baseline, the mean LVEF was $67.8 \pm 7.3\%$ and creatinine level was 1.2 ± 0.4 mg/dl. The median BNP level was 195.0 (93.2 - 316.0) pg/ml. An overlap in the underlying cardiovascular diseases, including hypertension (39%), arrhythmia (55%), ischemic heart disease (18%), valvular disease (24%), and cardiomyopathy (15%), was noted in some patients.

Outcomes

The average doses of topiroxostat were 104.0 ± 32.5 mg at 12 weeks and 110.7 ± 25.0 mg at 24 weeks. The results related to the primary outcomes are shown in Fig. 2. The rate of change in the log-transformed BNP level, as a surrogate marker of HF, was significantly lower at week 24 than at week 0 (-3.4 ± 8.9 %, $p = 0.043$) (Fig. 2). The results pertaining to the secondary outcomes are presented in Table 2 and Fig. 3. There was a significant difference in the amount of change in the plasma BNP and log-transformed BNP levels between weeks 24 and 0 (-18.0 [$-57.7, 4.0$] pg/ml, $p = 0.041$, -0.16 ± 0.41 ln(pg/ml), $p = 0.040$, respectively). Topiroxostat significantly lowered the levels of serum UA ($p < 0.001$) and plasma XOR activity ($p < 0.001$). Topiroxostat also increased hypoxanthine ($p < 0.001$) and xanthine ($p < 0.001$) levels compared to those at the baseline. At week 24, BUN ($p = 0.004$), creatinine ($p = 0.009$), and cystatin C ($p = 0.01$) levels increased slightly but significantly. Regarding oxidative stress markers, urinary 8-OHdG/creatinine levels were decreased significantly ($p = 0.009$) compared to the baseline levels. The baseline and 24-week RHI values were not significantly different ($p = 0.13$). Correlation analysis was further performed, but no test variables were found to be correlated with decreased BNP levels. The most frequently reported AE was HF exacerbation (4 patients), which resulted in the discontinuation of topiroxostat in two patients. Gouty arthritis was reported in two patients in the safety population.

Figure 2 here

Figure 3 here

Discussion

In this study, the log-transformed BNP and urinary 8-OHdG/creatinine levels (oxidative stress markers) significantly improved in HFpEF patients with hyperuricemia or gout within 24 weeks after topiroxostat treatment. Increased oxidative stress and impaired vascular endothelial function have been demonstrated to be causes of HF in HFpEF patients⁵. Our findings suggest that topiroxostat might decrease oxidative stress, reduce intracellular uric acid levels, and improve the function of vascular endothelial cells, which are three possible mechanisms by which improved BNP levels, surrogate markers for HF, affect chronic HF.

Reactive oxygen species are produced via activation of xanthine oxidase, and XOR inhibitors reduce oxidative stress⁵. Accumulating evidence indicates that increase oxidative stress may promote left ventricular remodeling, and topiroxostat may decrease reactive oxygen species and inhibit left ventricular remodeling. Previous small-scale studies have suggested that purine analog XOR inhibitors reduce plasma BNP levels and improve vascular endothelial dysfunction²³⁻²⁵. Improved peripheral vascular endothelial function decreases the left ventricular afterload in the short term and ameliorates LV remodeling in the long term. Moreover, improved coronary artery endothelial function leads to ameliorated myocardial blood flow and decreased ischemia, which, in turn, improve left ventricular function. In the present study, a significant difference in the improvement of BNP levels, the surrogate marker of HF, was detected, but no significant difference in the improvement of vascular endothelial function was found. Vascular endothelial dysfunction might not be reversible if the patients are elderly and have a long history of HF²⁶. Large-scale, randomized, placebo-controlled studies have not yet shown that purine analog XOR inhibitors improve outcomes in chronic HF patients with hyperuricemia^{27,28}. Notably, topiroxostat has a

stronger inhibitory effect on XOR activity than purine analog XOR inhibitors^{14, 15}. As high XOR activity in HF leads to the onset of cardiovascular events²⁹, it is possible that the strong XOR inhibitory effect of topiroxostat might lead to decreased BNP levels, as demonstrated in the present study.

Some studies have suggested that increased cardiovascular events are associated with febuxostat use^{30, 31}. Compared to febuxostat, topiroxostat is a hybrid XOR inhibitor and has a different mechanism of action³². It remains unclear whether the increased mortality observed after treatment with febuxostat would be found after treatment with topiroxostat. In addition, because the mechanism by which febuxostat increases cardiovascular events is unclear, it cannot be concluded that the increase in cardiovascular events caused by febuxostat would also be seen after treatment with topiroxostat.

It has been reported that topiroxostat improves renal function and the urinary albumin/creatinine ratio^{33, 34}. However, the albumin/creatinine ratio did not improve in the present study, probably due to the small sample size. Furthermore, a deterioration of BUN, creatinine, and cystatin C levels was observed. Although the increase in diuretic use was unavoidable in two patients, it could not be concluded if volume depletion was influential because their mean body weight remained unchanged throughout the study. Previous studies have indicated that the progression rate of eGFR is 1.0 ml/min/1.73 m² per year³⁵. In the present study, most patients had overt albuminuria (>300 mg/gCr) and moderate-to-severe renal dysfunction (equivalent to stage 3 chronic kidney disease). It is known that poor renal function at baseline is associated with earlier progression of renal function deterioration³⁵. Therefore, it is possible that we observed a natural history of chronic kidney disease progression.

Limitations

There are several limitations to this study. First, this study did not include a control group, and blinding procedures were not performed. In addition, this study had an open-label design. Therefore, the presence of inherent bias cannot be ruled out and it also cannot be concluded that the BNP level reductions were caused by the administration of topiroxostat. Second, while the improvement in the log-transformed BNP levels and urinary 8-OHdG/creatinine levels by the administration of topiroxostat may prove useful in HFpEF patients, the amount of change in BNP level was small. Therefore, the clinical effect of topiroxostat on BNP, a surrogate marker for HF, remained limited. This pilot study was insufficient to confirm the clinical benefits owing to its small sample size. Correlation analysis was performed, but no test variables were found to be correlated with decreased BNP levels. Third, the study included patients from a single center. This study was a single-arm pilot study and a single hypothesis was tested. Further studies are needed to determine whether topiroxostat improves the outcomes of HFpEF patients.

Conclusion

In this study, the log-transformed BNP level significantly improved in HFpEF patients with hyperuricemia or gout. There was also a significant difference in the amount of change in the plasma BNP and log-transformed BNP levels. However, the amount of change in the plasma BNP level was small and the clinical effect of topiroxostat on BNP, a surrogate marker for HF, remained limited. Further randomized controlled trials with a control group, a larger sample size, and patients from multiple centers are needed to confirm our findings.

Acknowledgments

The authors gratefully acknowledge the assistance of Hirokazu Yamada in the statistical analyses and Miho Kondo, Sachi Arimura, and Yasunori Tomita (Soiken Holdings Inc., Tokyo, Japan) for their secretarial assistance.

Funding

This work was supported by Sanwa Kagaku Kenkyusho Co., Ltd.

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Figure legends

Fig. 1. Flow chart of patient enrollment in the SOUGHT study. The flow chart shows the number of patients screened, excluded, and registered. FAS, full analysis set.

Fig. 2. Change in log-transformed brain natriuretic peptide levels. Changes in brain natriuretic peptide (BNP) levels from baseline to 24 weeks after topiroxostat treatment.

Fig. 3. Results pertaining to the secondary study outcomes. (A) Changes in uric acid (UA) levels from baseline to each observation point. (B) Xanthine oxidoreductase (XOR) activity from baseline to each observation point. (C) 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels from baseline to each observation point. (D) Endothelial peripheral arterial tonometry (Endo-PAT) reactive hyperemia index (RHI) from baseline to 24 weeks after topiroxostat treatment.

Fig. 1

Fig. 2

Fig. 3

Table 1. Baseline characteristics of HFpEF patients (N = 33)

Demographics	
Age, years, mean $\pm$ SD	72 $\pm$ 10
Sex, female, n (%)	12 (36)
Male, n (%)	21 (64)
BMI, kg/m ² , mean $\pm$ SD	24.3 $\pm$ 5.2
NYHA class, n (%)	
I	10 (30)
II	23 (70)
Underlying disease (duplicated), n (%)	
Hypertension	13 (39)
Atrial fibrillation/Atrial flutter	20 (61)
Ischemic heart disease	6 (18)
Valvular disease	8 (24)
Cardiomyopathy	5 (15)
Vital signs, mean $\pm$ SD	
SBP, mmHg	131.8 $\pm$ 20.9
DBP, mmHg	69.7 $\pm$ 9.8
HR, beats per min	69.9 $\pm$ 12.5
Comorbidity, n (%)	
CKD	27 (82)
Hypertension	11 (33)
Dyslipidemia	22 (67)

Diabetes mellitus	10 (30)
Gout	1 (3)
Laboratory values, echocardiography data	
BNP, pg/ml, median (IQR)	195.0 (93.2-316.0)
Cre, mg/dl, mean $\pm$ SD	1.2 $\pm$ 0.4
UA, mg/dl, mean $\pm$ SD	8.0 $\pm$ 1.8
LVEF (%), mean $\pm$ SD	67.8 $\pm$ 7.3
Medication, n (%)	
ACE-i	10 (30)
ARB	13 (39)
β -blocker	15 (46)
Diuretics	24 (73)
Ca ²⁺ blocker	13 (39)
Anticoagulation	20 (61)
Antiplatelet	4 (12)
Statins	19 (58)
Diabetes drugs	10 (30)

ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CKD, chronic kidney disease; Cre, creatinine; DBP, diastolic blood pressure; HR, heart rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association classification; SBP, systolic blood pressure; SD, standard deviation; UA, uric acid.

1 **Table 2. Changes in the secondary endpoints from baseline to 24 weeks after**
 2 **topiroxostat treatment**

	0 W	24 W	p
Vital signs, mean $\pm$ SD			
Body weight, kg	63.4 $\pm$ 17.5	63.5 $\pm$ 17.1	0.90
BMI, kg/m ²	24.3 $\pm$ 5.2	24.3 $\pm$ 5.0	0.85
SBP, mmHg	131.8 $\pm$ 20.9	125.1 $\pm$ 19.0	0.10
DBP, mmHg	69.7 $\pm$ 9.8	66.7 $\pm$ 9.5	0.12
HR, beats per min	69.9 $\pm$ 12.5	71.9 $\pm$ 17.7	0.73
Blood test values, mean $\pm$ SD			
WBC, count/ μ l	5809.1 $\pm$ 2005.4	6172.7 $\pm$ 2307.5	0.18
Hb, g/dl	12.8 $\pm$ 2.0	12.5 $\pm$ 1.9	0.19
AST, IU/l	22.6 $\pm$ 6.6	24.8 $\pm$ 11.9	0.17
ALT, IU/l	18.5 $\pm$ 8.4	20.3 $\pm$ 11.7	0.22
T-Bil, mg/dl	0.7 $\pm$ 0.3	0.7 $\pm$ 0.3	0.58
LDL-C, mg/dl	99.3 $\pm$ 31.8	94.5 $\pm$ 28.7	0.07
TG, mg/dl	133.8 $\pm$ 102.9	148.7 $\pm$ 99.3	0.38
UA, mg/dl	8.0 $\pm$ 1.8	5.2 $\pm$ 2.0	< 0.001
XOR, pmol/h/ml	57.4 $\pm$ 62.0	8.9 $\pm$ 5.2	< 0.001
Hypoxanthine, μ M	2.1 $\pm$ 0.8	4.4 $\pm$ 2.4	< 0.001
Xanthine, μ M	0.7 $\pm$ 0.3	12.1 $\pm$ 7.0	< 0.001
Troponin T, ng/ml	0.02 $\pm$ 0.02	0.02 $\pm$ 0.02	0.74
hs-CRP, ng/ml	1754.7 $\pm$ 3045.1	2849.6 $\pm$ 6714.2	0.49

BNP, pg/ml, median (IQR)	195.0 (93.2-316.0)	158.5 (70.3-258.0)	0.041
Renal function, mean $\pm$ SD			
BUN, mg/dl	22.4 $\pm$ 8.1	25.2 $\pm$ 9.9	0.004
Cre, mg/dl	1.2 $\pm$ 0.4	1.3 $\pm$ 0.5	0.009
eGFR, mL/min/1.73 m ²	46.1 $\pm$ 15.6	44.4 $\pm$ 17.5	0.27
Cystatin C, mg/dl	1.5 $\pm$ 0.5	1.6 $\pm$ 0.6	0.01
Urinary albumin/Cre, mg/gCr,	441.6 $\pm$ 1103	342.6 $\pm$ 1118	0.17
Urinary L-FABP/Cre, μ g/gCr	13.5 $\pm$ 31.9	12.2 $\pm$ 37.4	0.93
Oxidative stress markers, mean $\pm$ SD			
Urinary 8OHdG/Cre, ng/mgCr	8.2 $\pm$ 8.2	6.2 $\pm$ 6.8	0.009
Echocardiography, mean $\pm$ SD			
LVEF (%)	67.8 $\pm$ 7.3	64.7 $\pm$ 8.8	0.06
LVMI, g/m ²	102.3 $\pm$ 55.4	92.2 $\pm$ 26.9	0.16
E/E'	16.0 $\pm$ 10.0	14.7 $\pm$ 7.2	0.12
E/A	1.1 $\pm$ 1.1	1.0 $\pm$ 0.7	0.62
LAD, mm	44.5 $\pm$ 8.5	43.7 $\pm$ 7.5	0.10
TAPSE, mm	17.1 $\pm$ 4.0	17.3 $\pm$ 4.0	0.45
TRPG, mmHg	27.3 $\pm$ 10.2	27.9 $\pm$ 8.2	0.55
Vascular endothelial function			
Endo-PAT RHI	2.0 $\pm$ 0.6	1.8 $\pm$ 0.5	0.13

3 ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index;

4 BNP, brain natriuretic peptide; BUN, blood urea nitrogen; Cre, creatinine; DBP, diastolic

blood pressure; E/A, mitral E/A ratio; E/E', mitral E/E' ratio; eGFR, estimated glomerular
 filtration rate; Endo-PAT, endothelial peripheral arterial tonometry; Hb, hemoglobin, HR,
 heart rate; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LAD,
 left atrial diameter; LDL-C, low-density lipoprotein-cholesterol; L-FABP, L-type fatty
 acid-binding protein; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass
 index; RHI, reactive hyperemia index; SD, standard deviation; SBP, systolic blood
 pressure; TAPSE, tricuspid annular plane systolic excursion; T-bil, total bilirubin; TG,
 triglyceride; TRPG, tricuspid regurgitation peak gradient; UA, uric acid; W, weeks; WBC,
 white blood cell; XOR, xanthine oxidoreductase; 8-OHdG, 8-hydroxy-2-deoxyguanosine.