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Uric Acid-Lowering Therapy with Febuxostat in Patients with Chronic Heart Failure and Hyperuricemia: A Prospective and Observational Cohort Study

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Background: Hyperuricemia is associated with poor clinical outcomes in several cardiovascular diseases, including heart failure (HF). However, whether lowering serum uric acid (SUA) levels improves the prognosis of HF remains insufficiently studied.

Aims: To evaluate whether urate-lowering therapy (ULT) with febuxostat confers clinical benefits in patients with HF and concomitant hyperuricemia.

Study Design: Prospective, observational cohort study.

Methods: Patients with chronic HF and hyperuricemia were enrolled and assigned either to a febuxostat group or to a non-ULT group and were followed prospectively for 5 years. The primary endpoint was all-cause mortality or rehospitalization for HF.

Results: Among 2005 patients, those with higher SUA levels experienced more endpoint events. After propensity score matching, we found that febuxostat therapy significantly reduced the incidence of primary endpoints in patients with HFwith preserved ejection fraction (HFpEF) [$p = 0.012$; hazard ratios (HR), 0.744; 95% confidence intervals (CI), 0.589-0.939], but not in those with HF with reduced ejection fraction (HFrEF) or mildly reduced ejection fraction (HFmrEF) ($p = 0.234$; HR, 0.894; 95% CI, 0.742-1.077). The benefits of febuxostat in HFpEF were most evident in patients within the highest tertiles of B-type natriuretic peptide (BNP) ($p = 0.021$; HR, 0.647; 95% CI, 0.436-0.960) and SUA ($p = 0.025$; HR, 0.651; 95% CI, 0.441-0.963).

Conclusion: High SUA levels are associated with increased all-cause mortality and rehospitalization for HF. Febuxostat-mediated SUA reduction significantly improved clinical outcomes in patients with HFpEF, particularly those with elevated SUA and BNP levels.

INTRODUCTION

Heart failure (HF) remains a major economic burden worldwide owing to the complexity of its progression and treatment. With the aging population in China expected to increase substantially in the coming years, it is important to identify comorbidities that affect HF prognosis and to explore novel therapeutic targets.

Hyperuricemia is defined as a serum uric acid (SUA) concentration > 420 μmol/L, confirmed on two separate occasions. Its relationship with cardiovascular outcomes remains controversial. Our previous work reported that lower SUA levels in hypertensive adults were associated with a reduced risk of progression to HF with preserved ejection fraction (HFpEF).[1] Similarly, Huang et al.[2] found that hyperuricemia was associated with higher all-cause and cardiovascular mortality in patients with HF, possibly due to upregulation of xanthine oxidase. In contrast, Ogino et al.[3] reported no clear correlation between lowering SUA and hemodynamic impairment in chronic HF. Given the evolving conceptual framework of HF in recent years[4], it is necessary to reassess whether each HF subtype is linked to adverse outcomes related to hyperuricemia.

In this study, we aimed to evaluate whether lowering SUA with febuxostat influences the incidence of clinical endpoints in patients with HF and to identify potential factors that may modify this association.

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MATERIALS AND METHODS

Study design

This was a prospective, observational cohort study conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Medical Ethics Committee of the Ninth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (approval number: SH9H-2018-T81-2, date: 14.02.2019). All participants provided informed consent and were allocated to the appropriate study group.

Patients

Patients hospitalized between January 2013 and December 2018 were screened for chronic HF. Eligible patients had a history of HF with symptoms or signs such as dyspnea, fatigue, or edema, elevated plasma natriuretic peptides [B-type natriuretic peptide (BNP) ≥ 35 ng/L or N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 125 ng/L], and echocardiographic evidence of structural abnormalities or changes in left ventricular ejection fraction (LVEF). HF subtypes were defined as follows: HFrEF, LVEF < 40%; HF with mildly reduced ejection fraction (HFmrEF), LVEF 40-50%; and HFpEF, LVEF > 50%. In addition, all eligible patients had untreated hyperuricemia, defined as fasting SUA > 420 μmol/L on two separate occasions. Exclusion criteria were prior use of urate-lowering therapy (ULT), severe renal dysfunction [estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, calculated using the CKD-EPI 2009 formula], or severe hepatic dysfunction. Patients were followed prospectively for 5 years. Febuxostat exposure was assessed using pharmacy claims data over rolling 60-month period. Patients who discontinued febuxostat for > 30 consecutive days were deemed ineligible; only those with continuous febuxostat use were included. At the end of follow-up, patients lost to follow-up or with missing data were excluded from the final analysis.

Propensity score matching

Propensity score matching (PSM) was applied to minimize bias arising from the non-randomized study design. Clinically relevant baseline variables included in the matching process were age, sex, body mass index, dyslipidemia, hypertension, diabetes, smoking status, ischemic heart disease, stroke, chronic obstructive pulmonary disease, atrial fibrillation, gout, New York Heart Association functional class, heart rate, systolic blood pressure, diastolic blood pressure, eGFR, SUA, hemoglobin, BNP, LVEF, left atrium diameter, E/e', concomitant medications, and history of coronary revascularization or HF device therapy. Patients were matched 1:1 using nearest-neighbor matching without replacement, with a caliper width of 0.2 standard deviations (SDs) of the logit-transformed propensity scores. Adequacy of matching was assessed by evaluating postmatch balance across covariates.

In the febuxostat group, patients initially received febuxostat 40 mg once daily. The dose was adjusted as follows: reduced to 20 mg/day or 10 mg/day if SUA < 360 μmol/L or increased to 60 mg/day if SUA ≥ 360 μmol/L.

Clinical outcomes

The primary endpoint was a composite of all-cause mortality and/or rehospitalization for HF. Patients underwent clinical follow-up by telephone interview and/or outpatient visit every 3 months after hospital discharge. For those who did not attend scheduled clinic visits, telephone interviews were conducted annually. The primary efficacy outcome was defined as the time to the first occurrence of the composite endpoint.

Statistical analysis

Statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) and R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were summarized as frequencies and percentages, and continuous variables as means ± SDs or medians with interquartile ranges, as appropriate. Normality of continuous variables was assessed prior to testing. For normally distributed variables, Student's t test or one-way ANOVA was applied; for non-normally distributed variables, the Mann-Whitney U test was used. Associations between categorical variables were assessed using the chi-squared test. Competing risks were analyzed using the Fine-Gray model. A Cox proportional hazards regression model was established to examine the association between risk factors and the composite endpoint. Variables with $p < 0.10$ in univariable analysis, as well as clinically important predictors (e.g., diabetes mellitus, hemoglobin, febuxostat use), were included in the multivariable model. Multicollinearity was assessed using tolerance values and variance inflation factors, and the proportional hazards assumption was tested using Schoenfeld residuals. HRs with 95% confidence intervals (CIs) was reported. Kaplan-Meier survival analysis with log-rank testing was performed to evaluate event-free survival and between-group differences. A two-tailed p -value < 0.05 was considered statistically significant.

RESULTS

Patients

A total of 4,359 patients were enrolled, including 2,227 with HFpEF and 2,132 with HFrEF or HFmrEF. After applying hyperuricemia screening and exclusion criteria, 67 HFpEF patients and 55 HFrEF/HFmrEF patients were excluded (36 due to severe hepatic or renal dysfunction, 86 due to loss to follow-up or missing data, and 22 due to discontinuation of ULT). Ultimately, 2005 patients with hyperuricemia were included: 1,067 with HFpEF and 938 with HFrEF/HFmrEF. The incidence of hyperuricemia was higher in the HFpEF group than in the HFrEF/HFmrEF group ($p = 0.010$). Baseline characteristics are summarized in Table 1. Among the 2005 patients with hyperuricemia, 897 received ULT, including 725 prescribed febuxostat, 106 prescribed benzbromarone, and 66 prescribed allopurinol. For PSM, 1,067 patients with HFpEF (318 febuxostat users and 749 non-febuxostat controls) and 938 patients with HFrEF/HFmrEF (407 febuxostat users and 531 non-febuxostat controls) were considered. After PSM, 362 patients receiving febuxostat in the HFrEF/HFmrEF group were matched to balanced controls (Table 2), and 255 patients receiving febuxostat in the HFpEF group were matched to 255 controls (Table 3). The study flow is illustrated in Figure 1.

TABLE 1. Baseline Characteristics of HFpEF, HFmrEF and HFrEF.

	HFrEF/HFmrEF (LVEF < 50%)	HFpEF (LVEF ≥ 50%)	*p* value
n	938 (46.7%)	1067 (53.2%)	0.010
Age (years)	68 (9)	70(11)	< 0.001
Women (gender)	393 (41.9%)	587 (55.0%)	< 0.001
BMI (kg/m^2)	24.6 ± 2.3	25.9 ± 3.7	< 0.001
Medical history			
IHD	509 (54.3%)	422 (39.6%)	< 0.001
Prior PCI	286 (30.5%)	192 (18.0%)	< 0.001
Prior CABG	50 (5.3)	36 (3.4)	0.036
Hypertension	718 (76.5%)	902 (84.5%)	< 0.001
T2DM	277 (29.5%)	321 (30.1%)	0.787
Atrial fibrillation	306 (32.6%)	424 (39.7%)	0.001
Stroke	76 (8.1%)	105 (9.8%)	0.175
COPD	104 (11.1%)	80 (7.5%)	0.005
Smoking	366 (39.0%)	298 (27.9%)	< 0.001
Dyslipidemia	286 (30.5%)	341 (32.0%)	0.479
Gout	80 (8.5%)	91 (8.5%)	1.000
HF device-therapies			
ICD	12 (1.3%)	20 (1.9%)	0.289
CRT-P	9 (1.0%)	0 (0.0%)	0.001
CRT-D	8 (0.9%)	0 (0.0%)	0.002
Medications			
ACEI/ARB	713 (76.0%)	718 (67.3%)	< 0.001
Beta-blocker	674 (71.9%)	654 (61.3%)	< 0.001
Spironolactone	404 (43.1%)	327 (30.6%)	< 0.001
Diuretics	598 (63.8%)	613 (57.5%)	0.015
Anticoagulant	140 (14.9%)	163 (15.3%)	0.827
Antiplatelet	470 (50.1%)	527 (49.4%)	0.749
Statin	463 (49.4%)	438 (41.0%)	< 0.001
Febuxostat	407 (43.4%)	318 (29.8%)	< 0.001
Benzbromarone	60 (6.4%)	46 (4.3%)	0.037
Allopurinol	36 (3.8%)	30 (2.8%)	0.199
Clinical status			
NYHA class, in classes I-IV	88 (9.4%)/411 (43.8%)/390 (41.6%)/49 (5.2%)	68 (6.4%)/470 (44.0%)/466 (43.7%)/63 (5.9%)	0.081
Heart rate (bpm)	80.1 ± 10.7	79.6 ± 11.1	0.257
Systolic BP (mmHg)	129.7 ± 13.6	131.7 ± 13.6	0.001
Diastolic BP (mmHg)	77.2 ± 8.4	78.1 ± 8.7	0.023
Laboratory variables			
eGFR (mL/min/1.73 m^2)	58.6 ± 10.4	60.9 ± 12.5	< 0.001
SUA	493.5 (107)	486.0 (95)	0.209
Haemoglobin (g/dL)	12.1 ± 1.5	12.1 ± 1.6	0.235
BNP (pg/mL)	776 (318)	765 (319)	0.011
Echo data			
LVEF (%)	41.2 ± 4.2	60.0 ± 4.6	< 0.001
LAD (mm)	42.9 ± 5.3	41.4 ± 4.5	< 0.001
E/e'	14.4 ± 4.0	12.8 ± 4.4	< 0.001

Data are presented as mean ± SD (for normally-distributed continuous variables), median (IQR) (for non-normally distributed continuous variables) or number (%) of subjects (for categorical variables).

HFpEF: heart failure with preserved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; BMI, body mass index; IHD, ischaemic heart disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; T2DM, type 2 diabetes mellitus; COPD, chronic obstructive pulmonary disease; HF, heart failure; ICD, implantable cardioverter defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; CRT-D, cardiac resynchronization therapy-defibrillator; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin II receptor blocker; NYHA, New York Heart Association functional class; BP, blood pressure; eGFR, estimated glomerular filtration rate; SUA, serum uric acids; BNP: B-type natriuretic peptides; LVEF, left ventricular ejection fraction; LAD, left atrium diameter; E/e', mitral Doppler early velocity/mitral annular early velocity; SD, standard deviation; IQR, interquartile range.

TABLE 2. Baseline Characteristics of HFrEF/HFmrEF after PSM.

	Non-ULT	Febuxostat	*p* value
n	362	362	
Age (years)	68 (9)	68 (10)	0.914
Women (gender)	156 (43.1%)	150 (41.4%)	0.652
BMI (kg/m^2)	24.6 ± 2.5	24.7 ± 2.3	0.532
Medical history			
IHD	187 (51.7%)	198 (54.7%)	0.413
Prior PCI	108 (29.8%)	109 (30.1%)	0.935
Prior CABG	21 (5.8%)	15 (4.1%)	0.305
Hypertension	273 (75.4%)	275 (76.0%)	0.862
T2DM	97 (26.8%)	97 (26.8%)	1.000
Atrial fibrillation	117 (32.3%)	115 (31.8%)	0.873
Stroke	23 (6.4%)	27 (7.5%)	0.558
COPD	37 (10.2%)	44 (12.2%)	0.409
Smoking	119 (32.9%)	122 (33.7%)	0.637
Dyslipidemia	114 (31.5%)	116 (32.0%)	0.873
Gout	33 (9.1%)	40 (11.0%)	0.388
HF device-therapies			
ICD	6 (1.7%)	4 (1.1%)	0.524
CRT-P	2 (0.6%)	3 (0.8%)	1.000
CRT-D	4 (1.1%)	1 (0.3%)	0.373
Medications			
ACEI/ARB	266 (73.5%)	273 (75.4%)	0.551
Beta-blocker	250 (69.1%)	258 (71.3%)	0.516
Spironolactone	148 (40.9%)	159 (43.9%)	0.408
Diuretics	223 (61.6%)	228 (63.0%)	0.701
Anticoagulant	50 (13.8%)	55 (15.2%)	0.598
Antiplatelet	181 (50.0%)	182 (50.3%)	0.941
Statin	185 (51.1%)	180 (49.7%)	0.710
Clinical status			
NYHA class, in classes I-IV	33 (9.1%)/165 (45.6%)/143 (39.5%)/21 (5.8%)	31 (8.6%)/152 (42.0) %/166 (45.9%)/13 (3.6%)	0.242
Heart rate (bpm)	80.1 ± 10.7	80.2 ± 11.0	0.864
Systolic BP (mmHg)	129.4 ± 12.9	130.7 ± 14.0	0.202
Diastolic BP (mmHg)	77.8 ± 7.2	77.0 ± 8.1	0.173
Laboratory variables			
eGFR (mL/min/1.73 m^2)	58.2 ± 11.4	58.5 ± 10.4	0.762
SUA	503.0 (104.3)	495.5 (103.3)	0.083
Haemoglobin (g/dL)	12.1 ± 1.4	12.1 ± 1.5	0.735
BNP (pg/mL)	786.5 (301)	771.5 (320)	0.873
Echo data			
LVEF (%)	42.0 ± 4.0	41.5 ± 4.4	0.126
LAD (mm)	42.8 ± 5.4	42.7 ± 4.9	0.815
E/e'	14.2 ± 3.2	14.4 ± 5.0	0.421

Data are presented as mean ± SD (for normally-distributed continuous variables), median (IQR) (for non-normally distributed continuous variables) or number (%) of subjects (for categorical variables).

ULT, urate lowering therapy; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; BMI, body mass index; IHD, ischaemic heart disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; T2DM, type 2 diabetes mellitus; COPD, chronic obstructive pulmonary disease; HF, heart failure; ICD, implantable cardioverter defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; CRT-D, cardiac resynchronization therapy-defibrillator; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin II receptor blocker; NYHA, New York Heart Association functional class; BP, blood pressure; eGFR, estimated glomerular filtration rate; SUA, serum uric acids; BNP, B-type natriuretic peptides; LVEF, left ventricular ejection fraction; LAD, left atrium diameter; E/e', mitral Doppler early velocity/mitral annular early velocity; SD, standard deviation; IQR, interquartile range.

TABLE 3. Baseline Characteristics of HFpEF after PSM.

	Non-ULT	Febuxostat	*p* value
n	255	255	
Age (years)	70 (12)	70 (10)	0.431
Women (gender)	150 (58.8%)	143 (56.1%)	0.531
BMI (kg/m^2)	26.1 ± 3.8	25.9 ± 3.8	0.726
Medical history			
IHD	95 (37.3%)	95 (37.3%)	0.855
Prior PCI	47 (18.4%)	41 (16.1%)	0.482
Prior CABG	8 (3.1%)	11 (4.3%)	0.483
Hypertension	222 (87.1%)	220 (86.3%)	0.794
T2DM	79 (31.0%)	79 (31.0%)	1.000
Atrial fibrillation	102 (40.0%)	94 (36.9%)	0.466
Stroke	29 (11.4%)	23 (9.0%)	0.380
COPD	13 (5.1%)	15 (5.9%)	0.697
Smoking	80 (31.4%)	97 (38.0%)	0.114
Dyslipidemia	85 (33.3%)	84 (32.9%)	0.925
Gout	23 (9.0%)	27 (10.6%)	0.551
HF device-therapies			
ICD	2 (0.8%)	5 (2.0%)	0.450
Medications			
ACEI/ARB	178 (69.8%)	173 (67.8%)	0.633
Beta-blocker	164 (64.3%)	159 (62.4%)	0.646
Spironolactone	74 (29.0%)	79 (31.0%)	0.629
Diuretics	135 (52.9%)	151 (59.2%)	0.153
Anticoagulant	45 (17.6%)	40 (15.7%)	0.552
Antiplatelet	121 (47.5%)	128 (50.2%)	0.535
Statin	106 (41.6%)	112 (43.9%)	0.591
Clinical status			
NYHA class, in classes I-IV	15 (5.9%)/131 (51.4%)/91 (35.7%)/18 (7.1%)	17 (6.7%)/121 (47.5%)/97 (38.0%)/20 (7.8%)	0.845
Heart rate (bpm)	78.6 ± 11.9	79.8 ± 11.5	0.283
Systolic BP (mmHg)	131.4 ± 11.8	131.3 ± 12.9	0.889
Diastolic BP (mmHg)	76.8 ± 8.6	77.7 ± 8.5	0.262
Laboratory variables			
eGFR (mL/min/1.73 m^2)	59.9 ± 14.3	59.5 ± 13.6	0.758
SUA	499 (95)	499 (107)	0.147
Haemoglobin (g/dL)	12.1 ± 1.7	12.1 ± 1.7	0.929
BNP (pg/mL)	767 (330)	745 (312)	0.411
Echo data			
LVEF (%)	60.9 ± 5.2	60.3 ± 4.7	0.216
LAD (mm)	41.2 ± 4.3	41.4 ± 4.8	0.554
E/e'	12.6 ± 5.8	12.5 ± 4.7	0.716

Data are presented as mean ± SD (for normally-distributed continuous variables), median (IQR) (for non-normally distributed continuous variables) or number (%) of subjects (for categorical variables).

ULT, urate lowering therapy; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; BMI, body mass index; IHD, ischaemic heart disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; T2DM, type 2 diabetes mellitus; COPD, chronic obstructive pulmonary disease; HF, heart failure; ICD, implantable cardioverter defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; CRT-D, cardiac resynchronization therapy-defibrillator; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin II receptor blocker; NYHA, New York Heart Association functional class; BP, blood pressure; eGFR, estimated glomerular filtration rate; SUA, serum uric acids; BNP, B-type natriuretic peptides; LVEF, left ventricular ejection fraction; LAD, left atrium diameter; E/e', mitral Doppler early velocity/mitral annular early velocity; SD, standard deviation; IQR, interquartile range.

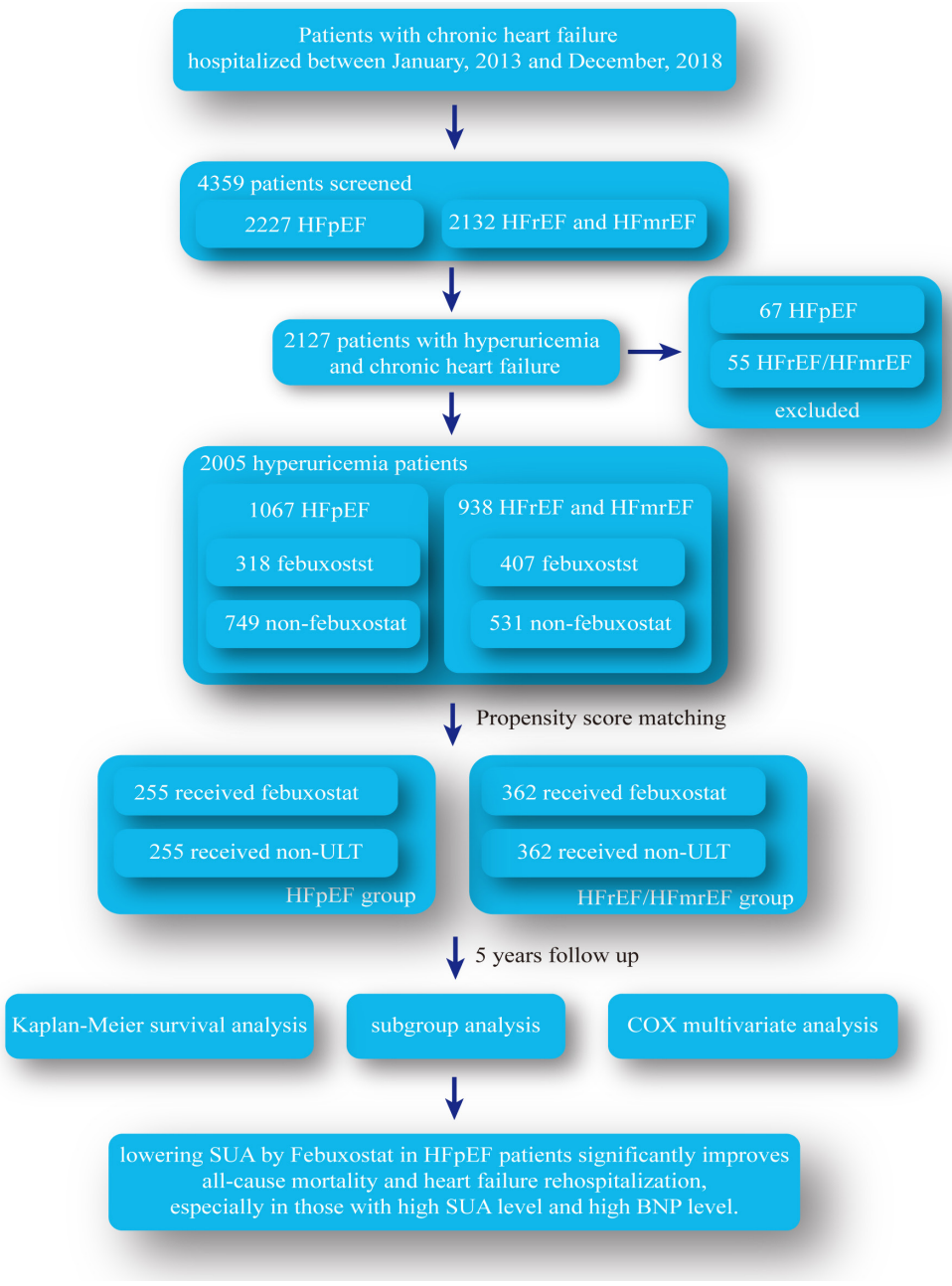

FIG. 1. A flowchart describing the study procedure.
HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; ULT, urate lowering therapy; SUA, serum uric acids; BNP, B-type natriuretic peptides.

SUA groups

To further assess the impact of SUA on HF outcomes, patients in each HF subgroup were stratified into tertiles (low, middle, and high SUA levels). Kaplan-Meier survival analyses were performed separately for the HFrEF/HFmrEF and HFpEF groups to evaluate the association between SUA level and the incidence of the composite endpoint. In the HFrEF/HFmrEF group, patients with middle and high SUA levels experienced significantly more endpoint events compared with those in the low SUA group (Figure 2a; $p < 0.001$ by log-rank test; HR, 1.228; 95% CI, 1.096-1.376). A similar trend was observed in the HFpEF group, where higher SUA levels were associated with a greater incidence of endpoints (Figure 2b; $p = 0.002$ by log-rank test; HR, 1.288; 95% CI, 1.109-1.496).

Clinical endpoints

Among the 362 patients treated with febuxostat in the HFrEF/HFmrEF subgroup, 216 reached the composite endpoint, which did not differ significantly from the untreated group (n = 229, $p = 0.321$). Kaplan-Meier analysis of cumulative incidence also showed no significant benefit of febuxostat in this subgroup (Figure 3a; $p = 0.234$ by log-rank test; HR, 0.894; 95% CI, 0.742-1.077). These findings suggest that febuxostat treatment did not significantly affect the incidence of the composite endpoint over 5 years in HFrEF/HFmrEF patients. In contrast, febuxostat treatment was associated with a significantly lower incidence of the composite endpoint in HFpEF patients (128 in the febuxostat group vs. 158 in the untreated group; $p = 0.007$). Kaplan-Meier curves further confirmed this benefit, showing improved cumulative incidence in the febuxostat group (Figure 3b; $p = 0.012$ by log-rank test; HR, 0.744; 95% CI, 0.589-0.939).

Specifically, in the HFrEF subgroup, 152 patients in the non-ULT group and 140 patients in the febuxostat group died from all causes ($p = 0.363$). Similarly, 197 patients in the non-ULT group and 195 in the febuxostat group experienced rehospitalization for HF ($p = 0.881$). In the HFpEF subgroup, 99 patients in the non-ULT group and 81 in the febuxostat group died from all causes ($p = 0.095$). Rehospitalization for HF occurred in 143 patients in the non-ULT group compared with 114 in the febuxostat group ($p = 0.010$). When accounting for all-cause mortality as a competing risk, the incidence of HF rehospitalization differed significantly between groups in HFpEF patients ($p = 0.0095$; Figure 3c).

Predictors of major endpoints

To identify potential risk and protective factors for the composite endpoint, multivariable Cox regression analysis was performed. In HFrEF/HFmrEF patients, atrial fibrillation, ACEI/ARB treatment, LVEF category, SUA category, and BNP category were independent predictors of the composite endpoint (Figure 4a). In HFpEF groups, febuxostat prescription, SUA category, and BNP category were significant predictors (Figure 4b). Subgroups analyses stratified

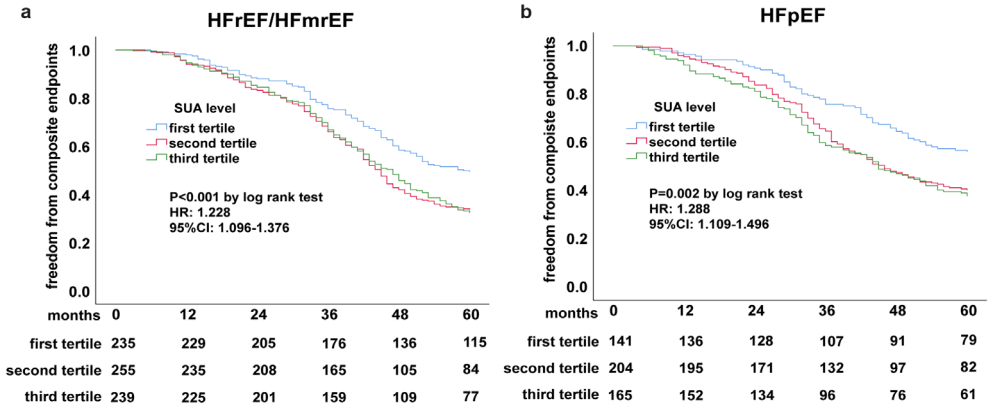

FIG. 2. (a, b) Kaplan-Meier survival analysis on HFrEF/HFmrEF and HFpEF patients tertiled by SUA level.

HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; SUA, serum uric acids; HR, hazard ratio, CI, confidence interval.

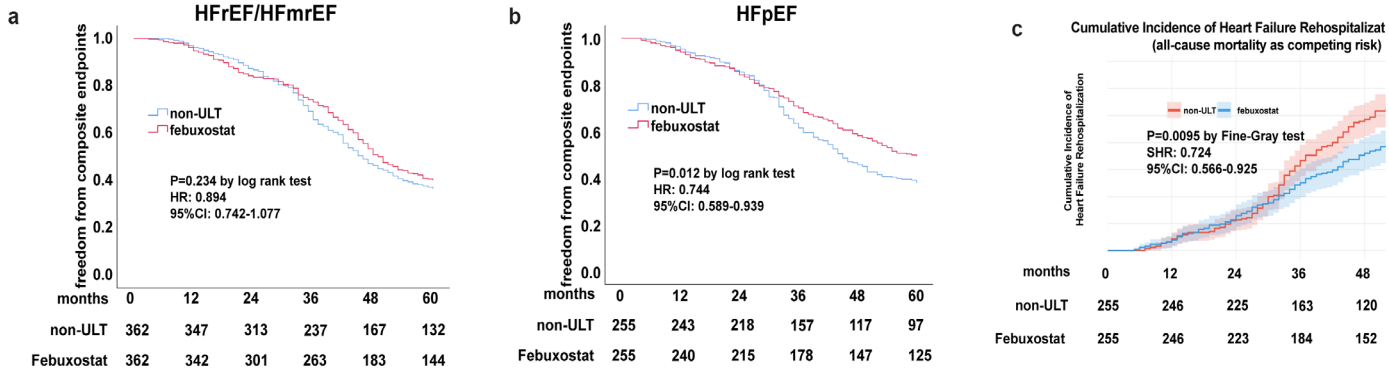

FIG. 3. (a-c) Kaplan-Meier survival analysis on HFrEF/HFmrEF and HFpEF patients treated with Febuxostat or without urate lowering therapy and Cumulative incidence of heart failure rehospitalization when setting all-cause mortality as competing risk in HFpEF patients.

HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; ULT, urate lowering therapy; HR, Hazard Ratio, SHR, subdistribution hazard ratio; CI, confidence interval.

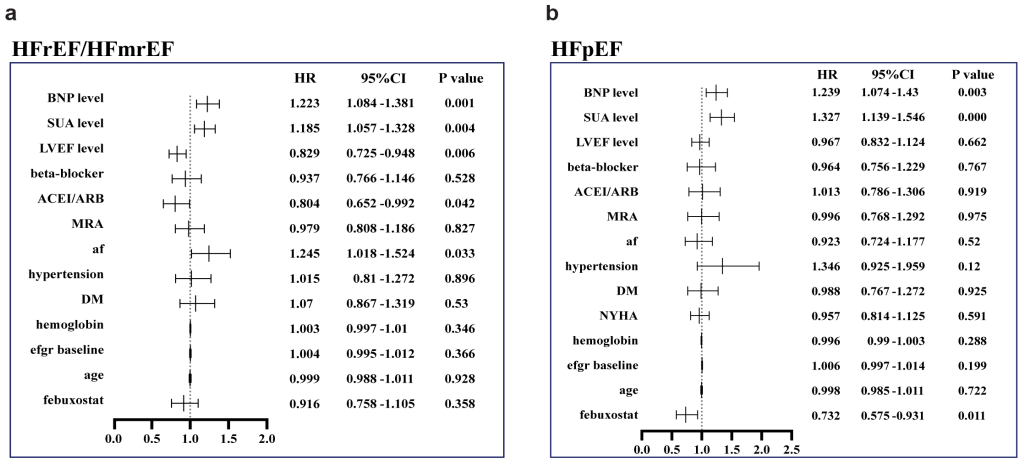

FIG. 4. (a, b) Forest plot of COX multivariate analysis on HFrEF/HFmrEF and HFpEF patients.
HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; BNP, B-type natriuretic peptides; SUA, serum uric acids; LVEF, left ventricular ejection fraction; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin II receptor blocker; af, atrial fibrillation; DM, diabetes mellitus.

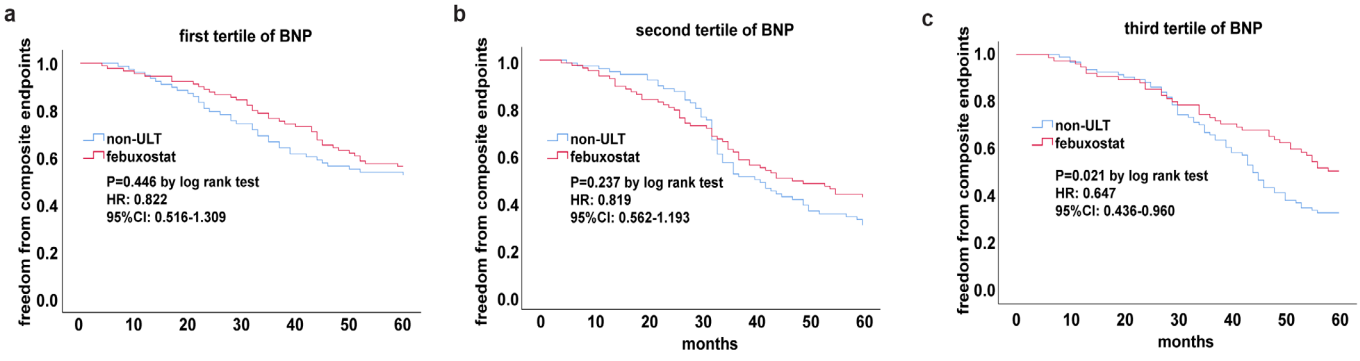

FIG. 5. (a-c) Kaplan-Meier survival analysis on BNP-tertiled HFpEF patients treated Febuxostat or without urate lowering therapy.
BNP, B-type natriuretic peptides. ULT, urate lowering therapy; HR, hazard ratio; CI, confidence interval.

by tertiles of BNP or SUA showed that the beneficial effects of febuxostat on HFpEF outcomes were most pronounced in patients in the highest BNP tertile (p = 0.021; HR, 0.647; 95% CI, 0.436-0.960; Figures 5a-c) and in the highest SUA tertile (p = 0.025; HR, 0.651; 95% CI, 0.441-0.963; Figures 6a-c). These findings suggest that febuxostat may be most effective in patients with HFpEF and severe hyperuricemia.

Changes in renal function and SUA levels

During long-term follow-up of HFrEF/HFmrEF patients, we obtained 342 renal function and SUA reports in the febuxostat group and 320 in the non-ULT group. Analysis showed that febuxostat significantly improved renal function (eGFR, 0.760 ± 4.3168 mL/min/1.73 m^2 in the febuxostat group vs. -2.122 ± 5.1602 mL/min/1.73 m^2 in the non-ULT group, $p < 0.001$) and lowered SUA levels [-129.0 (62.50) µmol/L vs. -35 (32.75) µmol/L, $p < 0.001$]. In the HFpEF group, a total of 207 (febuxostat group) and 217 (non-ULT group) reports likewise showed significant improvements in renal function (0.633 ± 3.6070 mL/min/1.73 m^2 vs. -2.111 ± 5.0052 mL/min/1.73 m^2, $p < 0.001$) and SUA levels [-128.5 (57) µmol/L vs. -29 (52.5) µmol/L, $p < 0.001$].

Adverse events

Clinically reported adverse effects of febuxostat include hepatic dysfunction.[5] Among our participants, 16 patients developed mild hepatic dysfunction; 14 of these cases resolved spontaneously after dose reduction, and patients were able to continue ULT. Two patients discontinued febuxostat due to hepatic dysfunction.

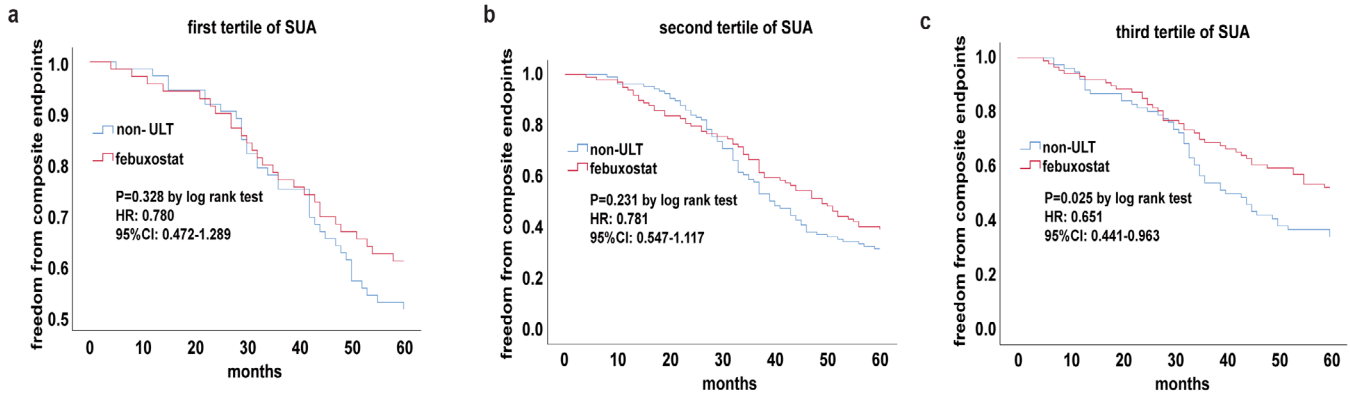

FIG. 6. Kaplan-Meier survival analysis on SUA-tertiled HFpEF patients treated with Febuxostat or without urate lowering therapy.
SUA, serum uric acids, ULT, urate lowering therapy; HR, hazard ratio; CI, confidence interval.

DISCUSSION

In this study, we found that febuxostat therapy significantly improves all-cause mortality and reduces HF rehospitalization in patients with HFpEF, particularly in those with elevated SUA and BNP levels. These findings provide insight into future treatment strategies for patients with HF complicated by hyperuricemia.

Clinically, allopurinol, benzbromarone, and febuxostat are considered first-line options for the treatment of hyperuricemia.[6] In Asia, however, allopurinol has been associated with adverse effects such as erythroderma and allergic reactions; therefore, its use is recommended only after HLA-B5801 genetic testing.[7] Benzbromarone promotes uric acid excretion and is effective in a substantial proportion of patients, but its efficacy depends on adequate fluid intake, which may be harmful for patients with HF, especially during the acute phase. Concerns have been raised about the potential cardiac adverse effects of febuxostat, but the evidence remains controversial. The CARES study reported that febuxostat was associated with increased rates of all-cause and cardiovascular mortality compared with allopurinol, although the overall incidence of cardiovascular events was unchanged.[8] In contrast, the FAST study demonstrated that febuxostat was non-inferior to allopurinol in terms of the primary cardiovascular endpoint and that long-term use was not associated with an increased risk of death or serious adverse events.[9] In Asian populations, the FREED study further showed that febuxostat reduces the incidence of cardiovascular events.[10] Although CARES, FAST, and FREED did not fully establish ULT as a therapeutic target, their results suggest that lowering SUA in patients with HF, particularly HFpEF, may influence prognosis. Reflecting this evolving evidence, the UK Medicines and Healthcare products Regulatory Agency recently revised its recommendation for febuxostat use in patients with cardiovascular diseases from "avoid treatment" to "use with caution". This highlights the urgent need for further studies on the cardiovascular safety of febuxostat. Our study adds to the growing body of evidence by showing that febuxostat improves all-cause mortality and reduces HF rehospitalization in patients with HFpEF.

Data from a 30-year follow-up study indicate that elevated SUA levels are correlated with a higher prevalence of HF[11], and hyperuricemia has been associated with increased all-cause and cardiovascular mortality.[2] However, whether lowering SUA improves clinical outcomes in patients with HF remains uncertain. In HFrEF, the association between hyperuricemia and patient outcomes remains controversial.[12] Given the characteristic myocyte death and remodeling, HFrEF is primarily marked by reduced pumping capacity. Thus, some researchers have proposed that the role of hyperuricemia in the initiation of HFpEF is less central than factors such as neurohormonal activation (RAAS, SNS) or ischemia-induced myocardial injury.[13] Elevated SUA may represent a marker of advanced disease and diuretic use, rather than a primary driver of cardiac dysfunction, making SUA-targeted treatment less applicable in HFrEF.[14] In contrast, in HFpEF[15], systemic inflammation, endothelial dysfunction, oxidative stress, microvascular dysfunction, and other metabolic factors are thought to contribute to disease induction.[16,17] Uric acid is considered a key driver of the inflammatory-oxidative cycle in HFpEF, making it a more direct and potentially impactful therapeutic target. Xanthine oxidase activity, among other processes, has been proposed as a contributor to oxidative stress and ROS generation.[18] Given this, we suggest that inhibition of xanthine oxidase activity by its inhibitors (XOIs, such as febuxostat) may improve systemic metabolism, reduce cellular oxidative stress, and ultimately enhance HFpEF clinical outcomes. In our study, we concluded that febuxostat indeed provided significant improvement in HFpEF outcomes. This finding is consistent with our previous reports showing that SUA predicts HFpEF incidence and that lowering SUA in hypertensive patients can prevent HFpEF onset.[1,19,20] It is also in line with previous studies identifying SUA as a prognostic factor for HFpEF outcomes, where endothelial dysfunction has been proposed as a key mediator of its effects.[21] Others have suggested that ventricular remodeling and myocardial fibrosis may explain the impact of SUA.[22]

Despite these findings, controversies remain regarding how hyperuricemia contributes to cardiovascular disorders and adverse

HF outcomes. Several potential mechanisms have been proposed. In patients with hypertension, the inflammatory effects of SUA, along with insulin resistance and oxidative stress, are thought to play central roles.[23,24] These processes promote the accumulation of extracellular matrix proteins, stimulate fibroblast differentiation, and trigger fibrotic remodeling in the hearts.[25] Fibrosis of cardiac tissue severely impairs cardiac contraction and cardiac output, leading to poor clinical outcomes in patients with HF. In addition, insulin resistance in patients with hyperuricemia causes systemic metabolic disorders and is characterized by impaired insulin signaling. This deficiency weakens glucose-derived energy supply and favors fatty acid oxidation, which underlies lipid toxicity in HFpEF.[26] Moreover, SUA itself may induce oxidative stress in multiple organs.[27] ROS-induced oxidative stress is a key cause of myocyte dysfunction and is proposed to play a pivotal role in the pathogenesis of HFpEF.[28] In 2022, Nishino et al.[21] reported that lowering SUA improved prognosis in patients with hyperuricemia and HFpEF; however, they did not investigate the efficacy of specific ULT drugs or the outcomes of subgroups of patients with hyperuricemia. Taken together, our study demonstrated that lowering SUA with febuxostat confers protection in patients with HFpEF.

This study has several limitations. First, it was conducted in a single center with a relatively small sample size; the conclusions would be strengthened by a multicenter, large-scale study. Second, the design was prospective and observational, whereas randomized controlled trials would provide more robust evidence. Third, greater population diversity (including non-Asian participants) should be considered in patient enrollment. Finally, unmeasured confounders such as medical history may have influenced the outcomes.

Ethics Committee Approval: Ethical approval was obtained from the Medical Ethics Committee of the Ninth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (approval number: SH9H-2018-T81-2, date: 14.02.2019).

Informed Consent: All participants provided informed consent and were allocated to the appropriate study group.

Data Sharing Statement: The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Authorship Contributions: Concept- H.Z., J.G.; Design- H.Z., J.G.; Supervision- C.W.; Funding- J.G.; Data Collection or Processing- J.K., X.Q., M.W., H.Zh.; Writing- J.K.

Conflict of Interest: The authors declare that they have no conflict of interest.

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