

## Supplementary Material

Supplementary Table 1. Baseline patient's characteristics by sex-specific uric acid tertiles

Characteristic	Uric acid level in tertiles (mg/dL)			P-value
	≤5.0 for women & ≤6.0 men	5.1-6.4 for women & 6.1-7.6 for men	>6.4 for women & >7.6 for men	
N.	1262	1201	1371	
Age, years	66.0 (57.0, 73.0)	66.0 (56.0, 73.0)	66.0 (56.0, 73.0)	0.56
Female	378 (30.0%)	330 (27.5%)	435 (31.7%)	0.062
White race	754 (59.7%)	745 (62.0%)	822 (60.0%)	0.44
Atrial fibrillation	327 (25.9%)	314 (26.1%)	429 (31.3%)	0.002
Ischemic heart disease	852 (67.5%)	764 (63.6%)	840 (61.3%)	0.004
Hypertension	783 (62.0%)	710 (59.1%)	799 (58.3%)	0.12
Diabetes mellitus	370 (29.3%)	357 (29.7%)	472 (34.4%)	0.007
Myocardial infarction	117 (9.3%)	132 (11.0%)	100 (7.3%)	0.005
Stroke	98 (7.8%)	99 (8.2%)	110 (8.0%)	0.91
NYHA III/IV	334 (26.5%)	351 (29.2%)	489 (35.7%)	<0.001
LVEF, %	34 (29, 37)	34 (28, 37)	31 (25, 36)	<0.001
SBP, mmHg	128 (114, 140)	127.5 (114, 140)	120.0 (110, 135)	<0.001
Heart rate, bpm	72 (64, 80)	72 (64, 80)	72 (65, 82)	0.001
BMI, Kg/m <sup>2</sup>	26.6 (23.9, 29.8)	27.1 (24.3, 30.4)	27.3 (24.4, 31.1)	<0.001
eGFR, ml/min/1.73m <sup>2</sup>	74.8 (61.9, 90.6)	68.7 (56.9, 82.1)	58.0 (46.6, 71.0)	<0.001
eGFR ≤60 ml/min/1.73m <sup>2</sup>	280 (22.2%)	379 (31.6%)	729 (53.8%)	<0.001
Potassium, mmol/L	4.4 (4.2, 4.7)	4.5 (4.2, 4.8)	4.5 (4.1, 4.8)	0.52
Sodium, mmol/L	140 (138, 142)	140 (138, 142)	140 (138, 142)	0.085
Hemoglobin, g/dL	13.9 (12.9, 14.8)	14.1 (13.0, 15.1)	13.9 (12.7, 14.9)	0.001
Uric acid, mg/dL	4.8 (4.3, 5.5)	6.5 (6.1, 7.1)	8.5 (7.9, 9.7)	<0.001
Beta blocker	862 (68.3%)	896 (74.6%)	1000 (72.9%)	0.001
MRA	395 (31.3%)	445 (37.1%)	664 (48.4%)	<0.001
Diuretics	916 (72.6%)	973 (81.0%)	1251 (91.2%)	<0.001
Statin	501 (39.7%)	501 (41.7%)	509 (37.1%)	0.058

Legend: NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist.

Supplementary Table 2. Outcome associations by sex-specific tertiles of uric acid at baseline

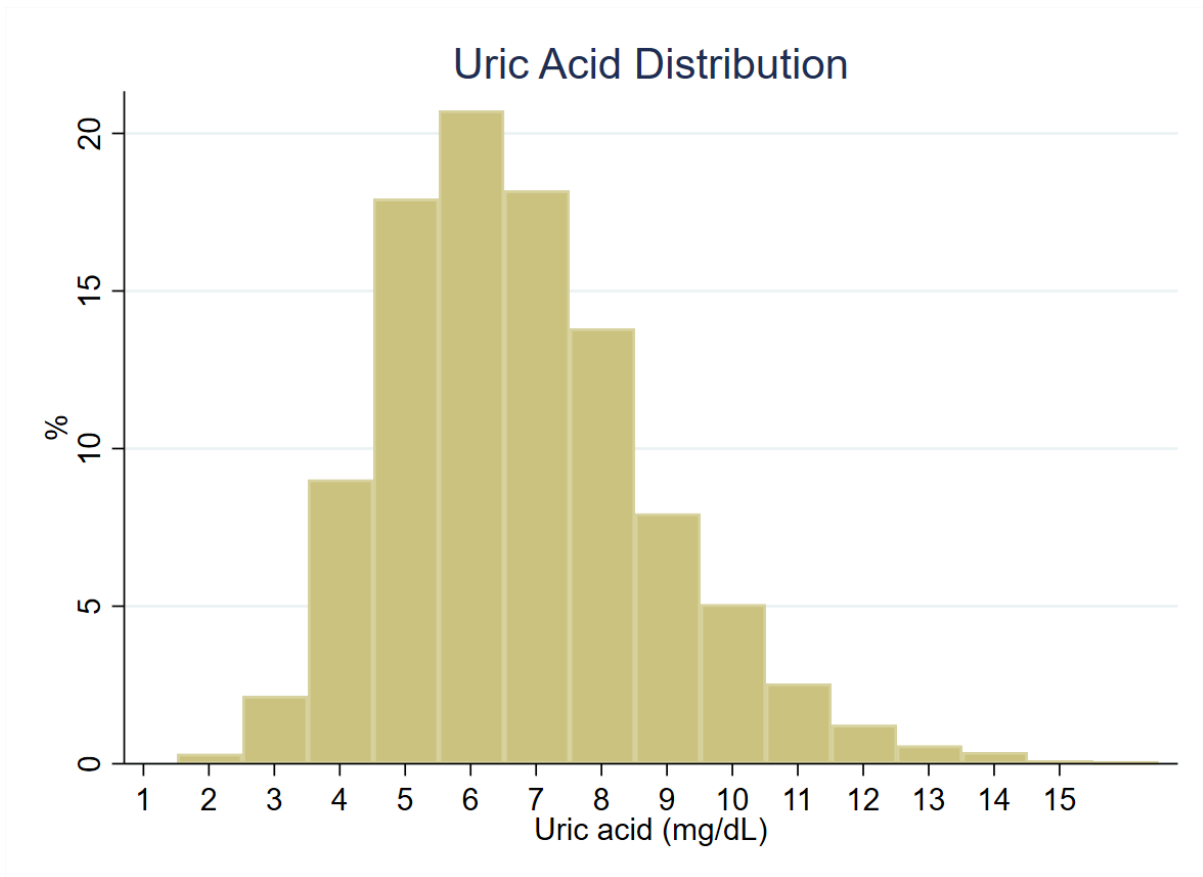
Outcome/UA tertile (mg/dL)	n/N events (%)	Adj. HR (95%CI)	P-value
<b>Cardiovascular death or HF hospitalization</b>			
≤5.0 for women & ≤6.0 men	357/1262 (28.3)	Referent	-
5.1-6.4 for women & 6.1-7.6 for men	432/1201 (36.0)	1.31 (1.12-1.53)	0.001
>6.4 for women & >7.6 for men	680/1371 (49.6)	1.65 (1.42-1.92)	<0.001
<b>Cardiovascular death</b>			
≤5.0 for women & ≤6.0 men	227/1262 (18.0)	Referent	-
5.1-6.4 for women & 6.1-7.6 for men	266/1201 (22.2)	1.32 (1.08-1.60)	0.006
>6.4 for women & >7.6 for men	433/1371 (31.6)	1.58 (1.30-1.92)	<0.001
<b>All-cause death or all-cause hospitalization</b>			
≤5.0 for women & ≤6.0 men	453/1262 (35.9)	Referent	-
5.1-6.4 for women & 6.1-7.6 for men	508/1201 (42.3)	1.19 (1.04-1.37)	0.013
>6.4 for women & >7.6 for men	756/1371 (55.1)	1.46 (1.27-1.68)	<0.001
<b>All-cause death</b>			
≤5.0 for women & ≤6.0 men	354/1262 (28.1)	Referent	-
5.1-6.4 for women & 6.1-7.6 for men	369/1201 (30.7)	1.10 (0.94-1.29)	0.24
>6.4 for women & >7.6 for men	577/1371 (42.1)	1.35 (1.15-1.57)	<0.001

Legend: UA, uric acid; HF, heart failure.

Adj., models adjusted on age, race, atrial fibrillation, ischemic HF etiology, hypertension, diabetes, myocardial infarction, NYHA class, ejection fraction, systolic blood pressure, heart rate, body mass index, estimated glomerular filtration rate, sodium, hemoglobin, beta blocker use, MRA use, diuretic use, and randomized losartan dose.

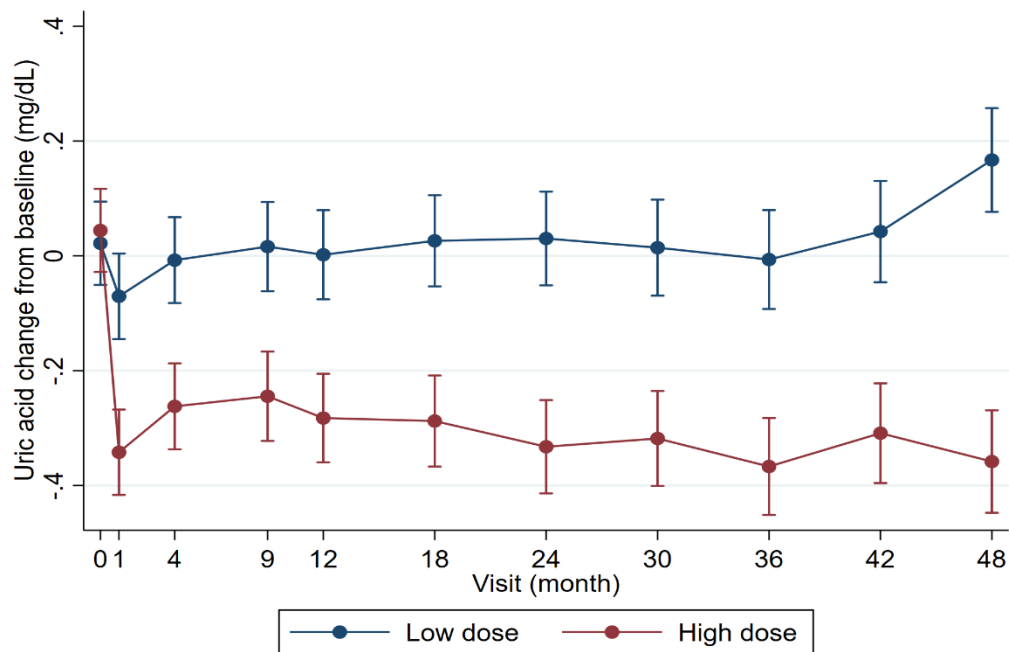
No significant interactions were found between randomized treatment (high vs. low losartan dose) and baseline uric acid levels: cardiovascular death or HF hospitalization interaction P =0.69; cardiovascular death interaction P =0.50; all-cause death or all-cause hospitalization interaction P =0.55, all-cause death interaction P =0.40.

Supplementary Figure 1. Distribution of uric acid levels at baseline

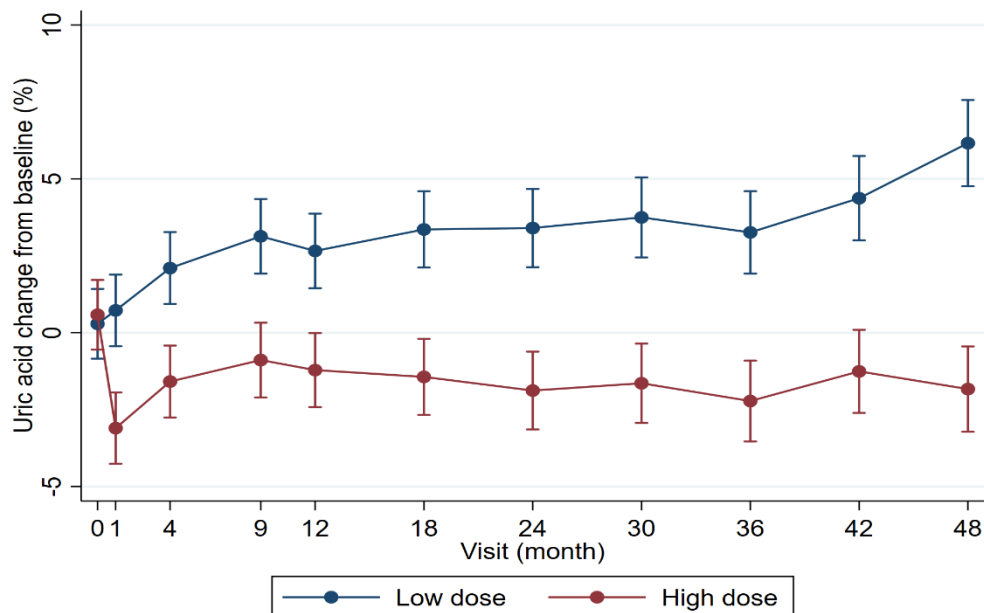


Supplementary Figure 2. Effect of high vs. low losartan dose on the change (both absolute and relative) of uric acid levels over time

A) Absolute uric acid change

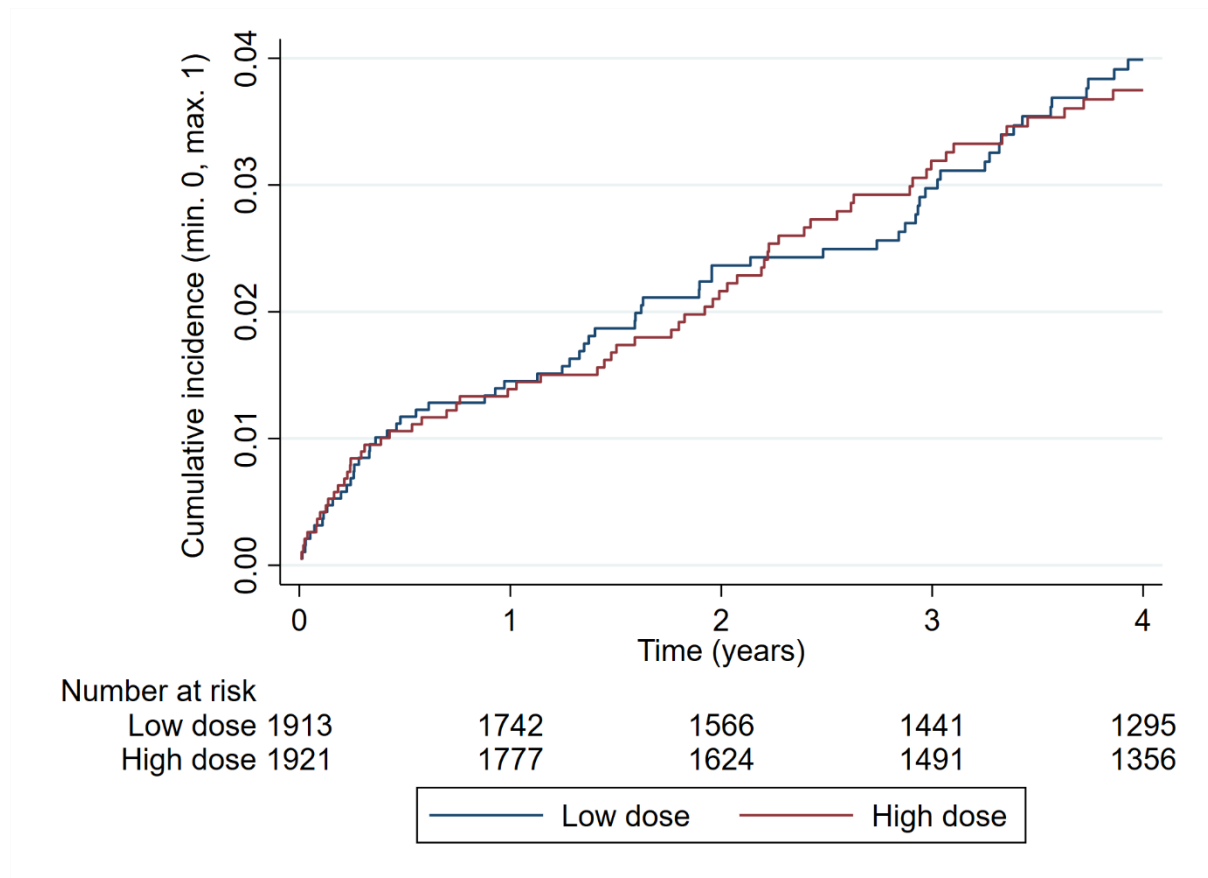


B) Relative uric acid change



Caption: Compared to low dose, high dose losartan reduced uric acid levels by -0.27 (-0.34 to -0.21) mg/dL on average which was equivalent to a -4% (-5% to -3%) relative change,  $P < 0.001$ .

Supplementary Figure 3. Incidence of gout throughout the follow-up by treatment group



Caption: No significant differences were observed on the incidence of gout between treatment groups: Low dose losartan n/N events (%) 74/146 (3.9); high dose losartan n/N events (%) 72/146 (3.8); HR 0.95, 95%CI 0.69-1.31, P =0.76. Only 19 nephrolithiasis episodes were recorded: Low dose losartan n/N events (%) 7/19 (0.4); high dose losartan n/N events (%) 12/19 (0.6), P =0.26.