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Original article

Association of serum uric acid with benefits of intensive blood pressure control

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ABSTRACT

Introduction and objectives: Intensive systolic blood pressure (SBP) control improved outcomes in the Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial. Whether the serum uric acid concentration at baseline alters the benefits of intensive SBP control is unknown.

Methods: The STEP trial was a randomized controlled trial that compared the effects of intensive (SBP target of 110 to < 130 mmHg) and standard (SBP target of 130 to < 150 mmHg) SBP control in Chinese patients aged 60 to 80 years with hypertension. The primary outcome was a composite of cardiovascular disease events. This post hoc analysis was performed to examine whether the effects of intensive SBP intervention differed by the baseline uric acid concentration using 2 models: restricted cubic spline curves and subgroup analyses, both based on the Fine-Gray subdistribution hazard model in the analysis of the primary outcome and secondary outcomes (excluding all-cause death). In the analysis of all-cause death, the Cox regression model was used. We also examined the change in the follow-up uric acid concentrations.

Results: Overall, the risk of the primary outcome rose as the cumulative uric acid concentration increased in both the intensive and standard treatment groups. Patients with intensive treatment had a lower multivariable-adjusted subdistribution hazard ratio for the primary outcome, but with a wide overlap of 95%CI. Next, we stratified patients according to their baseline uric acid concentration (tertile 1 [T1], < 303.0 μmol/L; tertile 2 [T2], 303.0 to < 375.8 μmol/L; and tertile 3 [T3], ≥375.8 μmol/L). Subgroup analyses using tertiles provided HRs and 95%CI in T1 (HR, 0.55; 95%CI, 0.36–0.86; $P = .008$), T2 (HR, 0.80; 95%CI, 0.56–1.14; $P = .22$) and T3 (HR, 0.86; 95%CI, 0.60–1.21; $P = .39$), with an interaction P value of .29. The results for most of the secondary outcomes followed the same trends.

Conclusions: There was no evidence that the benefit of the intensive SBP control differed by baseline uric acid concentrations. This trial was registered at ClinicalTrial.gov (Identifier: NCT03015311).

Asociación del nivel de ácido úrico en suero con los beneficios del control intensivo de la presión arterial

Palabras clave:
Presión arterial
Hipertensión
Control intensivo de la presión arterial
Ácido úrico

RESUMEN

Introducción y objetivos: El control intensivo de la presión arterial sistólica (PAS) mejora los resultados de la estrategia de control de la presión arterial en el ensayo STEP con pacientes ancianos hipertensos. Sin embargo, se desconoce si los niveles de ácido úrico pueden afectar los beneficios del control intensivo de la PAS.

Métodos: El ensayo STEP fue un estudio controlado y aleatorizado que comparó el efecto del control intensivo (PAS objetivo de 110 o < 130 mm Hg) frente al tratamiento estándar (PAS objetivo de 130 o < 150 mm Hg) de la PAS en pacientes chinos hipertensos de entre 60 y 80 años. El objetivo primario incluyó un conjunto de eventos asociados a la enfermedad cardiovascular. Se utilizaron los modelos de curvas *spline* cúbicas restringidas y análisis de subgrupos para estudiar si los efectos del control intensivo de la PAS difieren en función las concentraciones basales de ácido úrico. Ambos modelos se basaron en la subdistribución de riesgos de Fine-Gray para el análisis del objetivo primario y los objetivos secundarios. El modelo de regresión de Cox se utilizó para el análisis de muerte por cualquier causa. También se analizaron las concentraciones de ácido úrico durante el seguimiento.

Resultados: El riesgo del objetivo primario se incrementó con el incremento de la concentración de ácido úrico tanto en el grupo de tratamiento intensivo como en el de tratamiento estándar. Los pacientes bajo

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tratamiento intensivo mostraron menor subdistribución (ajustada de forma multivariable) del cociente de riesgo para el objetivo primario, aunque con un amplio solapamiento del IC95%. La estratificación de pacientes por terciles de concentración de ácido úrico mostró un CR de 0,55 (IC95%, 0,36-0,86; p = 0,008) para el tercil 1 (ácido úrico < 303,0 μmol/l), de 0,80 (IC95%, 0.56-1.14; p = 0,22) para el tercil 2 (AcU 303,0 a < 375,8 μmol/l) y de 0,86 (IC95%, 0,60–1,21; p = 0,39) para el tercil 3 (AcU ≥ 375,8 μmol/l); p = 0,29 para la interacción. Las tendencias fueron similares para la mayoría de las variables secundarias. *Conclusiones:* El beneficio del control intensivo de la PAS no difiere en función de las concentraciones basales de ácido úrico. Registrado en ClinicalTrial.gov (Identificador: NCT03015311).

Abbreviations

SBP: systolic blood pressure

INTRODUCTION

Hypertension is the foremost contributor to disability and premature mortality worldwide.[1] Cannon et al.[2] reported that 25% of patients with untreated hypertension had hyperuricemia, defined as a uric acid concentration of > 7.0 mg/dL in men and ≥ 6.0 mg/dL in women,[3] and that the rate of hyperuricemia was extremely high in patients who were taking diuretics (50%) and those with malignant hypertension (> 75%). An elevated uric acid concentration has emerged as a potentially modifiable cardiovascular risk factor in patients with hypertension,[4] with a 3- to 5-fold increased risk of cardiovascular events compared with patients who have hypertension with normal serum uric acid concentrations.[5]

Among elderly patients, asymptomatic hyperuricemia has been reported to be a strong risk factor for refractory hypertension.[6] More importantly, among hospitalized elderly patients with hypertension, the presence of hyperuricemia is associated with the need for more antihypertensive drugs for blood pressure control, more diuretic use, and less blood pressure reduction in response to medical treatment.[7] These findings suggest that an elevated serum uric acid concentration blunts the blood pressure response to antihypertensive therapy.

Recently, several large-scale clinical trials have supported the positive effects of intensive blood pressure control. For example, in the Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial, intensive blood pressure control improved outcomes in elderly patients aged 60 to 80 years.[8]

Given the complex interactions between blood pressure and serum uric acid, the present study was performed to expand on previously reported findings by providing a more detailed analysis of primary and secondary outcomes according to baseline uric acid concentrations.

METHODS

Study population and intervention

The present study involved a post hoc analysis of the STEP trial. The methods and results for the primary outcome have been published elsewhere.[8,9] In brief, the STEP trial was a prospective, multicenter, randomized controlled trial performed at 42 clinical centers throughout China. The main inclusion criteria were as follows: *a)* age of 60 to 80 years, *b)* a history of hypertension and treatment with antihypertensive medication or systolic blood pressure (SBP) of 140 to 190 mmHg in 3 screening visits, and *c)* a record of the patient's baseline uric acid concentration. The main exclusion criterion was a history of ischemic or hemorrhagic stroke. The detailed inclusion and exclusion criteria were previously described in the study protocol.[9] The patients were randomly assigned in a 1:1 ratio to receive 1 of 2 therapies: intensive treatment (target SBP of < 130 mmHg) or standard treatment (target SBP of < 150 mmHg).[8]

This study was a post hoc analysis of the STEP trial, which was approved by the ethics committees of Fu Wai Hospital and all collaborating centers, and all the enrolled patients provided written informed consent. Therefore, no further approval was required in the present study. Clinical trial registration number: NCT03015311.

Blood pressure and uric acid measurements

The office blood pressure measurements were performed by trained personnel (physicians or nurses) using an office blood pressure monitor (OMRON Healthcare, United States). Before measurement, the participants rested quietly in a seated position for at least 5 minutes, and their blood pressure was then measured 3 times at 1-minute intervals by trial staff (observed). Both the office blood pressure and laboratory data (including the uric acid concentration, tested in Beijing CIC Clinical Laboratory) were obtained in a standard manner during all baseline and follow-up clinic visits. Details regarding quality control have been provided in previous studies.[9]

Trial outcomes

As previously described in the study protocol,[8,9] the primary outcome was a composite endpoint including death from cardiovascular causes, stroke, acute decompensated heart failure, coronary revascularization, acute coronary syndrome, and atrial fibrillation. The secondary outcomes were the components of the primary outcome and all-cause death.

Statistical analysis

In the restricted cubic spline analyses, primary outcome, and secondary outcomes (excluding all-cause death) were analyzed based on the Fine-Gray subdistribution hazard model. In the analysis of all-cause death, the Cox regression model was used. For death from all causes, we used cox.zph() to test the proportional hazards assumption for a Cox regression model. For other endpoints, we used the Fine-Gray subdistribution hazard model to build a dataset, then tested the proportional hazards assumption use cox.zph(). The associations between the uric acid concentration and all endpoints were evaluated on a continuous scale with restricted cubic spline curves. This is a multivariate analysis, including adjusted prognostically relevant variables (age, sex, body mass index, diastolic blood pressure, alanine aminotransferase, aspartate aminotransferase, urea, creatinine, triglycerides, high-density lipoprotein cholesterol, history of diabetes mellitus, estimated glomerular filtration rate).[10]

We included all participants with an available baseline uric acid concentration and stratified the them according to these con-

centrations (tertile 1 [T1], < 303.0 μmol/L; tertile 2 [T2], 303.0 to < 375.8 μmol/L; and tertile 3 [T3], ≥ 375.8 μmol/L). For continuous variables, the mean ± standard deviation (SD) were calculated; for categorical variables, the proportion was calculated in each category substratified by the uric acid concentration. The baseline characteristics for each stratum are depicted appropriately and were compared using the most suitable tests (such as analysis of variance, the chi-square test, and the Kruskal–Wallis test).

In the analyses of the primary outcome and secondary outcomes (excluding all-cause death), cumulative incidence was calculated for the 2 trial groups according to different strata using the Fine-Gray subdistribution hazard model and the results are presented as subdistribution hazard ratios.[11] In the analysis of all-cause death, the Cox regression model was used and the results are presented as hazard ratios (HR). The intention-to-treat approach was used in the present analysis. Although multiple events were recorded in this study and a single patient could develop more than 1 event, only the first event of any type per patient was used in the analysis. Model 1 was adjusted for potential confounders, which were significantly different between the intensive treatment group and the standard treatment group. *P* values for interaction in the subgroup analysis, and subdistribution hazard ratios or HR with 95% confidence intervals (95%CI) were used to compare the intensive and standard SBP control within each tertile.

To test the trend of uric acid concentrations during the follow-up years, the mixed effect regression model was used by the function lme() of package nlme. In the fixed effect, the dependent variable was follow-up uric acid concentration. The interaction between follow-up years and treatment group provided the real differences between treatment groups. The autocorrelation among repeated measurements was accounted for in the random effect. The results of this analysis were translated into least square means (LS means). As a sensitivity analysis, the interactions between treatment with uric acid as continuous of endpoints were analyzed using Cox regression for all-cause mortality, and Fine & Gray regression for other primary and secondary outcomes. All analyses were performed with R software, version 3.6.3 (R Foundation for Statistical Computing, Austria). A 2-sided *P* value of < .05 was considered statistically significant.

RESULTS

Baseline characteristics in 3 stratifications of uric acid concentration

Table 1 summarizes the characteristics of the overall study population and each uric acid tertile. Patients were stratified into 3 tertiles (< 303.0 μmol/L, 303.0 to < 375.8 μmol/L, and ≥ 375.8 μmol/L) according to their baseline uric acid concentration. Overall, the mean ± SD age of the sample at baseline was 66.26 ± 4.83 years, the mean uric acid concentration at baseline was 347.26 ± 89.15 μmol/L, and nearly half (46.6%) of the patients were male. The mean body mass index was 25.58 ± 3.16 kg/m^2, and the mean SBP was 146.07 ± 16.65 mmHg. Baseline characteristics were well balanced between the intensive and standard treatment groups in each tertile (table 2), which is consistent with the findings of our main study.[8] This indicates that the inclusion of patients in the present study was representative.

Some examined characteristics differed by uric acid tertile; for example, patients in T1 were younger, were more likely to be female, were more likely to have a history of diabetes mellitus, had

Table 1
Baseline demographics for the STEP participants and for those in the 3 uric acid stratifications

	Overall (n = 8294)	Tertile 1 (n = 2762)	Tertile 2 (n = 2766)	Tertile 3 (n = 2766)	P
Intensive treatment	4132 (49.8)	1355 (49.1)	1393 (50.4)	1384 (50.0)	.602
Age	66.26 ± 4.83	66.11 ± 4.75	66.18 ± 4.75	66.48 ± 4.96	.010 [b]
Male sex	3867 (46.6)	803 (29.1)	1299 (47.0)	1765 (63.8)	< .001 [b]
BMI [a]	25.58 ± 3.16	25.08 ± 3.14	25.62 ± 3.11	26.06 ± 3.16	< .001 [b]
SBP, mmHg	146.07 ± 16.65	145.87 ± 16.62	146.15 ± 16.54	146.19 ± 16.80	.734
DBP, mmHg	82.47 ± 10.60	81.64 ± 10.34	82.66 ± 10.47	83.12 ± 10.93	< .001 [b]
ALT, U/L	18.36 ± 11.79	16.98 ± 11.56	18.06 ± 11.03	20.03 ± 12.51	< .001 [b]
AST, U/L	23.56 ± 9.82	22.72 ± 9.62	23.16 ± 8.76	24.80 ± 10.85	< .001 [b]
Urea, umol/L	5.66 ± 1.34	5.34 ± 1.23	5.64 ± 1.25	5.99 ± 1.44	< .001 [b]
CR, umol/L	73.24 ± 18.00	64.11 ± 12.64	72.50 ± 15.69	83.09 ± 19.64	< .001 [b]
Fasting serum glucose, mmol/L	6.13 ± 1.59	6.16 ± 1.69	6.13 ± 1.57	6.09 ± 1.50	.269
Triglycerides, mmol/L	4.88 ± 1.08	4.87 ± 1.05	4.86 ± 1.05	4.92 ± 1.15	.055
Total cholesterol, mmol/L	1.60 ± 1.07	1.40 ± 0.83	1.56 ± 1.02	1.83 ± 1.27	< .001 [b]
HDL-C, mmol/L	1.26 ± 0.31	1.33 ± 0.31	1.26 ± 0.30	1.19 ± 0.29	< .001 [b]
LDL-C, mmol/L	2.69 ± 0.88	2.68 ± 0.86	2.69 ± 0.86	2.70 ± 0.91	.656
Diabetes mellitus history	1586 (19.1)	583 (21.1)	505 (18.3)	498 (18.0)	.005 [b]
Hyperlipidemia history	3052 (36.8)	987 (35.7)	1016 (36.7)	1049 (37.9)	.240
Framingham score	28.59 ± 16.33	24.26 ± 14.59	28.27 ± 16.08	33.23 ± 16.98	< .001 [b]
Framingham risk score ≥15% No./total [c]	6422 (77.7)	1895 (69.0)	2141 (77.5)	2386 (86.6)	< .001 [b]
eGFR	109.28 ± 24.05	118.98 ± 23.32	109.47 ± 22.14	99.40 ± 22.58	< .001 [b]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CR, creatinine; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.
Values are expressed as No. (%) or mean ± standard deviation. Percentages may not add up to 100 because of rounding.
To convert the values for fasting serum glucose to milligrams per deciliter, divide by 0.05551. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for triglycerides to milligrams per deciliter, divide by 0.01129.
[a] Body-mass index is obtained by dividing weight in kilograms by height squared in meters.
[b] *P* value < .05.
[c] A Framingham risk score of 15% or higher indicates a high 10-year risk of cardiovascular disease.

Table 2
Baseline demographics for patients in the standard treatment group and the intensive treatment group based on 3 uric acid stratifications

	Tertile 1			Tertile 2			Tertile 3		
	Standard treatment (n = 1407)	Intensive treatment (n = 1355)	*P* value	Standard treatment (n = 1373)	Intensive treatment (n = 1393)	*P* value	Standard treatment (n = 1382)	Intensive treatment (n = 1384)	*P*
Age	66.24 ± 4.74	65.97 ± 4.76	.16	66.17 ± 4.67	66.19 ± 4.84	.92	66.43 ± 4.99	66.53 ± 4.93	.61
Male sex	399 (28.4)	404 (29.8)	.42	651 (47.4)	648 (46.5)	.66	873 (63.2)	892 (64.5)	.51
BMI [a]	25.01 ± 3.12	25.14 ± 3.15	.30	25.66 ± 3.17	25.58 ± 3.06	.50	26.18 ± 3.09	25.95 ± 3.23)	.06
SBP, mmHg	146.08 ± 16.55	145.65 ± 16.71	.50	145.90 ± 16.42	146.40 ± 16.66	.43	145.96 ± 16.59	146.43 ± 17.01)	.47
DBP, mmHg	81.45 ± 10.25	81.83 ± 10.43	.33	82.50 ± 10.27	82.82 ± 10.66	.42	82.94 ± 10.99	83.30 ± 10.87)	.39
ALT, U/L	16.86 ± 12.06	17.11 ± 11.02	.57	18.14 ± 11.78	17.98 ± 10.25	.71	19.74 ± 11.69	20.32 ± 13.27)	.23
AST, U/L	22.52 ± 9.60	22.92 ± 9.63	.27	23.10 ± 8.18	23.22 ± 9.29	.73	24.63 ± 10.38	24.97 ± 11.30)	.41
Urea, umol/L	5.34 ± 1.26	5.35 ± 1.19	.92	5.61 ± 1.21	5.67 ± 1.29	.19	5.96 ± 1.41	6.02 ± 1.48)	.34
CR, umol/L	64.06 ± 12.64	64.16 ± 12.63	.84	72.67 ± 15.46	72.32 ± 15.91	.56	83.49 ± 20.08	82.69 ± 19.19)	.29
Fasting serum glucose, mmol/L	6.23 ± 1.79	6.09 ± 1.59[d]	.03 [b]	6.13 ± 1.47	6.13 ± 1.67	.88	6.14 ± 1.51	6.05 ± 1.49)	.13
Total cholesterol, mmol/L	4.85 ± 1.04	4.88 ± 1.05	.47	4.86 ± 1.02	4.87 ± 1.09	.75	4.93 ± 1.12	4.92 ± 1.18)	.76
Triglycerides, mmol/L	1.40 ± 0.83	1.40 ± 0.82	.97	1.55 ± 1.00	1.56 ± 1.04	.87	1.80 ± 1.15	1.86 ± 1.39)	.25
HDL-C, mmol/L	1.32 ± 0.30	1.33 ± 0.32	.46	1.26 ± 0.31	1.27 ± 0.30	.66	1.20 ± 0.30	1.19 ± 0.29)	.90
LDL-C, mmol/L	2.67 ± 0.86	2.69 ± 0.85	.58	2.69 ± 0.82	2.69 ± 0.89	.94	2.72 ± 0.93	2.68 ± 0.90)	.18
Diabetes mellitus history	315 (22.4)	268 (19.8)	.10	251 (18.3)	254 (18.2)	1.00	241 (17.4)	257 (18.6)	.47
Hyperlipidemia history	502 (35.7)	485 (35.8)	.98	484 (35.3)	532 (38.2)	.12	510 (36.9)	539 (38.9)	.29
Framingham score	24.48 ± 14.90	24.03 ± 14.25	.42	28.24 ± 16.08	28.30 ± 16.09	.91	33.09 ± 16.97	33.37 ± 16.99	.66
Framingham risk score ≥15% No./total [c]	963 (68.8)	932 (69.2)	.85	1076 (78.5)	1065 (76.6)	.26	1183 (86.0)	1203 (87.2)	.38
eGFR	118.85 ± 23.56)	119.13 ± 23.07	.75	109.17 ± 21.74	109.76 ± 22.52	.48	98.68 ± 22.10	100.13 ± 23.02	.09

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CR, creatinine; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.
The values are expressed as No. (%) or mean ± standard deviation. Percentages may not add up to 100 because of rounding. To convert the values for fasting serum glucose to milligrams per deciliter, divide by 0.05551. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for triglycerides to milligrams per deciliter, divide by 0.01129.

[a] Body-mass index is obtained by dividing weight in kilograms by height squared in meters.

[b] *P* value < .05

[c] A Framingham risk score of 15% or higher indicates a high 10-year risk of cardiovascular disease.

[d] Adjustment for fasting serum glucose.

a lower body mass index, baseline diastolic blood pressure, alanine aminotransferase concentration, aspartate aminotransferase concentration, urea concentration, creatinine concentration, triglyceride concentration, and Framingham Score, and had a higher estimated glomerular filtration rate ($P < .05$ for all) (table 1).

Further comparisons between the intensive and standard treatment groups were examined within each tertile. Except for fasting serum glucose concentration, all baseline characteristics were well balanced between the 2 trial groups by uric acid tertile (table 2).

Blood pressure

The overall trends in the different uric acid tertiles agreed well with the overall trends of each treatment group separately (figure 1 of the supplementary data). Additionally, the 2 treatment strategies in different uric acid tertiles led to a similarly rapid and sustained between-group difference in SBP (figure 2 of the supplementary data), which is similar to the findings of our previously published study.[8]

Uric acid concentration and clinical outcomes

Overall, the risk of the primary outcome rose as the cumulative uric acid concentration increased. This association was found in both the intensive treatment group and the standard treatment group (figure 1). The line representing multivariable-adjusted subdistribution HR for the primary outcome of patients receiving intensive treatment continued under the counterpart of patients receiving standard treatment (figure 1). However, the figures showed a wide overlap of the confidence intervals. The multivariable-adjusted subdistribution HR for the secondary outcomes except all-cause death showed similar trend (figure 2 and figure 3). In addition, our results showed that uric acid (as continuous and as tertiles) met the proportionality assumption for all endpoints.

Clinical outcomes in 3 stratifications of uric acid concentration

During the median follow-up period of 3.34 years, a total of 336 primary outcome events occurred in 144 of 4132 patients (3.5%; 1.0% per year) in the intensive treatment group and in 192 of 4162 patients (4.6%; 1.4% per year) in the standard treatment group, with a subdistribution HR of 0.74; 95%CI, 0.60-0.92; $P = .007$] (table 2 of the supplementary data). Therefore, intensive treatment considerably reduced the incidence of primary outcome events when compared with standard treatment, with an absolute difference of 1.1 percentage points.

The incidence of primary outcome events was significantly lower in T1 of intensive SBP intervention when compared with standard treatment (subdistribution HR, 0.55; 95%CI, 0.36-0.86; $P = .007$) (table 3 and figure 4A). Additionally, no significant benefit was derived from intensive treatment in patients in T2 and T3 when compared with standard treatment (table 3 and figure 4B,C). The Interaction P value between SBP control and uric acid stratification was .29. The results for most of the secondary outcomes were similar to those for the primary outcomes in different tertiles (table 3 of the supplementary data).

As a sensitivity analysis, the interaction between treatment with uric acid as a continuous variable revealed no significance (table 4 of the supplementary data).

Uric acid concentrations during follow-up

The results of the mixed effect regression model were translated into LS means (table 4). In the standard group, the uric acid concentrations at baseline, first visit, second visit and third visit were 347 μmol/L, 342 μmol/L, 341 μmol/L, and 333 μmol/L. In the standard group, the follow-up uric acid concentrations were 348 μmol/L, 344 μmol/L, 345 μmol/L, and 337 μmol/L, respectively. The P values revealed no significant differences over time between the 2 treatment groups (table 4).

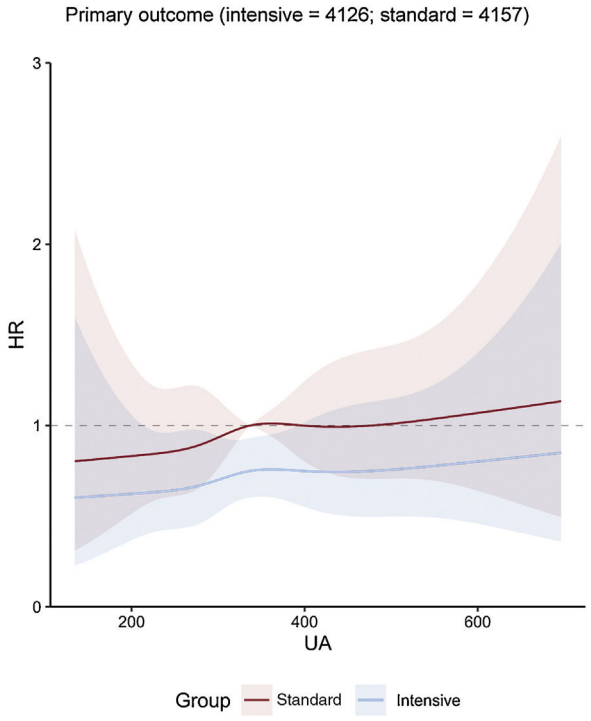

Figure 1. Central illustration. Cubic spline regression curves relating baseline uric acid concentrations as a continuous variable to the primary outcome. The figure shows HR with shadow 95% confidence intervals relating baseline uric acid concentrations to primary outcome under the Fine-Gray subdistribution hazard model in each SBP treatment arm, with baseline uric acid concentrations as predictor variables and covariable adjustment for age, sex, body mass index, DBP, ALT, AST, urea, creatinine, triglycerides, high-density lipoprotein cholesterol, history of diabetes mellitus, and estimated glomerular filtration rate. ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; HR, hazard ratio; UA, uric acid.

DISCUSSION

The results of the present study indicate that the effects of intensive SBP control on the primary outcome were not influenced by baseline uric acid concentrations either in cubic spline regression analyses or in tertile analyses.

Recently, many studies have revealed the association between uric acid and hypertension. High uric acid concentrations may contribute to a higher risk of hypertension, refractory, uncontrolled hypertension, and more aggressive drug treatment. A recent systematic review and meta-analysis revealed that a 1.0-mg/dL increase in the uric acid concentration is associated with a 13% increased risk of incident hypertension (95%CI, 1.06-1.20).[12] Asymptomatic hyperuricemia was also reported to be a strong risk factor for refractory hypertension in elderly patients.[6] Among patients with a mean age of 59.2 years treated with antihypertensive drugs, serum uric acid concentration was significantly associated with uncontrolled blood pressure even after adjustment for age, body mass index, and the estimated glomerular filtration rate.[13] Another study also showed that an elevated uric acid concentration impaired the efficacy of antihypertensive therapy in

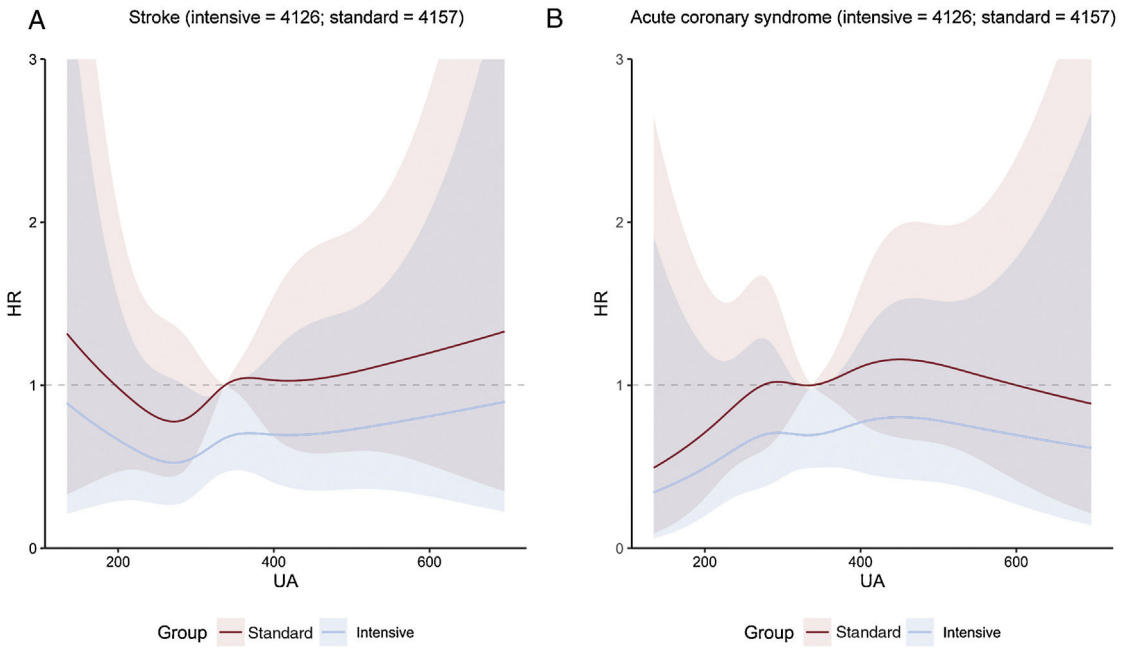

Figure 2. A: cubic spline regression curves relating baseline uric acid concentrations as a continuous variable to stroke. The figure shows HR with shadow 95% confidence intervals relating baseline uric acid concentrations to the primary outcome under the Fine-Gray subdistribution hazard model in each SBP treatment arm, with baseline uric acid concentrations as predictor variables and covariable adjustment for age, sex, body mass index, DBP, ALT, AST, urea, creatinine, triglycerides, high-density lipoprotein cholesterol, history of diabetes mellitus, and estimated glomerular filtration rate. B: cubic spline regression curves relating baseline uric acid concentrations as a continuous variable to acute coronary syndrome. The figure shows HR with shadow 95% confidence intervals relating baseline uric acid concentrations to the primary outcome under the Fine-Gray subdistribution hazard model in each SBP treatment arm, with baseline uric acid concentrations as predictor variables and covariable adjustment for age, sex, body mass index, DBP, ALT, AST, urea, creatinine, triglycerides, high-density lipoprotein cholesterol, history of diabetes mellitus, and estimated glomerular filtration rate. ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; HR, hazard ratio; UA, uric acid.

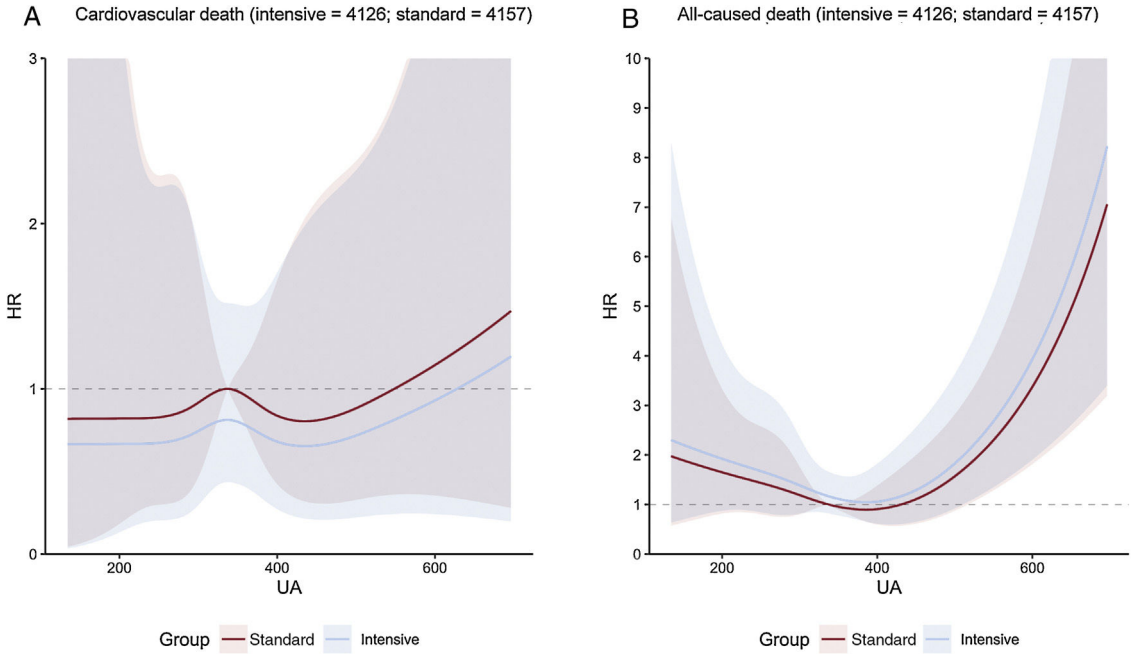

Figure 3. A: cubic spline regression curves relating baseline uric acid concentrations as a continuous variable to cardiovascular death. The figure shows HR with shadow 95% confidence intervals relating baseline uric acid concentrations to the primary outcome under the Fine-Gray subdistribution hazard model in each SBP treatment arm, with baseline uric acid concentrations as predictor variables and covariable adjustment for age, sex, body mass index, DBP, ALT, AST, urea, creatinine, triglycerides, high-density lipoprotein cholesterol, history of diabetes mellitus, and estimated glomerular filtration rate. B: cubic spline regression curves relating baseline uric acid concentrations as a continuous variable to all-caused death. The figure shows HR with shadow 95% confidence intervals relating baseline uric acid concentrations to the primary outcome under a Cox regression model in each SBP treatment arm, with baseline uric acid concentrations as predictor variables and covariable adjustment for age, sex, body mass index, DBP, ALT, AST, urea, creatinine, triglycerides, high-density lipoprotein cholesterol, history of diabetes mellitus, and estimated glomerular filtration rate. ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; HR, hazard ratio; UA, uric acid.

Table 3
Hazard ratios for the primary outcomes by uric acid stratification

Outcomes	Intensive treatment			Standard treatment			Crude model		Adjusted model 1 [c]			
	Total number	No. of events, %	% with event per year	Total number	No. of events, %	% with event per year	Subdistribution hazard ratio (95%CI)	*P*	Subdistribution hazard ratio (95%CI)	*P*	*P* for interaction
Primary outcome[a]											
Tertile 1 (n = 2762)	1355	31	0.69	1407	59	1.25	0.537 (0.348-0.829)	.005[b]	0.553 (0.358-0.856)	.008 [b]	.29
Tertile 2 (n = 2766)	1393	55	1.18	1373	66	1.44	0.808 (0.565-1.156)	.243	0.798 (0.559-1.140)	.215	
Tertile 3 (n = 2766)	1384	58	1.25	1382	67	1.45	0.853 (0.560-1.212)	.374	0.857 (0.603-1.217)	.389	

CI, confidence interval.
For the primary outcome except for death from any cause, the hazard ratios, 95% confidence intervals, and *P* value were calculated with the use of the Fine-Gray subdistribution hazard model for the competing risk of death.
[a] The primary outcome was a composite of stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes.
[b] $P < .05$.
[c] Adjustment for fasting serum glucose.

Table 4
Predicted mean levels of uric acid during follow-up

Uric acid (umol/L)	standard (n = 4162)		intensive (n = 4132)		P
Year	LS means	95%CI	LS means	95%CI	
Baseline	347	(344-350)	348	(345-350)	.761
Second	342	(338-345)	344	(341-348)	.256
Third	341	(338-344)	345	(342-348)	.103
Fourth	333	(330-336)	337	(334-340)	.0741

LS means, least square means; CI, confidence interval.
From a mixed effect regression model (least square means).

elderly patients with hypertension as reflected by the need for more antihypertensive drugs, more diuretic use, and blunted blood pressure responses.[7]

The potential mechanisms underlying how an elevated uric acid concentration may induce hypertension and reduce the protective effects of intensive treatment involve excessive renin-angiotensin-aldosterone system activation,[14,15] oxidative stress,[14–17] inflammation,[18–21] and insulin resistance.[22–25] Thus, based on evidence obtained from basic mechanism research, it is reasonable to hypothesize that uric acid-lowering therapy could be a therapeutic approach for hypertension. Some previous randomized controlled trials showed that reducing uric acid substantially decreased blood pressure in adolescents[26,27] and adults with chronic refractory gout,[28] whereas other randomized controlled trials[29,30] revealed no significant blood pressure reduction. These inconsistent results may be explained by differences in the methodology coupled with the effect of changes in kidney function on serum uric acid concentrations. For example, although reduction of uric acid did not lower ambulatory blood pressure in the overall population of adults with hyperuricemia and hypertension, there was a significant reduction in blood pressure in the prespecified subgroup of patients with normal kidney function.[29] Most Mendelian studies[31,32] did not support the association between blood pressure and uric acid. However, Mendelian studies have some limitations because they only involve gene-dependent associations, and although hyperuricemia has an important genetic component, it is primarily caused by lifestyle habits and diet.[33] In elderly patients, the effects of lowering uric acid concentrations on blood pressure control remain unclear. The Scientific Workshop of the National Kidney Foundation reported that the role of serum uric acid concentrations in hypertension remains to be determined and requires further investigation in large-scale trials.[34]

However, previous studies mainly focused on whether serum uric acid concentrations influence the occurrence or prognosis of hypertension. The evidence on whether baseline serum uric acid concentration blunts the benefits of intensive SBP control remains unknown. Our study used 2 models to detect the influence of uric acid concentration on the effects of SBP innervation. First, the results of spline analysis showed a wide overlap of the confidence intervals. Second, in subgroup analysis, interaction P value between treatment and uric acid stratification for primary outcome was nonsignificant. Moreover, in the sensitivity analysis, the interaction between treatment with uric acid as a continuous variable also revealed no significance. All these findings suggest that the effects of intensive SBP control were not influenced by baseline uric acid concentrations.

In the STEP trial, the patients began treatment with olmesartan medoxomil (an angiotensin receptor blocker) tablets (20 mg, once daily) or amlodipine besylate (a calcium channel blocker) tablets (5-10 mg, once daily) as an initial therapy not including hydrochlorothiazide.[8] Olmesartan does not significantly increase uric acid concentrations,[35,36] and antihypertensive therapy with

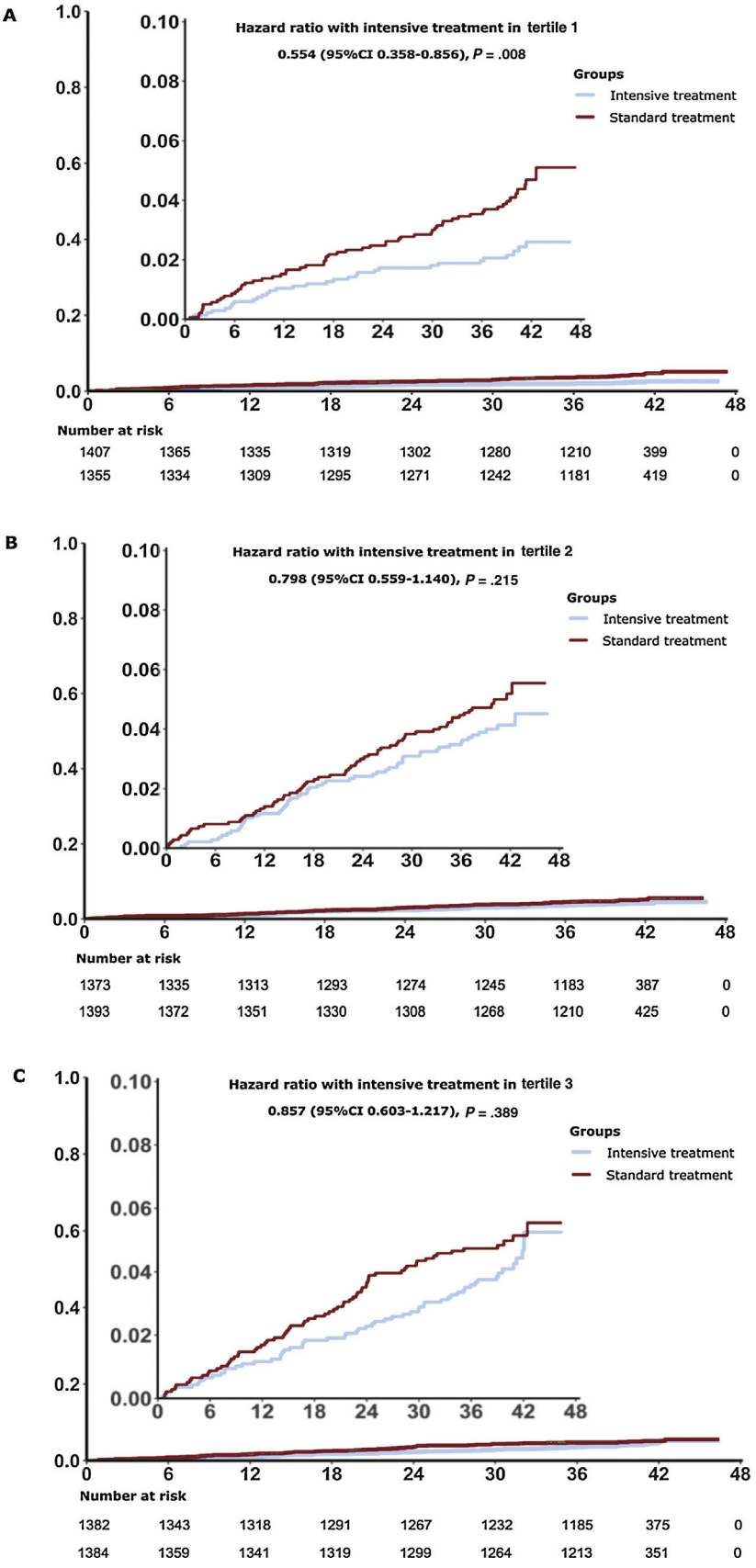

Figure 4. Cumulative incidence for the primary outcome by stratification of uric acid. Cumulative hazards over time are depicted for tertile 1 (A), tertile 2 (B), tertile 3 (C) associated hazard ratios (HRs). The lines depict the intensive and standard arms. The primary outcome was a composite of stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes. The hazard ratio, 95% confidence interval (CI), and *P* value for the primary outcome were calculated with the use of the Fine-Gray subdistribution hazard model for the competing risk of death. The inset shows the same data on an enlarged y-axis.

the dihydropyridine calcium channel blocker amlodipine (5-10mg) is associated with a reduced serum uric acid concentration.[37] In previous studies, however, thiazide therapy caused a 13% increase in plasma uric acid concentrations.[38] Although hydrochlorothiazide was not administered as initial therapy in the STEP trial, the intensive treatment group received a larger number of agents and was more likely to receive a combination of diuretics than the standard arm.[39] Thus, it is clinically significant to consider whether intensive blood pressure control elevates uric acid concentrations. The mixed effect regression model was used to test changes in follow-up uric acid concentrations according to the interaction between follow-up years and treatment groups. The results revealed no significant differences in uric acid concentrations over time between the 2 treatment groups (table 4).

Limitations

The main limitation of this study is that much of the reported variation in HR between the subgroups was caused by chance and that, in the absence of a statistically significant interaction, the best estimate of the effect of the intervention was given by the study-wide effect estimate, including all patients. In addition, the post hoc analysis of randomized controlled trials is subject to potential confounding factors. In this study, this disadvantage presented as large overlap of confidence intervals both in cubic spline regression analyses and tertile analyses.

CONCLUSIONS

Our study revealed no difference in the benefit of intensive SBP control in patients with different baseline uric acid concentrations. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

WHAT IS KNOWN ABOUT THE TOPIC?

- Previous studies have revealed the association between uric acid and hypertension. High uric acid concentrations may contribute to a higher risk of hypertension, refractory, uncontrolled hypertension, and more aggressive drug therapy. Elevated uric acid concentrations impaired the efficacy of antihypertensive therapy in elderly patients with hypertension, as reflected by the need for more antihypertensive drugs, greater diuretic use, and blunted blood pressure responses. This information indicates that uric acid concentrations may influence the benefits of intensive SBP control.

WHAT DOES THIS STUDY ADD?

- Our study revealed that no difference was observed in the benefit of intensive SBP control in patients with different baseline uric acid concentrations. We tested this conclusion using 2 models, including cubic spline regression analyses and tertile analyses. In addition, although the intensive treatment group received a larger number of agents and was more likely to received combined diuretics than the standard arm, no significant differences were found in uric acid concentrations over time between the 2 treatment groups.

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AUTHORS' CONTRIBUTIONS

X. Wang and J. Tan made substantial contributions to the conception and design of the study, data collection and analysis, and manuscript drafting and served as the equally contributing first authors of the manuscript. J. Cai and W. Zhang made substantial contributions to the study design, intellectual direction, and revision of the drafting of the manuscript. S. Zhang made substantial contributions to revision of the drafting of the manuscript. All authors read and approved the final manuscript.

CONFLICTS OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this paper.

APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.rec.2023.01.003

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