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The impact of serum uric acid on cardiovascular outcomes in the LIFE study

AUD HØIEGGEN, MICHAEL H. ALDERMAN, SVERRE E. KJELDSEN, STEVO JULIUS, RICHARD B. DEVEREUX, ULF DE FAIRE, FREJ FYHRQUIST, HANS IBSEN, KRISTER KRISTIANSON, OLE LEDERBALLE-PEDERSEN, LARS H. LINDHOLM, MARKKU S. NIEMINEN, PER OMVIK, SUZANNE OPARIL, HANS WEDEL, CONG CHEN, and BJÖRN DAHLÖF, FOR THE LIFE STUDY GROUP

Departments of Nephrology and Cardiology, Ullevaal University Hospital, Oslo, Norway; Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, New York City, New York; Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan; Division of Cardiology, Weill Medical College of Cornell University, New York City, New York; Karolinska University Hospital, Stockholm, Sweden; Helsinki University Central Hospital, Helsinki, Finland; Glostrup University Hospital, Glostrup, Denmark; Merck Research Laboratories, Scandinavia, Stockholm, Sweden; Viborg Hospital, Viborg, Denmark; Umeå University, Umeå, Sweden; Haukeland University Hospital, Bergen, Norway; University of Alabama Medical Center, Birmingham, Alabama; Nordic School of Public Health, Göteborg, Sweden; Merck Research Laboratories, Whitehouse Station, New Jersey; and Department of Medicine, Sahlgrenska Hospital/Östra, Göteborg, Sweden

The impact of serum uric acid on cardiovascular outcomes in the LIFE study.

Background. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study demonstrated the superiority of a losartan-based regimen over atenolol-based regimen for reduction of cardiovascular (CV) morbidity and mortality. It has been suggested that the LIFE study results may be related to the effects of losartan on serum uric acid (SUA). SUA has been proposed as an independent risk factor for CV morbidity and death.

Methods. Cox regression analysis was used to assess relationship of SUA and treatment regimens with the LIFE primary composite outcome (CV death, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke).

Results. Baseline SUA was significantly associated with increased CV events [hazard ratio (HR) 1.024 (95% CI 1.017–1.032) per 10 μmol/L, $P < 0.0001$] in the entire study population. The association was significant in women [HR = 1.025 (1.013–1.037), $P < 0.0001$], but not in men [HR = 1.009 (0.998–1.019), $P = 0.108$]. After adjustment for Framingham risk score (FRS), SUA was no longer significant in the entire study population [HR = 1.006 (0.998–1.014), $P = 0.122$] or in men [HR = 1.006 (0.995–1.017), $P = 0.291$], but was significant in women [HR = 1.013 (1–1.025), $P = 0.0457$]. The baseline-to-end-of-study increase in SUA (standard deviation, SD) was greater ($P < 0.0001$) in atenolol-treated subjects (44.4 ± 72.5 μmol/L) than in losartan-treated subjects (17.0 ± 69.8 μmol/L). SUA as a time-varying covariate was strongly associated with events ($P < 0.0001$) in the entire population. The contribution of SUA to the treatment effect of losartan on the primary composite end point was 29% (14%-107%), $P = 0.004$. The association between time-varying SUA and increased CV risk tended to be stronger in women ($P < 0.0001$) than in men ($P = 0.0658$), although the gender-outcome interaction was not significant ($P = 0.079$).

Conclusion. The increase in SUA over 4.8 years in the LIFE study was attenuated by losartan compared with atenolol treatment, appearing to explain 29% of the treatment effect on the primary composite end point. The association between SUA and events was stronger in women than in men with or without adjustment of FRS.

Key words: serum uric acid, hypertension, cardiovascular risk factors, losartan, atenolol, LIFE study.

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Several large epidemiologic studies have identified an association between increased serum uric acid (SUA) and cardiovascular risk in the general population [1–3], and among patients with hypertension [4]. Although this association has been known for over 50 years [5], interest in the field has recently been renewed. Some studies have claimed that SUA is an independent risk factor for cardiovascular disease (CVD) [6–7], whereas others have concluded that there is merely an association of SUA with other risk factors, including hypertension, renal disease, elevated lipoprotein levels, and use of diuretic agents [8]. Some investigators have suggested a stronger independent association of SUA with CVD in women than in men [9–10], and in blacks than in whites [10–11]. The association seems to be stronger in persons with hypertension [4, 12–14] or congestive heart failure [15] than in the general population. Several mechanisms by which SUA could have a direct pathogenic role in CVD have been suggested, but none have been confirmed in clinical studies. Hyperuricemia has been linked to endothelial

dysfunction [16–17] and impaired oxidative metabolism [18], platelet adhesiveness [19], disturbed hemorheology [20], and aggregation [21]. Uric acid is a marker of renal injury [22–23] and may induce renal disease in rodent models [24].

A feature of losartan that differentiates it from other angiotensin II type 1 receptor antagonists is its lowering of SUA [25] due to the ability of the losartan molecule (not its active metabolite) to interfere with urate reabsorption in the renal proximal tubule [26]. In normal as well as in hypertensive subjects, administration of losartan produces sustained reduction in SUA levels [27]. Angiotensin-converting enzyme (ACE) inhibitors and calcium-channel blockers also have modest uricosuric effects, but do not decrease SUA concentration [26]. Diuretics increase SUA levels, and β-blockers do not seem to affect SUA concentration.

Most important, treatment-induced reduction of SUA has never been shown to attenuate cardiovascular risk. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial—which was designed to compare the effects of losartan and atenolol treatment in a high-risk, hypertensive population with left ventricular hypertrophy—provides a unique opportunity not only to elucidate the association of baseline SUA and other cardiovascular risk factors with outcome in a high-risk population, but also to examine the association of change in SUA level during losartan therapy with prognosis.

METHODS

Participants

The LIFE study design, organization, clinical measures, end point definitions, basis for choice of comparative agents, statistical power calculations, recruitment details, baseline characteristics, 1-year follow-up, and primary results have been published [28–31]. Persons aged 55 to 80 years with previously treated or untreated hypertension and electrocardiographic (ECG) signs of left ventricular hypertrophy (LVH) were enrolled; 54% were women. Those with secondary hypertension, myocardial infarction, or stroke within the previous 6 months; angina pectoris requiring treatment with β-blockers or calcium antagonists; heart failure or left ventricular ejection fraction ≤40%; or a disorder that, according to the treating physician's opinion, required treatment with study medication or related drugs, were excluded. Eligible persons were randomly assigned to losartan- or atenolol-based regimens after 1 or 2 weeks of placebo if trough-sitting blood pressures were 160–200 mm Hg systolic, 95–115 mm Hg diastolic, or both. The trial protocol was approved by local ethics committees and performed in accordance with the Declaration of Helsinki. The study was overseen by an independent data and safety monitoring board. All participants gave written informed consent.

Procedures

Study procedures were recently described [31]. Participants were followed for a mean of 4.8 years with regular visits and increases in drug doses to reach a target blood pressure of less than 140/90 mm Hg. All screening, baseline, serial, annual, and end point ECGs were centrally assessed for signs of LVH, and were Minnesota coded at one reading center. The ECG core center also assessed silent and unrecognized myocardial infarctions. Because combined ECG assessment of QRS voltage and duration enhances the detection of LVH at acceptable levels of specificity, the product of QRS duration and Cornell voltage was used as the primary measure to recognize LVH.

Two central laboratories measured serum and plasma concentrations of hemoglobin, creatinine, alanine aminotransferase, glucose, uric acid, sodium, potassium, total and high-density lipoprotein (HDL) cholesterol, and urine concentrations of albumin and creatinine. SUA was measured by an enzymatic uricase method performed on a Hitachi 747–200 analyzer (Roche Diagnostics, Indianapolis, IN, USA) (United States laboratory), and PAP uricase method performed on a DAX96 analyzer (Roche Diagnostics) (European laboratory). Urine albumin concentration was determined by standard methods [32] by using a turbid metric method (Hitachi 717 analyzer, Boehringer Mannheim, Mannheim, Germany) [33] on a single urine specimen. Both serum and urine creatinine were analyzed using the Jaffé reaction without deproteinizing and then quantified by a photometric method by using the same analyzer. The urine albumin concentration (mg/L) was expressed as a ratio to urinary creatinine concentration (mmol/L), the urinary albumin: creatinine ratio (UACR), to provide a composite measure (mg/mmol) of renal glomerular capillary permeability adjusting for urine dilution [34]. In order to derive United States measures of UACR (mg/g), urine creatinine (mg/dL) is multiplied by 8.84. New-onset diabetes was assessed by the investigators according to the 1985 World Health Organization (WHO) criteria [35].

Follow-up of end points was stopped on September 16, 2001, when a sufficient number of primary end points for study power were predicted to have occurred. Participants then had a follow-up clinic visit or at least a vital status check within 6 weeks. All clinical data were verified from source documents before entry into a laptop-based, remote data-entry system by field monitors and electronic transfer to a central database.

Statistical methods

Analyses of cardiovascular end points were based on the intention-to-treat principle, consistent with all such analyses used in the LIFE trial. Participants who experienced more than one end point event were counted as

having had an event in all relevant end point analyses; however, only the first event in a specific category was counted in individual analyses.

The effect of baseline SUA on cardiovascular end points was assessed by a Cox regression model. The contribution of SUA to the losartan effect was assessed by a Cox regression model with SUA included as a time-varying covariate. The proportion of the losartan effect explained by SUA was calculated by comparing the estimated losartan effect before and after the adjustment for SUA [36]. Effects of other cardiovascular risk factors were controlled for by using the baseline Framingham risk score (FRS), which is based on gender, cholesterol, high-density lipoprotein cholesterol, smoking status, presence of diabetes and LVH, and systolic blood pressure [37]. Compared with an alternative multiple regression analysis entering the above variables separately, the FRS was a more conservative adjustment (i.e., minimized SUA effects), and, therefore, the preferred one.

Role of the funding source

All study data reside in the Merck & Co., Inc., database. Merck provided the study steering committee with free access to all data. The steering committee is free to interpret data and write manuscripts.

RESULTS

Baseline variables

Mean baseline serum uric acid (United States male 370, female 325; Europe male 358, female 300 μmol/L), hemoglobin, serum creatinine, cholesterol/HDL ratio, serum glucose, urine albumin, and diastolic blood pressure (DBP) were higher in men than in women. On the other hand, women were older, had a higher body mass index (BMI), higher total and HDL-cholesterol, systolic blood pressure (SBP), and were more likely to have isolated systolic hypertension (Table 1).

Serum creatinine, body weight, HDL-cholesterol, hemoglobin, total cholesterol/HDL ratio, BMI, serum glucose, DBP (but not SBP), and total cholesterol had significant univariate correlations with SUA (all <0.0001) (Table 2). Correlation coefficients for men and women are shown separately in Table 2. In a stepwise, multiple regression analysis with SUA as the dependent variable, serum creatinine, weight, hemoglobin, alcohol consumption (continuous), total cholesterol/HDL ratio, serum glucose, HDL-cholesterol, BMI, urine microalbuminuria, smoking (continuous), and number of prior antihypertensives were all independent explanatory variables (Table 3). Both BMI and weight remained selected, indicating that height may be an important predictor as well. Together, these variables explained 31% of the variation in SUA. Positive univariate relations of serum glucose and smoking with SUA became negative in the multiple regression analysis.

Baseline SUA was significantly associated with increased rate of the composite outcome of CV death, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke [hazard ratio (HR) 1.024 (1.017–1.032) per 10 μmol/L, $P < 0.0001$] (Fig. 1). The SUA-by-gender interaction was significant ($P = 0.0491$). In women, baseline SUA remained significantly associated with increased risk [HR =

Table 1. Baseline demographic and clinical characteristics

Characteristic	All patients ($N = 9193$)	Women ($N = 4963$)	Men ($N = 4230$)
Age *years*	66.94 (7.0)	67.69 (6.99)	66.07 (6.92)
Weight *kg*	78.63 (14.94)	73.58 (14.30)	84.56 (13.43)
Body mass index *kg/m²*	27.99 (4.78)	28.31 (5.33)	27.62 (4.01)
Hemoglobin *g/L*[a]	142.42 (12.06)	137.62 (10.15)	148.09 (11.68)
Serum creatinine *μmol/L*[b]	86.92 (20.20)	79.54 (17.53)	95.59 (19.68)
Serum uric acid *μmol/L*[c]	330.09 (78.19)	304.13 (71.90)	360.48 (74.21)
Total cholesterol *mmol/L*[d]	6.04 (1.12)	6.31 (1.11)	5.73 (1.06)
High density lipoprotein cholesterol *mmol/L*[d]	1.49 (0.44)	1.62 (0.44)	1.34 (0.37)
Cholesterol/high-density lipoprotein ratio	4.34 (1.39)	4.15 (1.33)	4.56 (1.43)
Serum glucose *mmol/L*[e]	6.02 (2.18)	5.95 (2.16)	6.10 (2.21)
Systolic blood pressure *mm Hg*	174.43 (14.29)	175.34 (14.07)	173.36 (14.46)
Diastolic blood pressure *mm Hg*	97.79 (8.88)	97.12 (8.86)	98.58 (8.84)
Isolated systolic hypertension %	14.4	16.1	12.5
Urine albumin *mmol/L*[f]	63.8 (230.26)	49.06 (201.80)	81.06 (258.62)

Isolated systolic hypertension, systolic blood pressure 160–200 mm Hg and diastolic blood pressure <90 mm Hg. Data are mean (standard deviation).
[a]To convert values to grams per deciliter, multiply by 0.1.
[b]To convert values to milligrams per deciliter, multiply by 0.0113.
[c]To convert values to milligrams per deciliter, multiply by 0.0168.
[d]To convert values to milligrams per deciliter, multiply by 38.67.
[e]To convert values to milligrams per deciliter, multiply by 18.015.
[f]To convert values to milligrams per deciliter, multiply by 0.1.

Table 2. Univariate correlations between baseline serum uric acid and cardiovascular risk factors

Variable	Rho value		
	All patients ($N = 9193$)	Women ($N = 4963$)	Men ($N = 4230$)
Serum creatinine *μmol/L*	0.428[b]	0.352[b]	0.259[b]
Weight *kg*	0.343[b]	0.275[b]	0.188[b]
HDL-cholesterol *mmol/L*	−0.307[b]	−0.270[b]	−0.134[b]
Cholesterol/HDL ratio	0.258[b]	0.256[b]	0.169[b]
Hemoglobin *g/L*	0.258[b]	0.115[b]	0.105[b]
Body mass index *kg/m²*	0.214[b]	0.300[b]	0.206[b]
Serum glucose *mmol/L*	0.131[b]	0.162[b]	0.039[a]
Diastolic blood pressure *mm Hg*	0.066[b]	0.010 (NS)	0.067[b]
Cholesterol *mmol/L*	−0.060[b]	0.007 (NS)	0.084[b]

NS, not significant.
[a]$P < 0.05$.
[b]$P < 0.0001$.

Table 3. Results of multiple regression analyses with SUA as dependent variable

Variable	Regression coefficient	Standard error	F value	Model R square	*P* value
Serum creatinine *μmol/L*	1.323[b]	0.042	1525.97	0.170	<0.0001
Weight *kg*	0.738[b]	0.096	669.81	0.238	<0.0001
Hemoglobin *g/100 mL*	0.759[b]	0.068	219.81	0.260	<0.0001
Alcohol *drinks/wk*	12.430[b]	0.820	148.99	0.275	<0.0001
Cholesterol/HDL ratio	5.705[b]	0.790	190.70	0.292	<0.0001
Serum glucose *mmol/L*	−3.292[b]	0.349	77.89	0.300	<0.0001
HDL-cholesterol *mmol/L*	−13.678[b]	2.699	24.22	0.303	<0.0001
BMI kg/m^2	1.272[b]	0.279	17.59	0.304	<0.0001
Urine albumin *mg/L*	0.011[a]	0.003	10.36	0.305	=0.0013
Smoking *cigarettes/day*	−1.453[a]	0.651	4.94	0.3055	=0.0263
Prior antihypertensives *N*	1.817[a]	0.852	4.55	0.3060	=0.0329

BMI, body mass index; HDL, high-density lipoprotein.
[a] $P < 0.05$.
[b] $P < 0.001$.

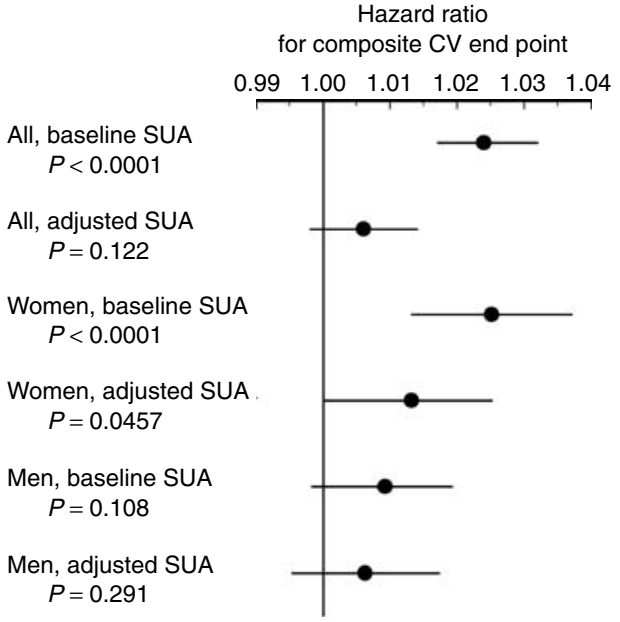

Fig. 1. Serum uric acid and cardiovascular risk per 10 μmol/L. Hazard ratios for composite cardiovascular outcome (stroke, myocardial infarction, and cardiovascular deaths) in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study related to baseline serum uric acid levels. When adjusted for Framingham risk score, the hazard ratios remained statistically significant only in women.

1.025 (1.013–1.037), $P < 0.0001$] (Fig. 1). In men, however, SUA was not significantly associated with increased events [HR = 1.009 (0.998–1.019), $P = 0.108$] (Fig. 1). After adjustment for FRS, SUA was no longer significant [HR = 1.006 (0.998–1.014), $P = 0.122$] in the whole population, and the SUA-by-gender interaction was not significant ($P = 0.421$); however, the association between baseline SUA and increased cardiovascular events was stronger in women ($P = 0.0457$) than in men ($P = 0.291$). In an alternative analysis including gender, age, smoking status, status of diabetes, systolic blood pressure, and ratio of cholesterol/HDL cholesterol separately, baseline SUA was significantly associated with CV events [HR = 1.015 (1.006–1.024), $P = 0.0005$]. The gender interaction was not significant ($P = 0.9068$). The SUA effect was significant in both women [HR 1.016 (1.003–1.029), $P = 0.014$] and men [HR = 1.013 (1.002–1.024), $P = 0.026$]. After adjustment for serum creatinine, which was not included in FRS, SUA was still related to the primary composite outcome ($P = 0.0032$), and after adjustment for albumin/creatinine ratio, SUA was still related to the primary composite outcome ($P < 0.0001$).

On-treatment SUA and composite cardiovascular end point

SUA as a time-varying covariate was significantly associated with increased risk in the whole population ($P < 0.0001$) (Fig. 2). Although the SUA-by-gender interaction was not significant ($P = 0.079$), the association between time-varying SUA and increased cardiovascular events tended to be stronger in women ($P < 0.0001$) than in men ($P = 0.0658$). After adjustment for FRS, SUA was no longer significant in the whole population ($P = 0.0913$). Although the SUA-by-gender interaction was not significant ($P = 0.282$), the association between time-varying SUA and increased cardiovascular events still tended to be stronger in women ($P = 0.032$) than in men ($P = 0.419$).

The risk difference between losartan and atenolol decreased from 15% to 11% after adjustment for SUA as a time-varying covariate. The estimated contribution of SUA to the losartan effect was 29% (14%, 107%), $P = 0.004$. For women, the risk difference between losartan and atenolol decreased from 19% to 16% after adjustment for SUA as a time-varying covariate. The estimated contribution of SUA to the losartan effect was 20% (7%, 98%), $P = 0.009$. For men, the risk difference between losartan and atenolol decreased from 11% to 9% after adjustment of SUA as a time-varying covariate, and the estimated contribution of SUA to the losartan effect was 18% (−127%, 177%), $P = 0.097$.

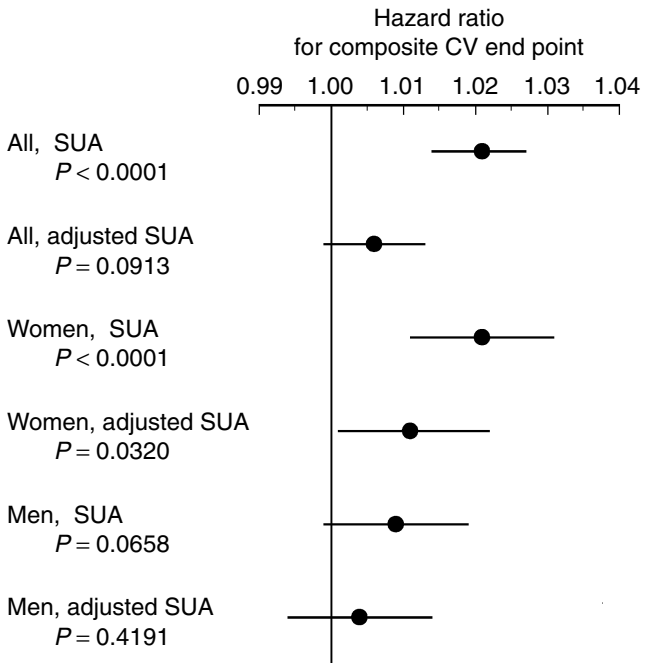

Fig. 2. Serum uric acid on treatment and cardiovascular risk per 10 μmol/L. Hazard ratios for composite cardiovascular outcome (stroke, myocardial infarction, and cardiovascular deaths) in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study related to on-treatment serum uric acid levels.

SUA, serum creatinine, and hemoglobin

The baseline-to-end-of study increase in SUA was greater in the atenolol group (44.4 ± 72.5 μmol/L) than in the losartan group (17.0 ± 69.8 μmol/L), $P < 0.0001$ (Fig. 3). The difference was significant after 1 year, and was maintained throughout the study. The difference was similar in men and women (Fig. 3). The distributions of the dose of blinded study treatment for patients at the end of follow-up or at occurrence of the first primary end point, if earlier, and the distribution of additional therapy on top of blinded study drug or hydrochlorothiazide were not substantially different in the two groups. The mean final losartan dose was 79 mg, and the mean final atenolol dose was 76 mg. Patients taking losartan were more likely to continue therapy, and the likelihood of receiving hydrochlorothiazide was the same in both groups.

Serum creatinine increased from 87.4 μmol/L ± 20.3 to 96.9 μmol/L ± 25.8 in the losartan group, and from 86.5 μmol/L ± 20.1 to 96.1 μmol/L ± 24.3 in the atenolol group from baseline to end of the study ($P = 0.337$) (Table 4). There was a strong positive association between serum creatinine and SUA at end of study ($r = 0.469$, $P < 0.0001$).

Hemoglobin decreased during the study and the decline was more pronounced in the losartan group (142.4 g/L ± 12.3 to 138.2 g/L ± 13.3) than in the atenolol group (142.5 g/L ± 11.6 to 141.0 g/L ± 13.6)

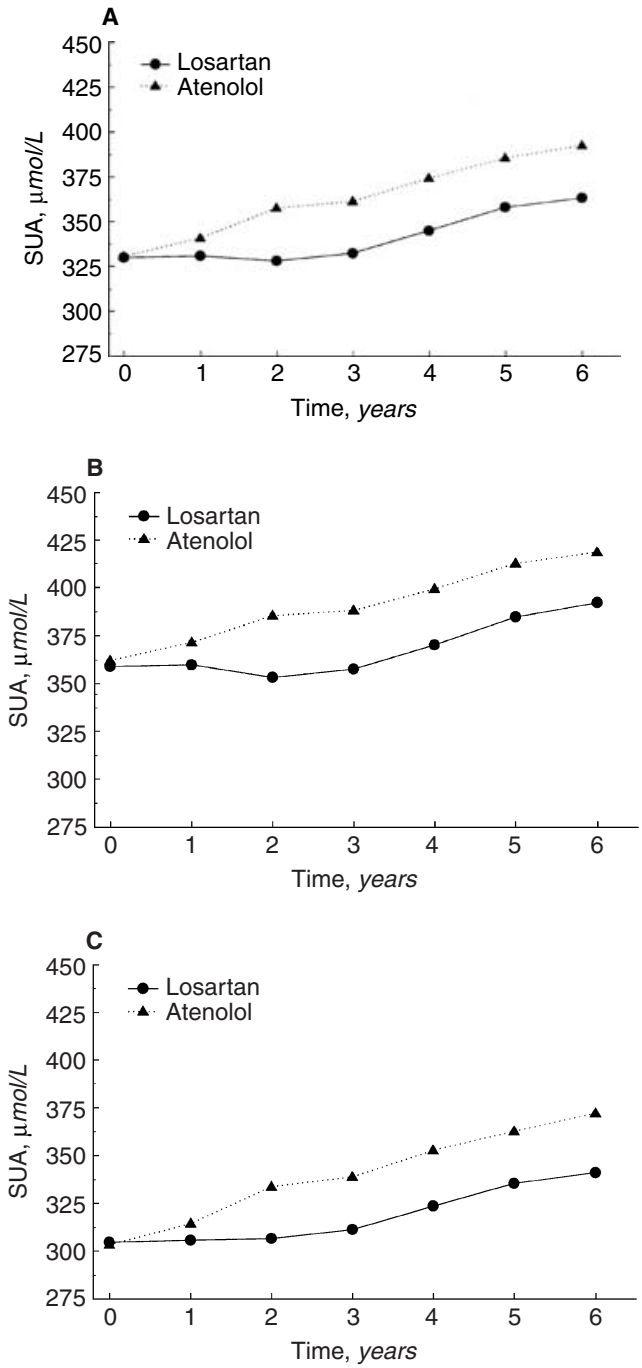

Fig. 3. Serum uric acid by treatment group and gender. The increase in serum uric acid throughout the study was significantly attenuated in the losartan compared to the atenolol-treated group. (*A*) Overall population ($P < 0.0001$). (*B*) Men ($P < 0.0001$). (*C*) Women ($P < 0.0001$). Year 0 refers to baseline.

(between-group difference, $P < 0.0001$) (Fig. 4). The in-treatment decreases were similar in men and women (Fig. 4). There was a positive association between end-of-study hemoglobin and SUA ($r = 0.174$, $P < 0.0001$; $P = 0.001$ for women, and $P = 0.610$ for men). Other variables (e.g., serum glucose, cholesterol, and HDL-cholesterol)

Table 4. Mean changes in selected laboratory values from baseline to end of study

	Losartan ($N = 4605$)			Atenolol ($N = 4588$)		
	Baseline	Year 5	Change	Baseline	Year 5	Change
Sodium *mmol/L*	140.111	139.538	−0.573	140.036	139.797	−0.239
Potassium *mmol/L*	4.141	4.109	−0.032	4.143	4.025	−0.118
SGPT (ALAT) μ*kat/L*	0.513	0.474	−0.039	0.511	0.480	−0.030
Glucose *mmol/L*	5.900	6.116	0.216	5.816	6.367	0.551
Total cholesterol *mmol/L*	6.096	5.748	−0.348	6.122	5.805	−0.317
HDL-cholesterol *mmol/L*	1.526	1.497	−0.030	1.516	1.417	−0.099
Serum creatinine μ*mol/L*	85.430	96.462	11.2	83.968	94.718	10.9

HDL = high-density lipoprotein.

did not change substantially during treatment in either group (Table 4).

DISCUSSION

In the LIFE study baseline SUA was significantly associated with increased occurrence of the composite end point of CV death, stroke, or myocardial infarction, even with adjustment for other cardiovascular risk factors in women, whereas in men, SUA was not associated with increased events in univariate analyses or adjusted for baseline Framingham risk score, but did have a weak association when established risk factors were considered separately. In addition, losartan, an angiotensin II type-1 receptor antagonist with effects on SUA unique within its drug class, significantly attenuated the increase in SUA compared with atenolol, a β-receptor blocker, during 4.8 years of follow-up in hypertensive adults with LVH. The contribution of SUA to the treatment effect of losartan on the primary composite end point (cardiovascular death, nonfatal and fatal myocardial infarction, nonfatal and fatal stroke) was estimated to be 29% (14%, 107%), $P = 0.004$. The contribution of SUA to the losartan effect tended to be stronger in women than in men.

The results from the LIFE study differ from other hypertension studies comparing treatment based on a drug from one of the newer classes with treatment based on an older drug (diuretic or β-blocker). To date, no other study of the treatment of essential hypertension has shown unequivocal reduction of cardiovascular morbidity and mortality beyond the effects of diuretics or β-blockers [38]. The unique uric acid–lowering effect of losartan may contribute to this novel finding. The LIFE study is also the first study to show that reducing SUA is associated with beneficial effect on outcomes in the treatment of hypertension.

The association between SUA and risk for cardiovascular events is well established, but whether this relationship is causal or not remains disputed. SUA may have a pathogenic role in cardiovascular disease, or may merely be a marker of other cardiovascular risk factors. Epidemiologic studies have been unable to answer this question, and controlled intervention studies in humans are lacking. Even though the LIFE study was not designed to address this issue, it provided a unique opportunity to study the effects of a drug that reduces SUA on cardiovascular outcomes in a high-risk hypertensive population.

The serum level of uric acid (which is filtered, reabsorbed, and secreted in the renal proximal tubules) is closely related to renal function and to hypertension. Serum creatinine is an independent cardiovascular risk factor [39, 40], and increased SUA values may reflect a decreased glomerular filtration rate (GFR) and may thereby be a marker of cardiovascular risk. SUA is also positively correlated with urinary albumin excretion [23]. After adjustment for these measures of renal function, SUA still predicted cardiovascular events in the LIFE study, indicating a more subtle relationship with renal mechanisms or one independent of renal function. Hyperuricemia in hypertension may be caused by decreased renal urate clearance independent of global changes in glomerular filtration, which may be mediated by an increase in serum lactate [41] that inhibits secretion of urate by the tubular anion-exchange transport system. Another possibility is that reduced uric acid excretion may be linked to increased proximal tubular reabsorbtion of sodium and water because reabsorbtion of urate, sodium, and water is conducted by the same transport system [42]. The novel concept that salt-dependent hypertension could result from renal microvascular injury with local ischemia could provide a pathogenic link for hyperuricemia with hypertension [43]. Hyperuricemia in humans is associated with renal vasoconstriction [23] and is positively correlated with plasma renin activity in hypertensive subjects [44], suggesting that SUA could have adverse effects that are mediated by renin-angiotensin-aldosterone system activation. Hyperuricemia may be a marker of renal disease or microvascular injury, but there is also evidence that hyperuricemia may lead to renal disease [45–46]. A novel mechanism has recently been suggested in a rodent model by which uric acid can stimulate the development of hypertension by stimulating renal afferent arteriopathy and tubulointerstitial disease, leading

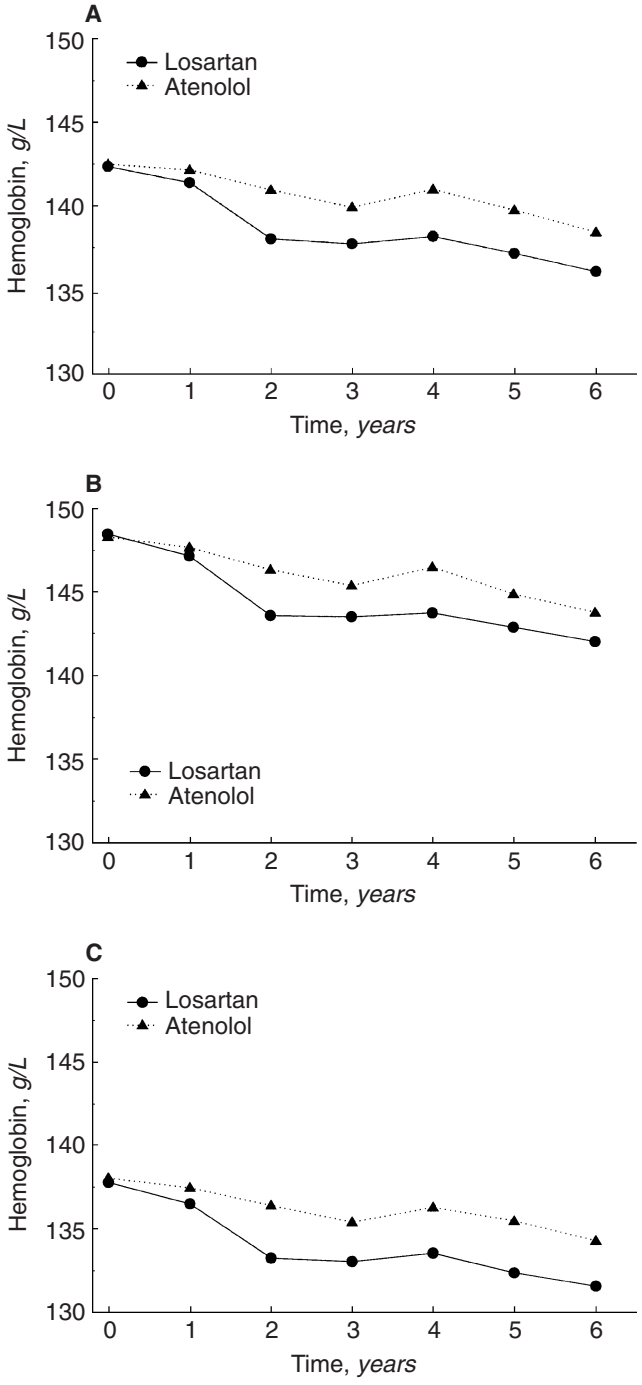

Fig. 4. Hemoglobin level by treatment group and gender. Hemoglobin decreased during the study and the decline was more pronounced in the losartan group than in the atenolol group. The differences in delta values were similar for men and women. (*A*) Overall population. (*B*) Men. (*C*) Women. Year 0 refers to baseline.

to hypertension [47–48]. Renal lesions and hypertension could be prevented/reversed by lowering uric acid levels and by treatment with an angiotensin-converting enzyme (ACE) inhibitor or arginine [46]. Whether uric acid has similar nephrotoxic and hypertension-promoting effects in humans deserves further investigation.

SUA has long been known to be associated with hemoglobin levels [49], and hyperuricemia is common in patients with polycythemia. The relationship may be explained by increased red cell degradation in subjects with increased red cell mass. Increased hematocrit, and thereby, blood viscosity, may link SUA and cardiovascular risk because impaired hemorheology is a well-documented risk factor for cardiovascular diseases [50–52], and hemoglobin is a predictor of events in the LIFE study [53]. Hemoglobin decreased more in the losartan-compared with the atenolol-treated group. The present study suggests an antierythropoietic effect of losartan even in non-transplanted individuals in accordance with some [54–55], but not all [56], previous studies. Another explanation for reduced hemoglobin concentration may be blood volume expansion and increased plasma volume secondary to blocked angiotensin II-mediated vasoconstriction, rather than reduced erythropoiesis. The number of erythrocytes was not measured in the present study.

If SUA level is an independent cardiovascular risk factor, one may speculate whether lower hemoglobin levels, and thereby, reduced cell degradation, would be accompanied by lower SUA, and thereby, reduced cardiovascular risk. Interestingly, there was a positive association between end-of-study hemoglobin and SUA in women, but not in men, which may partly explain the strong relationship between cardiovascular events and SUA in the women.

In accordance with reports from the Chicago Heart Association Detection Project [9] and NHANES I [10], we found an association between baseline SUA and cardiovascular events in women, but not in men. There was also a significantly stronger association between time-varying SUA and cardiovascular outcome in women than in men. Even though the gender difference seems to be a consistent finding, a plausible mechanism is lacking. A closer relationship between SUA and other cardiovascular risk factors in women than in men, as in the LIFE study population (Table 2), may be one explanation; the close relationship with SUA and age in women may be another. While SUA levels are similar in boys and girls during childhood, a gender difference appears at adolescence, with lower levels in women than in men. This is probably because of an increased renal clearance of urate related to estrogen in premenopausal women [57] and may also be related to lower hemoglobin levels in premenopausal women. After menopause, however, SUA increases in women and nearly reaches the levels in men of the same age. Women taking hormone replacement therapy have been shown to have significantly lower SUA than those who did not [58]. Wingrove et al [59] postulated that complex metabolic alterations associated with menopause, rather than age, were linked to the observed increase in SUA.

SUA increased in both treatment groups during the study period with an average of 10 μmol/L annually in the atenolol group and 6 μmol/L annually in the losartan group. At the time of a primary end point or the end of follow-up, 86% of patients in the losartan group versus 85% of patients in the atenolol group received hydrochlorothiazide without gender differences. The mean dose of hydrochlorothiazide was approximately 20 mg in each treatment group. For those who initiated hydrochlorothiazide during the trial, the average difference in SUA from start of the study to the next SUA measurement was 26 μmol/L (41 atenolol group, 12 losartan group). There were no meaningful results by separating those with an increase >59.5 μmol/L (1 mg/dL) and <59.5 μmol/L (1 mg/dL) in the present study. In addition, both groups experienced a reduction in renal function, as shown by increased serum creatinine during the mean 4.8-year study period. The decrease in renal function was similar in the two treatment groups and most likely reflected age-related reduction in glomerular filtration rate rather than either study drug action or effects of additional drugs or hydrochlorothiazide, which did not differ between the groups. The parallel changes in serum creatinine in the treatment groups made an adjustment for creatinine as a time-varying covariate less meaningful, as did the lack of change in plasma glucose in either group throughout the study. The possibility of an influence of other drugs affecting uric acid concentration is unlikely; however, this also was not controlled for in the study. The uric acid owering effect of losartan is the most reasonable explanation for the difference in SUA increase in the two groups. As a renal vasodilator, however, losartan may decrease renal vasoconstriction, thus facilitating increased tubular urate filtration compared with atenolol. Measurements of serum creatinine in the study cannot be used to exclude an improvement in glomerular filtration because small changes in GFR are not necessarily reflected as changes in serum creatinine.

Diuretics are frequently used as antihypertensive medication either alone or in combination with other drugs. The development of hyperuricemia and gout is a well-known side effect of this treatment regimen. In the LIFE study 373 patients had one or more gout attacks reported as adverse experiences, evenly divided between the two groups, with 185 in the atenolol group and 188 in the losartan group. The combination of losartan with a diuretic may be able to prevent hyperuricemia in antihypertensive treatment and makes losartan a desirable drug in combination with hydrochlorothiazide. Hyperuricemia occurring as a complication of diuretic therapy has been implicated as a risk factor for cardiovascular disease events. In the Systolic Hypertension in the Elderly Program (SHEP) trial, participants who developed hyperuricemia on chlorthalidone therapy suffered CVD events at a rate similar to that of placebo-treated participants [60].

CONCLUSION

The results of the LIFE study clearly support an association between SUA and cardiovascular events in hypertensive women. Furthermore, the present data suggest that attenuating the increase in SUA, whether this increase is related to a reduction in GFR or the use of diuretics, reduces cardiovascular events in a high-risk population. The unique results of the LIFE study may be due in part to the specific feature of reduction of SUA by losartan.

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Reprint requests to Aud Høieggen, M.D., Ph.D., Department of Nephrology, Ullevaal University Hospital, Oslo, Norway.
E-mail: aud.hoieggen@ioks.uio.no

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