

Supplementary

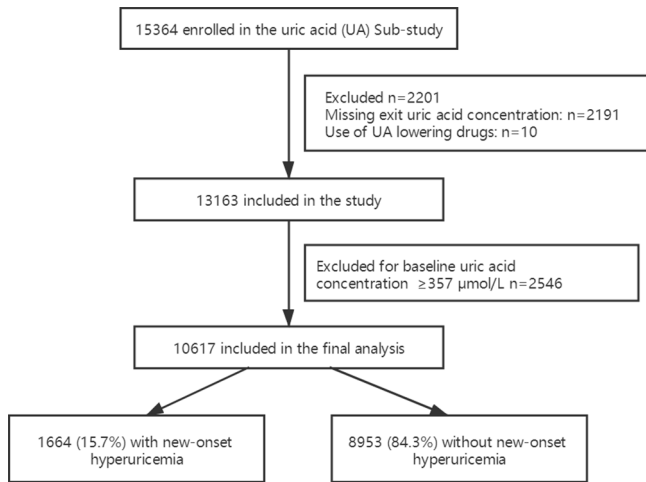


Figure S1 Flow chart of the current study participants.

Table S1 Characteristics of the participants with and without UA measurements at the exit visit in the UA sub-study of the CSPPT

Characteristics	Those without exit UA (n=2,201)	Those with exit UA (n=13,163)
Age, years	59.0±8.1	59.6±7.5
Male, n (%)	953 (43.3)	5,089 (38.7)
BMI, kg/m ²	25.4±3.7	25.7±3.5
Current smoking, n (%)	578 (26.3)	2,913 (22.1)
Current alcohol drinking, n (%)	554 (25.2)	2,987 (22.7)
Self-reported hyperlipidemia, n (%)	60 (2.7)	392 (3.0)
Self-reported diabetes, n (%)	92 (4.2)	480 (3.6)
Enalapril only treatment, n (%)	1,080 (49.0)	6,600 (50.1)
<i>MTHFR</i> C677T genotypes, n (%)		
CC	522 (23.7)	3,071 (23.3)
CT	1,105 (50.2)	6,588 (50.0)
TT	575 (26.1)	3,504 (26.6)
Blood pressure, mmHg		
Baseline SBP	167.3±20.9	168.5±20.9
Baseline DBP	95.7±12.0	95.3±11.9
Time-averaged on-treatment SBP	142.6±13.1	139.5±10.9
Time-averaged on-treatment DBP	85.5±8.5	83.5±7.3
Laboratory results		
Total cholesterol, mmol/L	5.8±1.2	5.7±1.2
Triglycerides, mmol/L	1.7±1.0	1.7±1.3
Folate, ng/mL	7.6±3.1	7.7±3.2
Fasting glucose, mmol/L	6.1±2.1	6.0±1.8
Total homocysteine, μmol/L	15.3±10	14.6±8.9
eGFR, mL/min/1.73m ²	94.2±13.9	94±13.0
Uric acid, μmol/L	299.4±82.7	293.9±79.3
Phosphate, mg/dL	4.0±0.7	4.1±0.8
Medication use, n (%)		
Antihypertensive drugs	1,014 (46.0)	6,578 (50.0)
Lipid-lowering drugs	14 (0.6)	117 (0.9)
Glucose-lowering drugs	39 (1.8)	239 (1.8)
Antiplatelet drugs	78 (3.5)	513 (3.9)

*, variables are presented as mean ± SD or n (%). BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; *MTHFR*, 5, 10-methylenetetrahydrofolate reductase; SBP, systolic blood pressure.

Table S2 Characteristics of study participants according to quartiles of time-averaged on-treatment SBP*

Characteristics	Time-averaged on-treatment SBP, mmHg				P value
	Q1 (<131.7) (n=2,654)	Q2 (131.7 to <138.3) (n=2,654)	Q3 (138.3 to <145.6) (n=2,654)	Q4 (≥145.6) (n=2,655)	
Age, years	57.8±7.0	59.1±7.4	60.2±7.4	60.7±7.5	<0.001
Male	793 (29.9)	851 (32.1)	851 (32.1)	855 (32.2)	0.203
BMI, kg/m ²	25.3±3.3	25.6±3.5	25.6±3.5	25.7±3.7	<0.001
Current smoking	447 (16.8)	495 (18.7)	539 (20.3)	561 (21.1)	0.004
Current alcohol drinking	427 (16.1)	518 (19.5)	509 (19.2)	520 (19.6)	<0.001
Self-reported hyperlipidemia	86 (3.2)	77 (2.9)	69 (2.6)	60 (2.3)	0.156
Self-reported diabetes	92 (3.5)	105 (4.0)	102 (3.8)	114 (4.3)	0.479
Enalapril only treatment, n (%)	1,313 (49.5)	1,332 (50.2)	1,329 (50.1)	1,350 (50.8)	0.799
<i>MTHFR</i> C677T genotypes, n (%)					0.260
CC	595 (22.4)	612 (23.1)	659 (24.8)	600 (22.6)	
CT	1,319 (49.7)	1,342 (50.6)	1,302 (49.1)	1,360 (51.2)	
TT	740 (27.9)	700 (26.4)	693 (26.1)	695 (26.2)	
Blood Pressure, mmHg					
Baseline SBP	157.9±16.4	164.8±17.7	171.7±18.8	181.3±22.4	<0.001
Baseline DBP	93.0±10.5	94.0±10.9	95.3±12.0	97.5±13.2	<0.001
Time-averaged on-treatment SBP	126.7±4.0	135.0±1.9	141.7±2.1	153.6±7.7	<0.001
Time-averaged on-treatment DBP	79.9±5.3	82.1±5.9	83.7±6.7	87.1±8.2	<0.001
Laboratory results					
Total cholesterol, mmol/L	5.7±1.2	5.7±1.2	5.7±1.2	5.7±1.2	0.479
Triglycerides, mmol/L	1.6±0.9	1.6±0.9	1.7±0.9	1.7±2.1	0.077
Folate, ng/mL	7.8±3.3	7.8±3.4	7.7±3.1	7.6±3.1	0.186
Fasting glucose, mmol/L	5.9±1.7	6.0±1.8	6.1±1.8	6.2±2.1	<0.001
Total homocysteine, μmol/L	13.8±8.7	13.9±8.0	14.0±8.2	14.5±8.4	0.022
eGFR, mL/min/1.73m ²	96.4±11.3	95.2±11.7	94.9±11.6	94.3±12.3	<0.001
Uric acid, μmol/L	259.6±52.4	265.5±51.2	265.4±52.1	269.3±51.9	<0.001
Phosphate, mg/dL	4.1±0.7	4.1±0.7	4.0±0.7	4.0±0.8	0.216
Medication use, n (%)					
Antihypertensive drugs	1,225 (46.2)	1,228 (46.3)	1,289 (48.6)	1,326 (49.9)	0.012
Lipid-lowering drugs	31 (1.2)	23 (0.9)	18 (0.7)	18 (0.7)	0.167
Glucose-lowering drugs	50 (1.9)	59 (2.2)	50 (1.9)	46 (1.7)	0.613
Antiplatelet drugs	101 (3.8)	113 (4.3)	88 (3.3)	88 (3.3)	0.202

*, variables are presented as mean ± SD or n (%). BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; *MTHFR*, 5, 10-methylenetetrahydrofolate reductase; SBP, systolic blood pressure.

Table S3 Association between time-averaged on-treatment blood pressure and change in uric acid concentrations*

Time-averaged on-treatment blood pressure, mmHg	Uric acid change, mean \pm SD, $\mu\text{mol/L}$	Crude model		Adjusted model [†]	
		β (95% CI)	P value	β (95% CI)	P value
Time-averaged on-treatment SBP, mmHg					
Per 10 mmHg increment	41.7 \pm 65.0	2.78 (1.64–3.92)	<0.001	–0.94 (–2.19 to 0.31)	0.142
Quartiles					
Q1 (<131.7)	37.2 \pm 60.5	Ref.		Ref.	
Q2 (131.7 to <138.3)	40.6 \pm 64.6	3.40 (–0.09 to 6.89)	0.057	1.29 (–2.12 to 4.69)	0.459
Q3 (138.3 to <145.6)	44.1 \pm 66.4	6.91 (3.42–10.40)	<0.001	1.04 (–2.46 to 4.53)	0.561
Q4 (\geq 145.6)	45.2 \pm 67.8	8.01 (4.52–11.50)	<0.001	–1.68 (–5.39 to 2.03)	0.374
P for trend		<0.001		0.390	
Time-averaged on-treatment DBP, mmHg					
Per 10 mmHg increment	41.7 \pm 65.0	4.14 (2.41–5.88)	<0.001	3.23 (0.97–5.48)	0.005
Quartiles					
Q1 (<78.5)	38.1 \pm 65.2	Ref.		Ref.	
Q2 (78.5 to <82.9)	40.0 \pm 64.4	1.90 (–1.60 to 5.39)	0.287	1.95 (–1.58 to 5.48)	0.280
Q3 (82.9 to <87.5)	43.0 \pm 63.5	4.83 (1.34–8.32)	0.007	4.60 (0.82–8.38)	0.017
Q4 (\geq 87.5)	45.8 \pm 66.4	7.65 (4.16–11.14)	<0.001	5.94 (1.68–10.20)	0.006
P for trend		<0.001		0.003	

* , change in uric acid concentrations was defined as the uric acid concentration at the exit visit minus that at baseline. [†] , adjusted for treatment group, age, sex, BMI, UA, fasting glucose, total cholesterol, TG, tHcy, folate, eGFR, smoking and drinking status, use of antihypertensive drugs, and SBP and DBP at baseline.

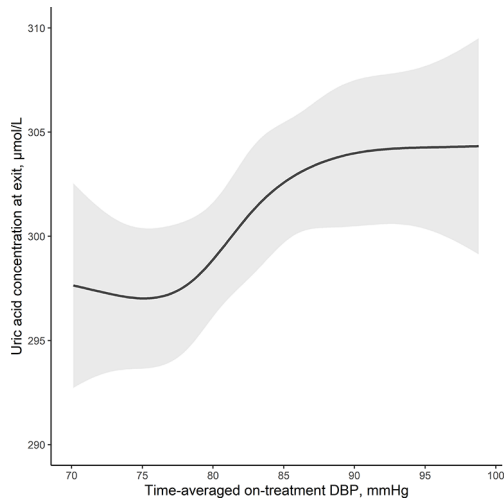
**Figure S2** Relation of time-averaged on-treatment DBP with exit uric acid concentrations.

Table S4 Association between time-averaged on-treatment DBP (clinical categories) and new-onset hyperuricemia

Time-averaged on-treatment DBP, mmHg	Events/N (%)	Crude model		Adjusted model*	
		OR (95% CI)	P value	OR (95% CI)	P value
Per 10 mmHg increment	1,664/10,617 (15.7)	1.16 (1.08–1.25)	<0.001	1.13 (1.02–1.26)	0.021
Categories 1					
<75	165/1,158 (14.2)	Ref.		Ref.	
75 to <80	342/2,332 (14.7)	1.03 (0.85–1.26)	0.742	1.06 (0.84–1.32)	0.633
80 to <85	450/3,108 (14.5)	1.02 (0.84–1.24)	0.849	1.06 (0.85–1.34)	0.587
85 to <90	385/2,343 (16.4)	1.18 (0.97–1.44)	0.095	1.22 (0.96–1.56)	0.110
≥90	322/1,676 (19.2)	1.43 (1.17–1.76)	<0.001	1.41 (1.07–1.86)	0.015
P for trend		<0.001		0.004	
Categories 2					
<85	957/6,598 (14.5)	Ref.		Ref.	
85 to <90	385/2,343 (16.4)	1.16 (1.02–1.32)	0.025	1.16 (0.99–1.34)	0.058
≥90	322/1,676 (19.2)	1.40 (1.22–1.61)	<0.001	1.33 (1.11–1.59)	0.002
P for trend		<0.001		0.001	
Categories 3					
<85	957/6,598 (14.5)	Ref.		Ref.	
≥85	707/4,019 (17.6)	1.26 (1.13–1.40)	<0.001	1.21 (1.06–1.39)	0.005

*, adjusted for treatment group, age, sex, BMI, UA, fasting glucose, total cholesterol, TG, tHcy, folate, eGFR, smoking and drinking status, use of antihypertensive drugs, and SBP and DBP at baseline. †, uric acid change was defined as the uric acid concentrations at the exit visit minus that at baseline.

Table S5 Concomitant medication usage during the treatment period according to the quartiles of time-averaged on-treatment DBP during the treatment period*

Medication, n (%)	Time-averaged on-treatment DBP, mmHg				P value
	Q1 (<78.5)	Q2 (78.5 to <82.9)	Q3 (82.9 to <87.5)	Q4 (≥87.5)	
Anti-hypertension drugs					
Calcium channel blockers	1959 (73.8)	2033 (76.6)	2221 (83.7)	2329 (87.7)	<0.001
Diuretics	1370 (51.6)	1434 (54.0)	1670 (62.9)	1924 (72.5)	<0.001
Glucose-lowering drugs	75 (2.8)	65 (2.4)	34 (1.3)	21 (0.8)	<0.001
Lipid-lowering drugs	4 (0.15)	3 (0.11)	2 (0.08)	1 (0.04)	0.572
Antiplatelet drugs	20 (0.8)	23 (0.9)	15 (0.6)	22 (0.8)	0.591

*, regular concomitant medication was defined as 180 or more cumulative days of taking the drug of interest.

Table S6 Association between time-averaged on-treatment blood pressure and new-onset hyperuricemia with further adjustment for the use of calcium channel blockers, diuretics, and glucose-lowering drugs during the treatment period

Time-averaged on-treatment blood pressure, mmHg	Events/N (%)	Adjusted model*	
		OR (95% CI)	P value
Time-averaged on-treatment SBP, mmHg			
Per 10 mmHg increment	1,664/10,617 (15.7)	0.95 (0.89–1.01)	0.081
Quartiles			
Q1 (<131.7)	332/2,654 (12.5)	Ref.	
Q2 (131.7 to <138.3)	389/2,654 (14.7)	0.95 (0.80–1.12)	0.528
Q3 (138.3 to <145.6)	446 /2,654 (16.0)	0.94 (0.79–1.12)	0.488
Q4 (\geq 145.6)	497/2,654 (18.7)	0.85 (0.71–1.02)	0.076
P for trend		0.083	
Time-averaged on-treatment DBP, mmHg			
Per 10 mmHg increment	1,664/10,617 (15.7)	1.09 (0.98–1.21)	0.129
Quartiles			
Q1 (<78.5)	394/2,654 (14.8)	Ref.	
Q2 (78.5 to <82.9)	354/2,654 (13.3)	0.89 (0.75–1.06)	0.191
Q3 (82.9 to <87.5)	431/2,654 (16.2)	1.09 (0.91–1.30)	0.367
Q4 (\geq 87.5)	485/2,655 (18.3)	1.17 (0.95–1.43)	0.140
P for trend		0.038	
Medians			
Q1–2 (<82.9)	748/5,308 (14.1)	Ref.	
Q3–4 (\geq 82.9)	916/5,309 (17.3)	1.20 (1.05–1.37)	0.009

*, adjusted for treatment group, age, sex, BMI, UA, fasting glucose, total cholesterol, TG, tHcy, folate, eGFR, smoking and drinking status, use of antihypertensive drugs, and SBP and DBP at baseline, plus use of diuretics, calcium channel blockers, and glucose-lowering drugs during the treatment period.

Table S7 Association between time-averaged on-treatment blood pressure and new-onset hyperuricemia with further adjustment for treatment (enalapril or enalapril-folic acid) compliance during the treatment period

Time-averaged on-treatment blood pressure, mmHg	Events/N (%)	Adjusted Model*	
		OR (95% CI)	P value
Time-averaged on-treatment SBP, mmHg			
Per 10 mmHg increment	1,664/10,617 (15.7)	0.98 (0.92–1.04)	0.478
Quartiles			
Q1 (<131.7)	332/2,654 (12.5)	Ref.	
Q2 (131.7 to <138.3)	389/2,654 (14.7)	1.00 (0.85–1.19)	0.966
Q3 (138.3 to <145.6)	446/2,654 (16.0)	1.03 (0.87–1.22)	0.717
Q4 (\geq 145.6)	497/2,655 (18.7)	0.94 (0.79–1.13)	0.507
P for trend		0.565	
Time-averaged on-treatment DBP, mmHg			
Per 10 mmHg increment	1,664/10,617 (15.7)	1.13 (1.02–1.26)	0.023
Quartiles			
Q1 (<78.5)	394/2,654 (14.8)	Ref.	
Q2 (78.5 to <82.9)	354/2,654 (13.3)	0.91 (0.76–1.08)	0.261
Q3 (82.9 to <87.5)	431/2,654 (16.2)	1.14 (0.95–1.36)	0.155
Q4 (\geq 87.5)	485/2,655 (18.3)	1.25 (1.02–1.53)	0.030
P for trend		0.005	
Medians			
Q1–2 (<82.9)	748/5,308 (14.1)	Ref.	
Q3–4 (\geq 82.9)	916/5,309 (17.3)	1.25 (1.10–1.44)	0.001

*, adjusted for treatment group, age, sex, BMI, UA, fasting glucose, total cholesterol, TG, tHcy, folate, eGFR, smoking and drinking status, use of antihypertensive drugs, and SBP and DBP at baseline, plus treatment (enalapril or enalapril-folic acid) compliance during the treatment period.

Table S8 Association between time-averaged on-treatment blood pressure and new-onset hyperuricemia with further adjustment for change in eGFR during the treatment period

Time-averaged on-treatment blood pressure, mmHg	Events/N (%)	Adjusted model*	
		OR (95% CI)	P value
Time-averaged on-treatment SBP, mmHg			
Per 10 mmHg increment	1,664/10,617 (15.7)	0.99 (0.93–1.05)	0.710
Quartiles			
Q1 (<131.7)	332/2,654 (12.5)	Ref.	
Q2 (131.7 to <138.3)	389/2,654 (14.7)	1.02 (0.85–1.22)	0.818
Q3 (138.3 to <145.6)	446/2,654 (16.0)	1.06 (0.89–1.27)	0.528
Q4 (\geq 145.6)	497/2,655 (18.7)	0.97 (0.80–1.16)	0.713
P for trend		0.775	
Time-averaged on-treatment DBP, mmHg			
Per 10 mmHg increment	1,664/10,617 (15.7)	1.14 (1.02–1.27)	0.021
Quartiles			
Q1 (<78.5)	394/2,654 (14.8)	Ref.	
Q2 (78.5 to <82.9)	354/2,654 (13.3)	0.91 (0.76–1.09)	0.318
Q3 (82.9 to <87.5)	431/2,654 (16.2)	1.16 (0.96–1.40)	0.134
Q4 (\geq 87.5)	485/2,655 (18.3)	1.30 (1.05–1.60)	0.015
P for trend		0.002	
Medians			
Q1–2 (<82.9)	748/5,308 (14.1)	Ref.	
Q3–4 (\geq 82.9)	916/5,309 (17.3)	1.28 (1.11–1.47)	<0.001

*, adjusted for treatment group, age, sex, BMI, UA, fasting glucose, total cholesterol, TG, tHcy, folate, eGFR, smoking and drinking status, use of antihypertensive drugs, and SBP and DBP at baseline, plus change in eGFR (defined as the eGFR at baseline minus that at exit) during the treatment period.

Table S9 Association between time-averaged on-treatment blood pressure and new-onset hyperuricemia with further adjustment for change in BMI during the treatment period

Time-averaged on-treatment blood pressure, mmHg	Events/N (%)	Adjusted model*	
		OR (95% CI)	P value
Time-averaged on-treatment SBP, mmHg			
Per 10 mmHg increment	1,664/10,617 (15.7)	0.97 (0.91–1.03)	0.290
Quartiles			
Q1 (<131.7)	332/2,654 (12.5)	Ref.	
Q2 (131.7 to <138.3)	389/2,654 (14.7)	0.96(0.81–1.14)	0.671
Q3 (138.3 to <145.6)	446/2,654 (16.0)	0.99 (0.84–1.18)	0.945
Q4 (\geq 145.6)	497/2,655 (18.7)	0.89 (0.74–1.07)	0.203
P for trend		0.256	
Time-averaged on-treatment DBP, mmHg			
Per 10 mmHg increment	1,664/10,617 (15.7)	1.09 (0.98–1.21)	0.112
Quartiles			
Q1 (<78.5)	394/2,654 (14.8)	Ref.	
Q2 (78.5 to <82.9)	354/2,654 (13.3)	0.89 (0.75–1.06)	0.208
Q3 (82.9 to <87.5)	431/2,654 (16.2)	1.09 (0.91–1.30)	0.375
Q4 (\geq 87.5)	485/2,655 (18.3)	1.18 (0.96–1.44)	0.114
P for trend		0.030	
Medians			
Q1–2 (<82.9)	748/5,308 (14.1)	Ref.	
Q3–4 (\geq 82.9)	916/5,309 (17.3)	1.20 (1.05–1.38)	0.009

*, adjusted for treatment group, age, sex, BMI, UA, fasting glucose, total cholesterol, TG, tHcy, folate, eGFR, smoking and drinking status, use of antihypertensive drugs, and SBP and DBP at baseline, plus change in BMI (defined as the BMI at baseline minus that at exit) during the treatment period.

Table S10 Association between time-averaged on-treatment blood pressure and new-onset hyperuricemia when UA concentrations <417 $\mu\text{mol/L}$ for male and <357 $\mu\text{mol/L}$ for female at baseline were included the analysis*

Time-averaged on-treatment blood pressure, mmHg	Events/N (%)	Crude model		Adjusted model [†]	
		OR (95% CI)	P value	OR (95% CI)	P value
Time-averaged on-treatment SBP, mmHg					
Per 10 mmHg increment	2,053/11,657 (17.6)	1.18 (1.13–1.23)	<0.001	0.99 (0.94–1.04)	0.614
Quartiles					
Q1 (<131.7)	413/2,914 (14.2)	Ref.		Ref.	
Q2 (131.7 to <138.3)	493/2,914 (16.9)	1.23 (1.07–1.43)	0.004	1.05 (0.90–1.23)	0.536
Q3 (138.3 to <145.6)	551/2,914 (18.9)	1.41 (1.23–1.62)	<0.001	1.06 (0.91–1.24)	0.431
Q4 (\geq 145.6)	596/2,915 (20.4)	1.56 (1.36–1.79)	<0.001	0.96 (0.82–1.13)	0.641
P for trend		<0.001		0.641	
Medians					
Q1–2 (<138.3)	906/5,828 (15.5)	Ref.		Ref.	
Q3–4 (\geq 138.3)	1,147/5,829 (19.7)	1.33 (1.21–1.46)	<0.001	0.93 (0.83–1.04)	0.197
Time-averaged on-treatment DBP, mmHg					
Per 10 mmHg increment	2,053/11,657 (17.6)	1.21 (1.14–1.29)	<0.001	1.12 (1.01–1.23)	0.024
Quartiles					
Q1 (<78.7)	465/2,914 (16.0)	Ref.		Ref.	
Q2 (78.7 to <83.1)	439/2,914 (15.1)	0.93 (0.81–1.08)	0.347	0.94 (0.80–1.10)	0.438
Q3 (83.1 to <87.7)	526/2,914 (18.1)	1.16 (1.01–1.33)	0.034	1.15 (0.97–1.36)	0.096
Q4 (\geq 87.7)	623/2,915 (21.4)	1.43 (1.25–1.64)	<0.001	1.30 (1.08–1.57)	0.005
P for trend		<0.001		<0.001	
Medians					
Q1–2 (<83.1)	904/5,828 (15.5)	Ref.		Ref.	
Q3–4 (\geq 83.1)	1,149/5,829 (19.7)	1.34 (1.22–1.47)	<0.001	1.20 (1.06–1.37)	0.004

*, hyperuricemia defined as a UA concentration \geq 417 $\mu\text{mol/L}$ in men or \geq 357 $\mu\text{mol/L}$ in women at the exit visit. [†], adjusted for treatment group, age, sex, BMI, UA, fasting glucose, total cholesterol, TG, tHcy, folate, eGFR, smoking and drinking status, use of antihypertensive drugs, and SBP and DBP at baseline.

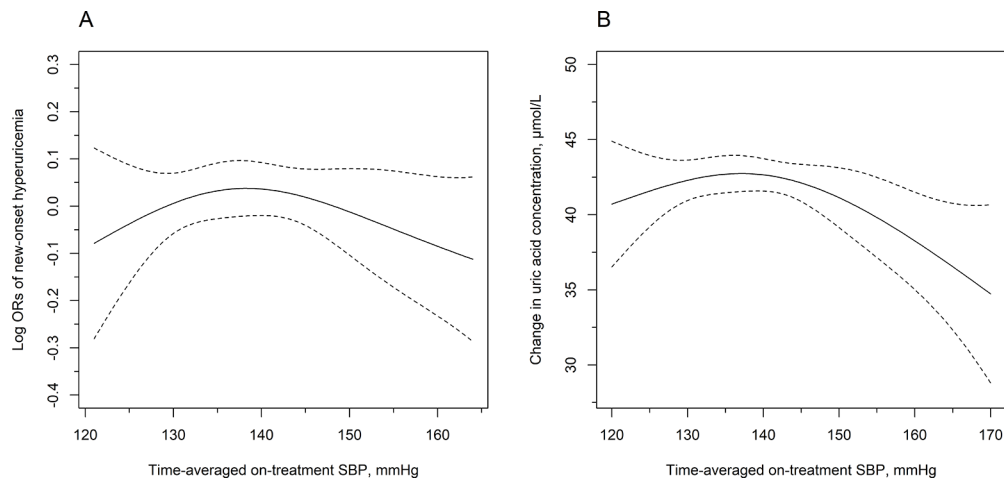


Figure S3 Relation of time-averaged on-treatment SBP with new-onset hyperuricemia (A) and change in uric acid concentrations (B).

Table S11 Association between time-averaged on-treatment systolic blood pressure (clinical categories) and study outcomes

Time-averaged on-treatment (SBP), mmHg	Values	Crude model		Adjusted model*	
		OR/ β (95% CI)	P value	OR/ β (95% CI)	P value
New-onset hyperuricemia, n (%)					
Per 10 mmHg increment	1,664/10,617 (15.7%)	OR 1.19 (1.14–1.25)	<0.001	OR 0.98 (0.93–1.04)	0.528
Categories					
<120	13/182 (7.1%)	Ref.		Ref.	
120 to <130	224/1,853 (12.1%)	OR 1.79 (1.00–3.20)	0.050	OR 1.57 (0.84–2.92)	0.160
130 to <140	593/3,998 (14.8%)	OR 2.26 (1.28–4.01)	0.005	OR 1.65 (0.89–3.05)	0.111
≥ 140	834/4,584 (18.2%)	OR 2.89 (1.64–5.11)	<0.001	OR 1.60 (0.86–2.97)	0.135
P for trend		<0.001		0.584	
Categories					
<120	13/182 (7.1%)	Ref.		Ref.	
≥ 120	1,651/10,435 (15.8%)	OR 2.44 (1.39–4.31)	0.002	OR 1.61 (0.88–2.97)	0.125
Uric acid change[†], $\mu\text{mol/L}$					
Per 10 mmHg increment	41.7 \pm 65.0	β 2.78 (1.64 to 3.92)	<0.001	β -0.94 (-2.19 to 0.31)	0.142
Categories					
<120	29.6 \pm 56.6	Ref.		Ref.	
120 to <130	36.9 \pm 59.3	β 7.28 (-2.60 to 17.15)	0.149	β 4.98 (-4.59 to 14.55)	0.308
130 to <140	40.9 \pm 64.8	β 11.28 (1.64 to 20.92)	0.022	β 6.26 (-3.13 to 15.64)	0.191
≥ 140	45.0 \pm 67.4	β 15.37 (5.76 to 24.98)	0.002	β 4.63 (-4.86 to 14.11)	0.339
P for trend		<0.001		0.975	
Categories					
<120	29.6 \pm 56.6	Ref.		Ref.	
≥ 120	41.9 \pm 65.1	β 12.36 (2.85 to 21.88)	0.011	β 5.48 (-3.80 to 14.76)	0.247

*, adjusted for treatment group, age, sex, BMI, UA, fasting glucose, total cholesterol, TG, tHcy, folate, eGFR, smoking and drinking status, use of antihypertensive drugs, and SBP and DBP at baseline; [†], uric acid change was defined as the uric acid concentrations at the exit visit minus that at baseline.

Table S12 Association between time-averaged blood pressure during the first 12-month treatment period and subsequent new-onset hyperuricemia

Time-averaged blood pressure during the first 12-month treatment period, mmHg	Events/N (%)	Crude model		Adjusted model*	
		OR (95% CI)	P value	OR (95% CI)	P value
Time-averaged SBP during the first 12-month treatment period, mmHg					
Per 10 mmHg increment	1,664/10,614 (15.7)	1.22 (1.17–1.27)	<0.001	1.04 (0.99–1.09)	0.130
Quartiles					
Q1 (<133.7)	306/2,649 (11.6)	Ref.		Ref.	
Q2 (133.7 to <141.7)	386/2,658 (14.5)	1.30 (1.11–1.53)	0.001	1.04 (0.88–1.24)	0.633
Q3 (141.7 to <150.8)	429/2,647 (16.2)	1.48 (1.26–1.73)	<0.001	1.08 (0.91–1.29)	0.380
Q4 (≥150.8)	543/2,660 (20.4)	1.96 (1.69, 2.29)	<0.001	1.13 (0.94–1.35)	0.199
P for trend		<0.001		0.181	
Time-averaged DBP during the first 12-month treatment period, mmHg					
Per 10 mmHg increment	1,664/10,614 (15.7)	1.22 (1.15–1.30)	<0.001	1.16 (1.06–1.27)	0.002
Quartiles					
Q1 (<79.6)	352/2,654 (13.3)	Ref.		Ref.	
Q2 (79.6 to <84.5)	400/2638 (15.2)	1.17 (1.00–1.36)	0.048	1.13 (0.95–1.34)	0.170
Q3 (84.5 to <89.7)	426/2667 (16.0)	1.24 (1.07–1.45)	0.005	1.17 (0.97–1.40)	0.094
Q4 (≥89.7)	486/2,655 (18.3)	1.47 (1.26–1.70)	<0.001	1.27 (1.04–1.55)	0.020
P for trend		<0.001		0.024	

*, adjusted for treatment group, age, sex, BMI, UA, fasting glucose, total cholesterol, TG, tHcy, folate, eGFR, smoking and drinking status, use of antihypertensive drugs, and SBP and DBP at baseline.

Table S13 Association between time-averaged blood pressure during the first 24-month treatment period and subsequent new-onset hyperuricemia

Time-averaged blood pressure during the first 24-month treatment period, mmHg	Events/N (%)	Crude Model		Adjusted Model*	
		OR (95% CI)	P value	OR (95% CI)	P value
Time-averaged SBP during the first 24-month treatment period, mmHg					
Per 10 mmHg increment	1,664/10,614 (15.7)	1.22 (1.17–1.27)	<0.001	1.02 (0.96–1.07)	0.522
Quartiles					
Q1 (<132.8)	310/2,653 (11.7)	Ref.		Ref.	
Q2 (132.8 to <140.0)	381/2,652 (14.4)	1.28 (1.09–1.50)	0.003	1.04 (0.87–1.24)	0.667
Q3 (140.0 to <148.2)	441/2,665 (16.5)	1.50 (1.28–1.75)	<0.001	1.10 (0.93–1.31)	0.269
Q4 (≥148.2)	532/2,657 (20.0)	1.89 (1.63–2.20)	<0.001	1.09 (0.91–1.30)	0.370
P for trend		<0.001		0.306	
Time-averaged DBP during the first 24-month treatment period, mmHg					
Per 10 mmHg increment	1,664/10,614 (15.7)	1.21 (1.13–1.29)	<0.001	1.16 (1.05–1.28)	0.003
Quartiles					
Q1 (<79.0)	373/2,647 (14.1)	Ref.		Ref.	
Q2 (79.0 to <83.8)	356/2,653 (13.4)	0.94 (0.81–1.10)	0.477	0.97 (0.82–1.16)	0.747
Q3 (83.8 to <88.6)	447/2,656 (16.8)	1.23 (1.06–1.43)	0.006	1.26 (1.05–1.51)	0.012
Q4 (≥88.6)	488/2,658 (18.4)	1.37 (1.18–1.59)	<0.001	1.29 (1.05–1.58)	0.013
P for trend		<0.001		0.001	

*, adjusted for treatment group, age, sex, BMI, UA, fasting glucose, total cholesterol, TG, tHcy, folate, eGFR, smoking and drinking status, use of antihypertensive drugs, and SBP and DBP at baseline.

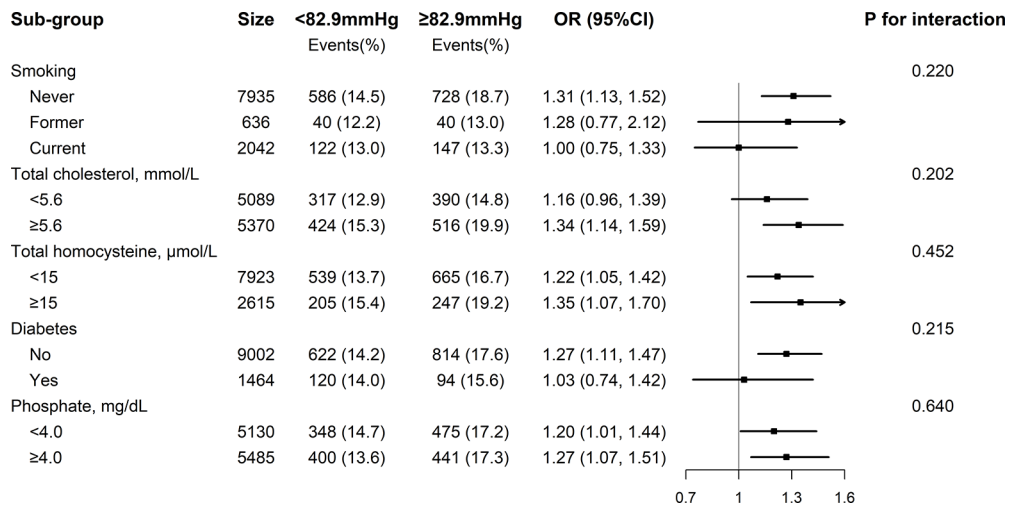


Figure S4 Stratified analyses of the association between time-averaged on-treatment DBP (median, <82.9 vs. ≥82.9 mmHg) and new-onset hyperuricemia.

Table S14 Post-matched participant characteristics according to propensity scores*

Characteristics	Time-averaged on-treatment SBP, mmHg			Time-averaged on-treatment DBP, mmHg		
	SBP <138.3 (n=3,335)	SBP ≥138.3 (n=3,335)	Standardized difference, %	DBP <82.9 (n=2,673)	DBP ≥82.9 (n=2,673)	Standardized difference, %
Baseline						
Age, years	59.6±7.4	59.4±7.3	2.2	59.3±6.9	59.3±7.0	0.9
Male, n (%)	2,268 (68.0)	2,270 (68.1)	0.1	1,853 (69.3)	1,842 (68.9)	0.8
BMI, kg/m ²	25.5±3.6	25.6±3.5	1.5	25.6±3.4	25.6±3.5	1.0
Current smoking	660 (19.8)	646 (19.4)	1.7	485 (18.1)	492 (18.4)	1.7
Current alcohol drinking	642 (19.3)	640 (19.2)	1.2	478 (17.9)	508 (19.0)	2.8
Self-reported hyperlipidemia	1,659 (49.7)	1,682 (50.4)	1.4	1,329 (49.7)	1,342 (50.2)	0.1
Self-reported diabetes	88 (2.6)	85 (2.5)	0.6	71 (2.7)	77 (2.9)	0.6
Enalapril only treatment, n (%)	135 (4.0)	134 (4.0)	0.2	89 (3.3)	85 (3.2)	0.4
<i>MTHFR</i> C677T genotypes, n (%)			0.9			0.3
CC	780 (23.4)	784 (23.5)		621 (23.2)	618 (23.1)	
CT	1,649 (49.4)	1,659 (49.7)		1,356 (50.7)	1,376 (51.5)	
TT	906 (27.2)	892 (26.7)		696 (26.0)	679 (25.4)	
SBP	167.8±16.6	167.3±17.1	3.4	168.1±19.8	168.3±21.1	0.1
DBP	94.8±11.6	94.8±11.1	0.1	94.8±8.6	95.2±8.7	4.9
Total cholesterol, mmol/L	5.7±1.2	5.7±1.1	0.4	5.7±1.2	5.7±1.2	0.8
Triglycerides, mmol/L	1.7±1.9	1.7±0.9	0.7	1.7±0.9	1.7±2.0	0.4
Folate, ng/mL	7.7±3.1	7.7±3.4	0.7	7.8±3.4	7.8±3.2	0.4
Fasting glucose, mmol/L	6.09±1.8	6.1±1.9	0.6	6.0±1.6	6.0±1.8	1.2
Total homocysteine, μmol/L	14.1±8.2	14.2±8.9	0.6	13.9±7.9	14.1±8.8	2.4
eGFR, mL/min/1.73m ²	95.0±12.1	95.1±11.5	0.6	95.3±11.6	95.4±11.6	1.2
Uric acid, μmol/L	264.3±52.3	265.9±51.6	2.6	264.7±51.8	265.0±52.0	2.0
Phosphate, mg/dL	4.1±0.8	4.1±0.7	0.9	4.1±0.7	4.1±0.8	1.1
Concomitant medication usage during the treatment period						
Calcium channel blockers	2,862 (85.8)	2,846 (85.3)	1.4	2,124 (79.5)	2,141 (80.1)	1.1
Diuretics	2,110 (63.3)	2,073 (62.2)	2.3	1,574 (58.9)	1,568 (58.7)	0.6
Glucose-lowering drugs	66 (2.0)	60 (1.8)	1.3	41 (1.5)	40 (1.5)	0.9
Lipid-lowering drugs	4 (0.1)	3 (0.1)	0.9	2 (0.1)	3 (0.1)	1.2
Antiplatelet drugs	25 (0.7)	23 (0.7)	0.7	17 (0.6)	25 (0.9)	2.5

*, variables are presented as mean ± SD or n (%). BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; *MTHFR*, 5, 10-methylenetetrahydrofolate reductase; SBP, systolic blood pressure.

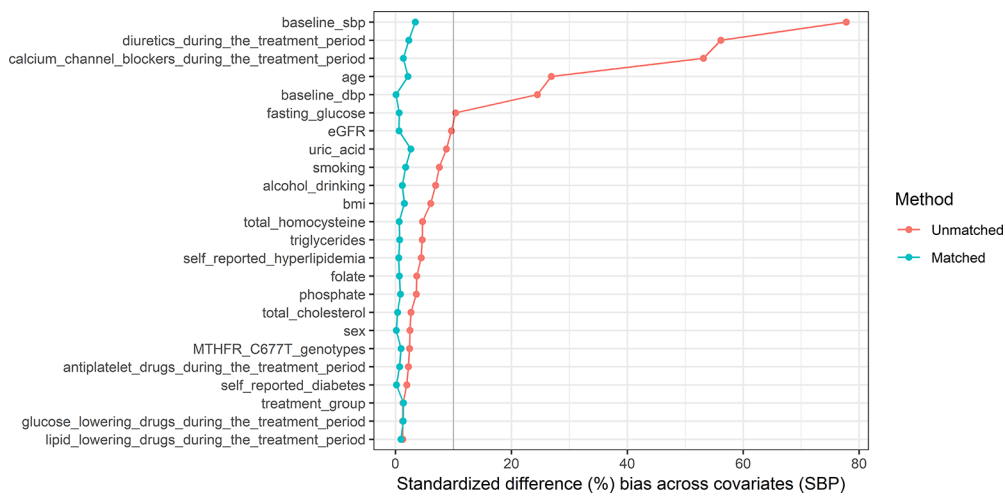


Figure S5 Standardized differences of participant characteristics before and after matched according to propensity scores by the median of time-averaged on-treatment SBP.

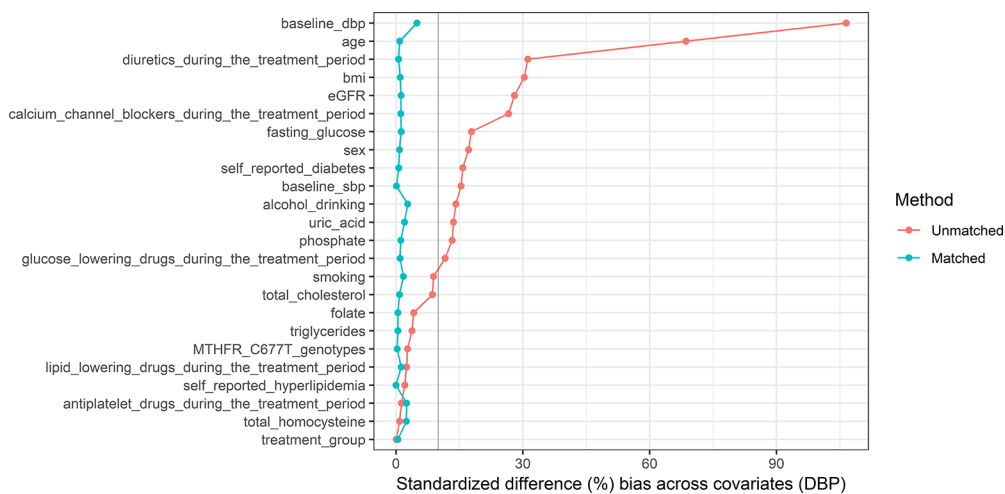


Figure S6 Standardized differences of participant characteristics before and after matched according to propensity scores by the median of time-averaged on-treatment DBP.

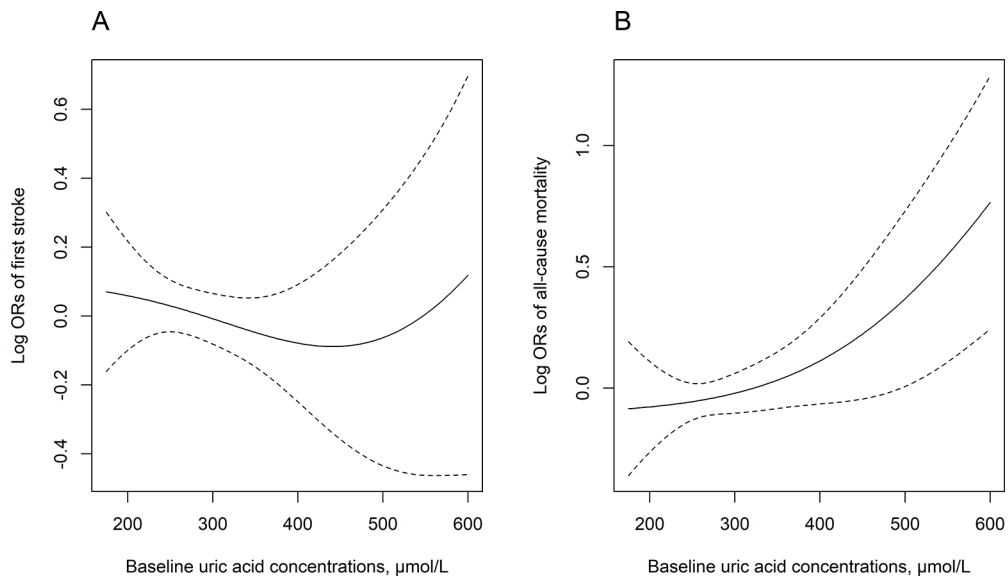


Figure S7 Relation of uric acid concentrations with stroke (A) and all-cause mortality (B).