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## High versus low dose losartan and uric acid: an analysis from HEAAL

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## **Abstract**

*Background:* Serum uric acid (SUA) is activated in catabolic, hypoxic, and inflammatory conditions characteristic of heart failure (HF) and is a source of reactive oxygen species. Losartan is unique among other angiotensin receptor blockers in reducing SUA.

*Objectives:* To study the patient characteristics and outcome associations by SUA levels, as well as the effect of high vs. low dose losartan on SUA levels in HF.

*Methods:* HEAAL was a double-blind trial, comparing the effect of two doses of losartan 150 (high dose) vs. 50 (low dose) mg/day among 3834 patients with symptomatic heart failure, a LVEF $\leq$ 40%, and known intolerance to angiotensin converting enzyme inhibitors. In the present study we studied the associations of SUA with outcomes and the effect of high vs. low dose losartan on SUA levels, incident hyperuricemia and gout.

*Results:* Patients with higher SUA had more comorbidities, worse renal function, were more symptomatic, used diuretics more frequently, and were 1.5 to 2-fold more likely to experience HF hospitalizations and cardiovascular death. The benefit of high dose losartan to improve HF outcomes was not influenced by baseline SUA levels (interaction  $P>0.1$ ). Compared with low dose, high dose losartan reduced SUA by -0.27 (-0.34 to -0.21) mg/dL,  $P<0.001$ . The incidence of hyperuricemia was reduced with high dose losartan, but the incidence of gout was not.

*Conclusions:* In HEAAL, hyperuricemia was associated with worse outcomes. High dose losartan reduced SUA and hyperuricemia more than low dose and the cardiovascular benefits of high dose losartan were not modified by SUA levels.

*Key-words:* uric acid; hyperuricemia; losartan dose.

**Abbreviations**

SUA, serum uric acid

HF, heart failure

CKD, chronic kidney disease

ARB, angiotensin receptor blocker

## **Introduction**

Serum uric acid (SUA) is generated by the enzyme xanthine oxidase that is activated in catabolic, hypoxic, or inflammatory conditions characteristic of heart failure (HF) and is a source of reactive oxygen species.<sup>1-3</sup> Comorbidities and medications such as chronic kidney disease (CKD) and diuretics are common in HF and may contribute to elevated SUA levels. Elevated SUA has been associated with higher risk of hospitalization and mortality, but causality has not been established.<sup>4,5</sup>

Controlled trials targeting the reduction of SUA either by inhibition of the synthesizing enzyme xanthine oxidase or by uricosuric therapy failed to improve outcomes in HF.<sup>6-8</sup> However, some therapies that improve HF outcomes also reduce SUA levels. For example, sacubitril/valsartan is thought to lower SUA via uricosuric effects combined with urate synthesis inhibition.<sup>9</sup> Sodium-glucose cotransporter 2 inhibitors (SGLT2i) markedly reduce SUA levels through a uricosuric effect, reduced oxidative stress and promotion of cellular autophagy.<sup>10-12</sup>

Losartan has been shown to reduce SUA more than other angiotensin receptor blockers (ARBs), without dose-response relationship in patients with hypertension.<sup>13,14</sup> Losartan is thought to exert an uricosuric effect through the inhibition of the renal organic anion transporter URAT1 (SLC22A12).<sup>15,16</sup>

In the present work we aim to study the patient characteristics and outcome associations by SUA levels, as well as the effect of high vs. low dose losartan on SUA levels in HF.

## **Methods**

## Study design and population

HEAAL was an international, multicentre, double-blind, event-driven trial, comparing the effect of two doses of losartan: 150 (high dose) vs. 50 (low dose) mg/day, among 3834 patients with symptomatic heart failure, a LVEF of 40% or less, stable cardiovascular medical therapy for at least 2 weeks, and known intolerance to angiotensin converting enzyme inhibitor (ACEi) defined as discontinuation of ACEi treatment because of one or more of the following adverse effects: cough, symptomatic hypotension, azotaemia, hyperkalemia, taste disturbance, gastrointestinal upset, or rash. Patients assigned to the high dose group received a mean of  $129 \pm 39$  mg of losartan daily and the patients assigned to the low dose group received a mean of  $46 \pm 11$  mg/daily. The median follow-up time was 4.7 (pct<sub>25-75</sub>, 3.5-5.5) years. Compared to low dose, high dose losartan reduced the composite of HF hospitalization or cardiovascular death: HR 0.87, 95%CI 0.79-0.97, P =0.009.<sup>17</sup>

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the ethics committee or institutional review board of every site. All patients provided written informed consent before randomization. HEAAL is registered with ClinicalTrials.gov, number NCT00090259.

SUA was measured at months 1, 4, 9, and 12 and at every 6-month visit thereafter.

In the present analysis, we studied the associations of SUA with the outcomes of cardiovascular death or HF hospitalization, cardiovascular death, all-cause death or all-cause hospitalization, and all-cause death. The cause of death and the primary cause of admission were determined by an Endpoint Classification Committee, whose members were masked to treatment assignment. Adverse events were

reported while patients were taking treatment and for 14 days after the end of treatment. Events were coded with the Medical Dictionary for Regulatory Activities (version 12).

### **Statistical analysis**

The baseline characteristics were compared between the baseline SUA tertiles, using ANOVA or Kruskal-Wallis tests, as appropriate. Continuous variables are expressed as median (percentile<sub>25-75</sub>) and categorical variables are presented as absolute numbers and percentages. The association between SUA and the study outcomes was studied across SUA tertiles with Cox models adjusted for age, sex, race, atrial fibrillation, ischemic HF etiology, hypertension, diabetes mellitus, prior myocardial infarction, NYHA class, left ventricular ejection fraction (LVEF), systolic blood pressure (SBP), heart rate, body mass index, estimated glomerular filtration rate (eGFR), sodium, hemoglobin, beta-blocker, mineralocorticoid receptor antagonists (MRA), and loop diuretic use, and randomized losartan dose. The effect of high vs. low dose losartan across the baseline SUA levels was assessed with a treatment-by-SUA interaction term in the Cox model. The effect of high vs. low dose losartan on SUA levels throughout the follow-up was studied using mixed effects models including baseline SUA levels and treatment-by-time interaction terms as dependent variables, and random intercept at the patient level. The effect of high vs. low dose losartan on incident gout was studied by means of a Cox model with treatment as independent variable and first occurrence of gout (i.e., first occurrence in a study visit recorded as free text) as outcome variable, in the subset of patients without gout at baseline. Landmark analysis at 1 month were used to study the associated between change in SUA levels (i.e., decrease vs. increase from baseline) and outcomes. A P-value <0.05 was accepted as the threshold for statistical



significance without correction for multiplicity of tests given the exploratory nature of this work. Statistical analyses were conducted in Stata® version 17 (StataCorp LP).

## Results

### Patient's baseline characteristics by uric acid levels

A total of 3816 (99.5% of HEAAL population) patients with available baseline SUA levels were included in the analysis. The baseline SUA tertiles were: tertile 1  $\leq 5.70$  mg/dL (n =1265), tertile 2  $\geq 5.70$  to  $\leq 7.30$  mg/dL (n =1212), tertile 3  $> 7.30$  mg/dL (n =1339). Compared to patients with lower SUA levels (tertile 1), those with higher SUA (tertile 3) were more frequently men, had more frequent atrial fibrillation and diabetes mellitus, were more symptomatic, had lower LVEF, SBP, and eGFR, and were more frequently treated with beta blockers, MRAs, and diuretics. *Table 1.*

Circulating SUA levels had a normal distribution. *Supplementary Figure 1.* Patient's baseline characteristics by sex-specific SUA tertiles are presented in the *Supplementary Table 1.*

### Outcome associations by uric acid levels

Compared to patients with lower SUA levels (tertile 1), those with higher SUA (tertile 3) were more likely to experience the composite outcome of cardiovascular death or HF hospitalization: adjusted HR 1.53, 95%CI 1.33-1.77, cardiovascular death: adjusted HR 1.95, 95%CI 1.66-2.29, composite of all-cause death or all-cause hospitalization: adjusted HR 1.42, 95%CI 1.19-1.70, and all-cause death: adjusted HR 1.24, 95%CI 1.11-1.38. The association between SUA levels and the composite outcome of cardiovascular death or HF hospitalization was not modified by sex (interaction P =0.21). The benefit of high dose losartan to reduce the composite of cardiovascular death or HF hospitalization was not influenced by baseline SUA

levels (interaction  $P = 0.82$ ). *Table 2 & Figure 1*. Outcome associations of sex-specific SUA tertiles are presented in the *Supplementary Table 2*, with similar results to those above described and presented in *Table 2*.

A decrease in SUA levels (compared to an increase) at 1 month was not associated with better outcomes: cardiovascular death or HF hospitalization HR 1.02, 95%CI 0.91-1.14,  $P = 0.74$ .

### **Effect of high dose losartan on uric acid levels and gout episodes**

Compared with low dose, high dose losartan reduced SUA levels by  $-0.27$  ( $-0.34$  to  $-0.21$ ) mg/dL on average ( $P < 0.001$ ), a reduction that was observed early after 1 month of follow-up and corresponded to a  $-4\%$  ( $-5\%$  to  $-3\%$ ) average relative change. *Figure 2 & Supplementary Figure 2*. The SUA reduction was more pronounced in patients with hyperuricemia (SUA  $> 7$  mg/dL) at baseline:  $-0.37$  ( $-0.49$  to  $-0.26$ ) mg/dL, than in patients without hyperuricemia (SUA  $\leq 7$  mg/dL) at baseline:  $-0.20$  ( $-0.29$  to  $-0.12$ ) mg/dL, interaction  $P = 0.011$ . The incidence of hyperuricemia (SUA levels  $> 7$  mg/dL) were also reduced with high dose losartan throughout the follow-up. *Figure 3*.

During the follow-up 146 events of gout were reported without differences between low and high dose losartan groups: HR 0.95, 95%CI 0.69-1.31,  $P = 0.76$ . Only 19 nephrolithiasis episodes were recorded without between group differences ( $P = 0.26$ ). *Supplementary Figure 3*.

## **Discussion**

This study shows that higher SUA levels were associated worse HF symptoms, poorer renal function and more frequent use of diuretics, and with a higher risk of

hospitalizations and mortality. High dose losartan reduced SUA levels and hyperuricemia more than low dose but did not reduce incident gout episodes. The benefit of high dose losartan to reduce the composite of HF hospitalization or cardiovascular death was not modified by baseline SUA levels.

Higher SUA levels in HF may reflect advanced stages of the disease, along with renal impairment and higher need of diuretics to mitigate congestion. Thus, hyperuricemia may be a marker of increased oxidative stress, inflammation, endothelial dysfunction and catabolic processes, all of which portend worse prognosis in HF.<sup>18</sup> Compared to low dose, high dose losartan reduced SUA levels by -0.3 mg/dL (-4%) on average, a reduction that was even more pronounced among patients with hyperuricemia at baseline. Importantly, the incidence of hyperuricemia throughout the follow-up was reduced significantly with high dose losartan. Previous studies in hypertension suggested that the effect of losartan to reduce SUA was not dose dependent, but treatment adherence issues might have occurred in the high dose group.<sup>13</sup> The present study shows that higher losartan doses produce greater SUA reductions than lower doses which are clinically important findings because high-dose losartan may be used to lower SUA levels beyond the proven clinical benefits of this drug.<sup>17</sup> Furthermore, the benefits of high dose losartan on morbidity and mortality were not modified by baseline SUA levels, supporting the up-titration of losartan to the maximum tolerated dose or 150 mg/day regardless of SUA levels.

Despite the hyperuricemia reductions, high dose losartan did not reduce incident gout. With only 146 events recorded (corresponding to a 4% cumulative incidence at 4 years), this study might have been underpowered to study the effect of high vs. low dose losartan on gout, because low dose losartan might have already mitigated the occurrence of gout. Still, despite the uricosuric mechanisms of losartan, high dose

was not associated with an increased risk of nephrolithiasis, with only 19 events recorded throughout the follow-up.<sup>15,16</sup>

Xanthine oxidase inhibitors such as allopurinol seem more effective than losartan in lowering SUA levels.<sup>7,19</sup>

The rapid effect of high dose losartan to reduce SUA (observed as early as 1 month i.e., the first post-randomization visit) may be of interest in the setting of concomitant use of other HF medications, SGLT2i in particular. This drug class, produces a rapid and pronounced SUA decrease (around -1 mg/dL on average).<sup>10-12</sup> Therefore, the combination of high dose losartan and a SGLT2i may be useful to reduce SUA levels in HF patients, and such combination may be worth investigating in future studies.

### **Limitations**

Some limitations should be acknowledged in our study. First, this is a post-hoc analysis of a randomized controlled trial which is affected by the biases inherent to observational studies, particularly the impossibility to infer causality. Second, post-randomization medications including the use of SUA-lowering and anti-gout medications were not registered in the dataset, and we could not assess medication changes after randomization. Third, diuretic doses or diuretic initiation throughout the follow-up was not available in the dataset; thus, we could not ascertain if diuretic use (or diuretic doses) throughout the follow-up could be associated with incident hyperuricemia and gout.

### **Conclusions**

In HEAAL, hyperuricemia was associated with worse outcomes. High dose losartan reduced SUA and hyperuricemia more than low dose, and the benefits of high dose losartan were not modified by baseline SUA levels.

**Funding**

None.

**Conflicts of interest**

The authors report not having relevant conflicts of interest regarding the content of this study.

**Ethics approval and consent to participate**

The study was approved by all relevant ethics committees and regulatory bodies. All participants provided written informed consent prior to study specific procedures.

**Consent for publication**

There is no data of individual persons included in the manuscript.

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Table 1. Baseline patient's characteristics by uric acid tertiles

Characteristic	Uric acid level in tertiles (mg/dL)			P-value
	≤5.70	5.71-7.30	>7.30	
N.	1265	1212	1339	-
Age, years	66 (58, 73)	65 (56, 73)	65 (56, 72)	0.010
Female	558 (44.1%)	315 (26.0%)	264 (19.7%)	<0.001
White race	742 (58.7%)	774 (63.9%)	793 (59.2%)	0.015
Atrial fibrillation	310 (24.5%)	356 (29.4%)	397 (29.6%)	0.005
Ischemic heart disease	829 (65.5%)	767 (63.3%)	845 (63.1%)	0.36
Hypertension	788 (62.3%)	727 (60.0%)	768 (57.4%)	0.037
Diabetes mellitus	384 (30.4%)	339 (28.0%)	472 (35.3%)	<0.001
Myocardial infarction	106 (8.4%)	144 (11.9%)	98 (7.3%)	<0.001
Stroke	94 (7.4%)	106 (8.7%)	106 (7.9%)	0.48
NYHA III/IV	347 (27.4%)	360 (29.7%)	460 (34.4%)	<0.001
LVEF, %	34 (29, 38)	33 (27, 37)	31 (25, 36)	<0.001
SBP, mmHg	130 (115, 140)	125 (112, 140)	120 (110, 135)	<0.001
Heart rate, bpm	72 (64, 80)	72 (64, 80)	72 (65, 82)	0.008
BMI, Kg/m <sup>2</sup>	27 (24, 30)	27 (24, 30)	27 (25, 31)	<0.001
eGFR, ml/min/1.73m <sup>2</sup>	73 (60, 89)	69 (57, 84)	59 (47, 72)	<0.001
eGFR ≤60 ml/min/1.73m <sup>2</sup>	318 (25.1%)	363 (30.0%)	707 (52.8%)	<0.001
Potassium, mmol/L	4.4 (4.2, 4.7)	4.5 (4.2, 4.8)	4.4 (4.1, 4.8)	0.61
Sodium, mmol/L	140 (138, 142)	140 (138, 142)	140 (138, 142)	0.25
Hemoglobin, g/dL	13.7 (12.7, 14.7)	14.2 (13.0, 15.1)	14.0 (12.9, 15.0)	<0.001
Uric acid, mg/dL	4.9 (4.3, 5.3)	6.5 (6.1, 6.9)	8.6 (7.9, 9.7)	<0.001
Beta blocker	855 (67.6%)	889 (73.3%)	1001 (74.8%)	<0.001
MRA	404 (31.9%)	452 (37.3%)	641 (47.9%)	<0.001
Diuretics	937 (74.1%)	972 (80.2%)	1215 (90.7%)	<0.001
Statin	489 (38.7%)	501 (41.3%)	514 (38.4%)	0.25

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.

Table 2. Outcome associations by 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>			
≤5.70	368/1265 (29.1)	Referent	-
5.71-7.30	418/1212 (34.5)	1.11 (0.96-1.28)	0.15
>7.30	673 /1339 (50.3)	1.53 (1.33-1.77)	<0.001
<b>Cardiovascular death</b>			
≤5.70	232/1265 (18.3)	Referent	-
5.71-7.30	251/1212 (20.7)	1.14 (0.96-1.37)	0.14
>7.30	434/1339 (32.4)	1.95 (1.66-2.29)	<0.001
<b>All-cause death or all-cause hospitalization</b>			
≤5.70	740/1265 (58.5)	Referent	-
5.71-7.30	755/1212 (62.3)	1.05 (0.87-1.26)	0.63
>7.30	997/1339 (74.5)	1.42 (1.19-1.70)	<0.001
<b>All-cause death</b>			
≤5.70	355/1265 (28.1)	Referent	-
5.71-7.30	355/1212 (29.3)	1.05 (0.94-1.16)	0.38
>7.30	581/1339 (43.4)	1.24 (1.11-1.38)	<0.001

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

Adj., models adjusted on age, sex, 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 =0.82; cardiovascular death interaction P =0.53; all-cause death or all-cause hospitalization interaction P =0.13, all-cause death interaction P =0.49.

Figure 1. Cumulative incidence of cardiovascular death or HF hospitalization events by tertiles of uric acid at baseline

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

Figure 2. Effect of high vs. low losartan dose on uric acid levels over time

Caption: Compared to low dose, high dose losartan reduced uric acid levels by -0.27 (-0.34 to -0.21) mg/dL on average,  $P < 0.001$ . The serum uric acid reduction was more pronounced in patients with hyperuricemia (uric acid  $>7$  mg/dL) at baseline -0.37 (-0.49 to -0.26) mg/dL than in patients without hyperuricemia (uric acid  $\leq 7$  mg/dL) at baseline -0.20 (-0.29 to -0.12) mg/dL, interaction  $P = 0.011$ .

Figure 3. Proportion of patients with hyperuricemia (uric acid levels >7 mg/dL) throughout the follow-up

Caption: High dose losartan decreased the proportion of patients with hyperuricemia throughout the follow-up.

The overall odds ratio for new onset hyperuricemia was 0.71, 95%CI 0.58-0.88, P =0.002 in favour of high dose losartan.