

An initial reduction in serum uric acid during angiotensin receptor blocker treatment is associated with cardiovascular protection: a post-hoc analysis of the RENAAL and IDNT trials

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Objective: Increased levels of serum uric acid (SUA) are thought to be an independent risk marker for cardiovascular complications. Treatment with the angiotensin receptor blocker (ARB) losartan lowers SUA in contrast to other ARBs. Whether reductions in SUA during ARB therapy are associated with cardiovascular protection is unclear. We aimed to investigate this.

Method: In a post-hoc analysis of the Reduction of Endpoints in Non insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy (IDNT) trials we determined whether the short-term effect of losartan and of irbesartan on SUA is related with long-term cardiovascular outcome by means of Cox regression.

Results: Compared to placebo, losartan significantly changed SUA [−0.16 mg/dl; 95% confidence interval (CI) −0.01 to −0.30; $P=0.031$], whereas irbesartan did not (−0.09 mg/dl; (95% CI 0.09 to −0.28; $P=0.30$). Each 0.5 mg/dl decrement in SUA during losartan treatment in the first 6 months resulted in a reduction in the risk of cardiovascular outcomes by 5.3% (95% CI 0.9 to 9.9; $P=0.017$). Losartan reduced the risk of cardiovascular outcomes by 9.2% (95% CI −7.9 to 23.6). Adjustment for the 6-month change in SUA attenuated the treatment effect to 4.6% (95% CI −16.2 to 22.0), suggesting that part of the cardiovascular protective effect of losartan is attributable to its short-term effect on SUA.

Conclusion: Losartan but not irbesartan significantly lowers SUA compared to placebo in patients with type 2 diabetes and nephropathy. The degree of reduction in SUA explains part of the cardiovascular effect of losartan. This supports the hypothesis that SUA is a modifiable risk factor for cardiovascular disease, at least in type 2 diabetics with nephropathy.

Keywords: angiotensin receptor blocker, cardiovascular disease, losartan, uric acid, type 2 diabetes

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; IDNT, Irbesartan Diabetic

Nephropathy Trial; IQR, interquartile range; RENAAL, Reduction of Endpoints in Non insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan; SUA, serum uric acid; UACR, urinary albumin creatinine ratio; URAT1, urate transporter 1

INTRODUCTION

Disease management in patients with diabetes is focused on targeting cardiovascular risk factors towards normalcy: HbA1c is targeted with antidiabetic agents, blood pressure with antihypertensive agents, mainly angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), and cholesterol with statins. The magnitude of the short-term reduction in these established risk factors induced by treatment serves to monitor the effectiveness of the therapy to achieve long-term cardiovascular protection.

In addition to these established risk factors, a number of studies have shown that increased serum uric acid (SUA) is also independently associated with increased risk of cardiovascular morbidity and mortality in patients with diabetes [1–3]. The independent association between SUA and cardiovascular outcome raises the possibility that interventions that reduce SUA are cardiovascular-protective. Several drugs, registered for varying indications, have been shown to reduce SUA [4]. Of interest in this respect is the ARB losartan, which reduces SUA through inhibition of urate

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reabsorption in the proximal tubule. This is a drug-specific effect and is not observed with other ARBs [5]. Whether an initial reduction in SUA during treatment with losartan is associated with cardiovascular protection has not yet been documented.

The aim of the present study was to assess whether the long-term cardiovascular protective effect of an ARB could be attributed to its short-term effect on SUA. To this end we used the data of two different hard outcome trials in patients with type 2 diabetes and nephropathy, one trial assessing the effect of losartan (SUA-lowering drug) and one trial assessing the effect of irbesartan (non-SUA-lowering drug).

METHOD

Study design

The present study was conducted in patients participating in the Reduction of Endpoints in Non insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) or Irbesartan Diabetic Nephropathy Trial (IDNT) trial. Both randomized placebo-controlled trials had similar rationale, study, design, and outcome [6,7]. In brief, the overall aim of these trials was to test the efficacy of an ARB (losartan in RENAAL; irbesartan in IDNT) on renal (primary endpoint) and cardiovascular outcomes (secondary endpoint) in patients with type 2 diabetes and nephropathy. The IDNT trial also included a calcium channel blocker (amlodipine) treatment arm, which was excluded from the current analysis. Inclusion criteria of both trials were similar and consisted of a diagnosis of type 2 diabetes, presence of nephropathy, and age between 30 and 70 years. Patients with insulin-dependent diabetes or renal disease not related to diabetes were excluded in both trials. Patients with unstable angina, myocardial infarction, cerebrovascular accident, cardiac artery bypass graft, or angioplasty occurring in the previous months before study entry were excluded, as were patients with heart failure. Concomitant therapy with ARB, ACEi or aldosterone antagonists was prohibited in either trial. All participants gave written informed consent. Both trials were approved by local medical ethics committees and conducted according to the guidelines of the declaration of Helsinki.

Measurements and outcomes

During the study blood and urine samples were regularly collected for laboratory measurements, including SUA, HbA1c, serum creatinine, potassium, cholesterol, hemoglobin, and urinary albumin-to-creatinine ratio (UACR). The present study focused on the change in SUA during ARB treatment. The change in SUA was defined as the difference between the baseline and 6-month value. The 6-month value was chosen because most cardiovascular risk markers were recorded at 6 months, ARB treatment effects were considered fully present, and relatively few events occurred during the initial 6 months. The estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet for Renal Disease (MDRD) study formula [8].

The primary endpoint in the present study was the original cardiovascular endpoint in both trials defined as the composite of myocardial infarction, stroke,

hospitalization for heart failure, revascularization procedure or cardiovascular death. Since both the RENAAL and IDNT trials showed that ARB treatment significantly reduced the incidence of hospitalization for heart failure, the association between an initial reduction in SUA and hospitalization for heart failure was assessed separately. All cardiovascular outcomes in both trials were adjudicated by an independent blinded committee using rigorous definitions.

Statistical analysis

All patients with available baseline and 6-month SUA values were included in the present analysis. Mean SUA levels at each follow-up visit were calculated in the ARB and placebo group of the trials separately. The mean difference in the change in SUA between ARB and placebo treatment was assessed by a two-sided t-test. To determine which parameters were associated with a change in SUA at 6 months, a multivariable linear regression model was used. Baseline characteristics as well as initial changes in systolic and diastolic blood pressure, HbA1c, UACR, and eGFR were included in the multivariable linear regression model. A backward selection procedure was applied for selection of covariates for the final model ($\alpha = 0.1$).

The impact of a change in SUA on cardiovascular outcomes was assessed by a Cox regression model. The multivariable Cox regression model was adjusted for age, sex, baseline values of SUA, UACR, eGFR, hemoglobin, blood pressure, diuretic use and treatment assignment and 6-month changes in blood pressure, UACR, and eGFR. Since urinary UACR had a skewed distribution, a logarithmic transformation of UACR was required to obtain the most optimal fit.

To test the contribution of SUA on the ARB treatment effect, SUA up to 6 months was used as a continuous time-varying covariate in a Cox regression model. The proportion of the ARB effect explained by SUA was calculated as the difference between the ARB effect before and after adjustment for changes in SUA [9].

All analyses were conducted with STATA version 11 (Stata statistical Software, Texas, USA). Descriptives are shown as mean with standard deviation (SD), or median with interquartile range according to normal or skewed distributions. A two-sided *P*-value of 0.05 or less indicated the nominal level of statistical significance.

RESULTS

In the present study, a total of 2387 patients (90% of all ARB or placebo-assigned patients) with baseline and 6-month SUA data available were included. As shown in Table 1, all risk parameters at baseline were well balanced between the placebo and ARB treatment groups of both the RENAAL and IDNT trials. Mean SUA was 6.7 ± 1.7 mg/dl among patients in the RENAAL trial and 6.8 ± 1.9 mg/dl in the IDNT trial.

Figure 1 shows the mean SUA levels during follow-up in the RENAAL and IDNT trials separately. In the RENAAL trial, SUA increased to 6.89 mg/dl in the placebo group, whereas it remained 6.73 mg/dl during the initial 6 months in the losartan group, resulting in a mean group difference of 0.16 mg/dl [95% confidence interval (CI) 0.01 to 0.30 mg/dl;

TABLE 1. Baseline characteristics of the RENAAL and IDNT population

Characteristic	RENAAL		IDNT	
	Placebo (n = 664)	Losartan (n = 678)	Placebo (n = 519)	Irbesartan (n = 526)
Age (years)	60.2 (7.6)	60.0 (7.3)	58.3 (8.2)	59.2 (7.1)
Male, n (%)	421 (63.4)	422 (62.2)	370 (71.3)	345 (65.6)
Systolic BP (mmHg)	153 (20)	152 (19)	158 (20)	160 (19)
Diastolic BP (mmHg)	82 (11)	82 (10)	87 (11)	87 (11)
Total cholesterol (mg/dl)	228 (56)	226 (55)	226 (61)	227 (53)
HbA1C (%)	8.4 (1.6)	8.5 (1.6)	8.2 (1.8)	8.1 (1.7)
Uric acid (mg/dl)	6.74 (1.7)	6.73 (1.7)	6.83 (1.9)	6.81 (1.8)
Hemoglobin (mg/dl)	12.4 (1.8)	12.5 (1.8)	13.0 (1.9)	13.0 (1.9)
UACR (mg/g) ^a	1261 (568–2475)	1168 (538–2540)	1508 (755–2682)	1456 (799–2791)
eGFR (ml/min per 1.73 m ²)	39.8 (12.7)	39.5 (11.8)	48.2 (18.5)	46.8 (17.1)
Serum creatinine (mg/dl)	1.9 (0.5)	1.9 (0.5)	1.7 (0.6)	1.7 (0.5)
Concomitant medication				
ACEi or ARB, n (%)	329 (49.6)	368 (54.3)	248 (47.8)	243 (46.2)
β blocker, n (%)	122 (18.3)	128 (18.9)	99 (19.1)	93 (17.7)
CCB, n (%)	484 (72.9)	488 (72.0)	202 (38.9)	208 (39.5)
Diuretic, n (%)	384 (57.8)	394 (58.1)	241 (46.4)	245 (46.6)

Characteristics of patients with available baseline and 6-month SUA measurements are shown. Mean and standard deviations are shown unless otherwise indicated.

CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate.

^aMedian (IQR).

$P=0.031$; Fig. 1]. From 6-month and on, the level of SUA increased both in the placebo and losartan group. The SUA level started to rise at 6 months in the losartan group. The 'apparent' fall observed beyond 36 months in the placebo group is likely to be attributable to 'drop-out' of patients in the placebo group with high SUA levels. In the IDNT trial, SUA increased to 7.33 mg/dl in the placebo group during the initial 6 months, which was comparable with the increase to 7.22 mg/dl observed in the irbesartan-treated group resulting in a nonsignificant mean group difference of 0.09 mg/dl (-0.09 to 0.28 mg/dl; $P=0.30$; Fig. 1 and Table 2).

The effect of losartan on uric acid appeared to be independent of other patient characteristics. In a multivariable regression analysis, adjustment for baseline characteristics and 6-month changes in these characteristics, most notably changes in UACR and eGFR, treatment with losartan was independently associated with a reduction in SUA at 6 months ($P < 0.001$).

Since treatment with losartan reduced SUA compared to placebo, we further explored the relationship between a 6-month change in SUA and the risk of subsequent cardiovascular outcomes in the RENAAL trial. Figure 2 shows the risk for adverse cardiovascular outcome and hospitalization for heart failure according to the distribution of 6-month change in SUA. After controlling for baseline characteristics and changes in risk factors we observed an almost linear relationship between the 6-month change in uric acid and risk for adverse cardiovascular outcomes as well as risk for hospitalization for heart failure. Each initial 0.5 mg/dl reduction in SUA was independently associated with a reduction in the risk of subsequent cardiovascular outcomes of 5.3% (0.9 to 9.9%; $P=0.017$) and hospitalization for heart failure of 11.6% (4.7 to 18.8%; $P=0.001$).

To investigate whether the effect of losartan on cardiovascular outcomes can be explained by its short-term effect on SUA, we assessed the impact of a reduction of SUA on losartan's effect on cardiovascular outcomes. Adjustment of

the cardiovascular treatment effect of losartan for 6-month change in SUA attenuated the effect from 9.2% (-7.9 to 23.6%) to 4.6% (-16.2 to 22.0%), suggesting that part of the cardiovascular-protective effect of losartan is attributable to its effect on SUA. The treatment effect of irbesartan on cardiovascular outcomes in the IDNT trial was 12.1% (-8.3 to 28.6%). Adjustment of the treatment effect of irbesartan on cardiovascular outcomes for its effect on SUA marginally attenuated the cardiovascular-protective effect to 11.0% (-11.4 to 28.9%).

DISCUSSION

The present study demonstrates that losartan compared with placebo reduced SUA in patients with diabetes and nephropathy. This effect appeared to be a drug-specific effect since the ARB irbesartan did not have such an effect. The reduction in SUA during the initial 6 months was in turn associated with a reduction in risk for subsequent cardiovascular events, independently of other cardiovascular risk factors. The short-term effect of losartan on SUA appeared to explain a substantial part of its overall treatment effect on cardiovascular events.

A number of epidemiological studies have indicated that increased SUA is a strong predictor of cardiovascular outcome in the diabetic population, hypertensive population and general population [1–3,10–14]. In patients with type 2 diabetes, higher SUA concentrations were independently associated with a significant increase in the incidence of stroke [2]. An Italian diabetes cohort study demonstrated that each increment in SUA increased the risk of cardiovascular mortality by 27%, independent of other cardiovascular risk factors [1]. These studies imply that SUA may help in cardiovascular risk stratification beyond traditional cardiovascular risk factors. Although the majority of the studies suggest that SUA is an independent risk factor for cardiovascular complications, it should be noted that not all studies are in agreement. A longitudinal population-based

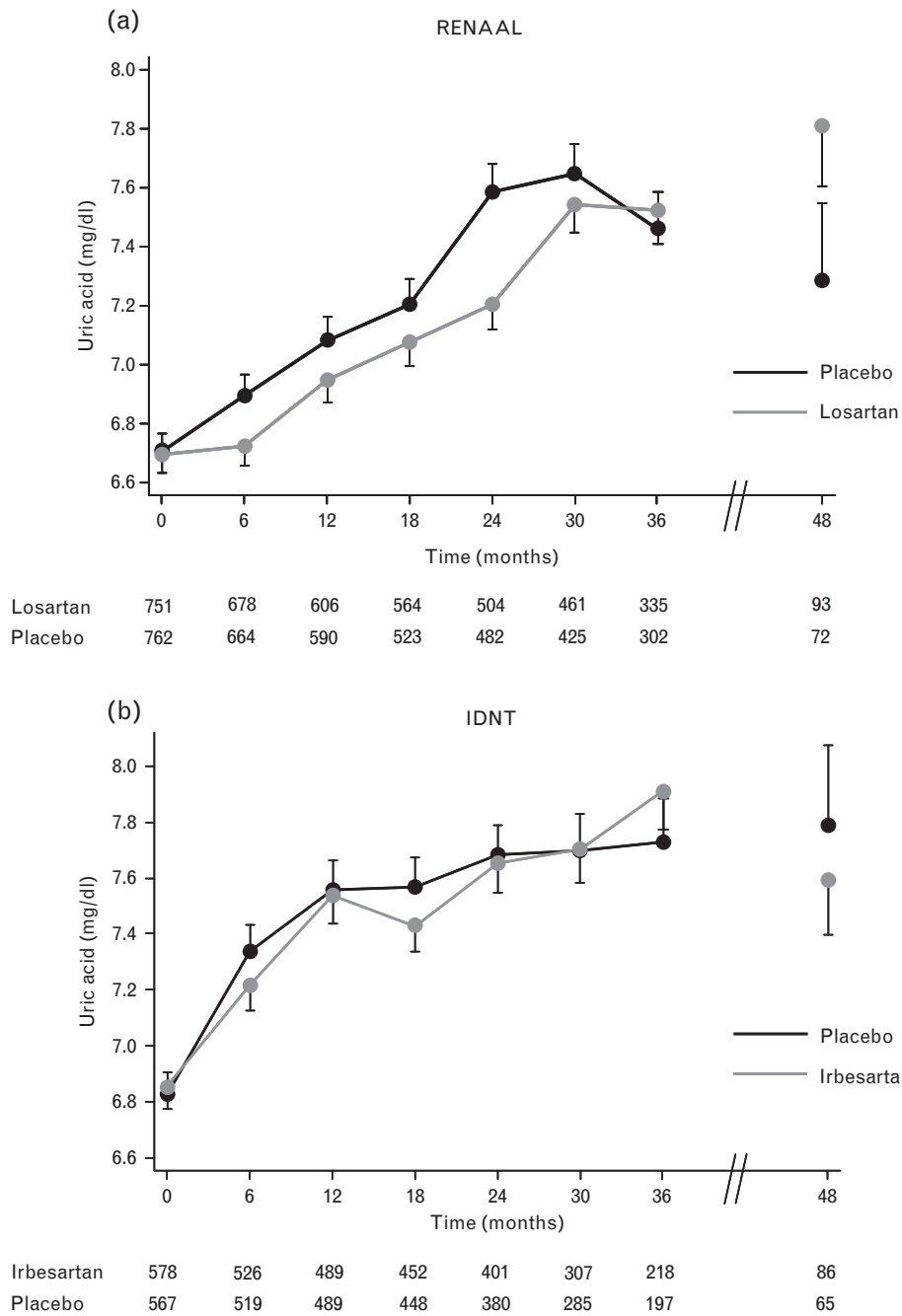


FIGURE 1 Mean uric acid levels during follow-up in the RENAAL (upper graph) and IDNT (bottom graph) trials. The bars indicate the standard error of the mean. The numbers under the graph indicate the number of patients with available measurements.

TABLE 2. Six-month changes in cardiovascular risk parameters in the RENAAL and IDNT trials

Change in parameters	RENAAL		IDNT	
	Placebo (n = 664)	Losartan (n = 678)	Placebo (n = 519)	Irbesartan (n = 526)
Δ Uric acid (mg/dl)	0.2 (1.4)	0.0 (1.3)	0.5 (1.4)	0.4 (1.6)
Δ UACR (%)	+4.7	-28.8	-7.6	-39.3
Δ eGFR (ml/min per 1.73 m ²)	-1.4	-2.2	-2.2	-2.7
Δ Systolic BP (mmHg)	-0.3 (20)	-5.4 (19)	-11.3 (21)	-17.8 (22)

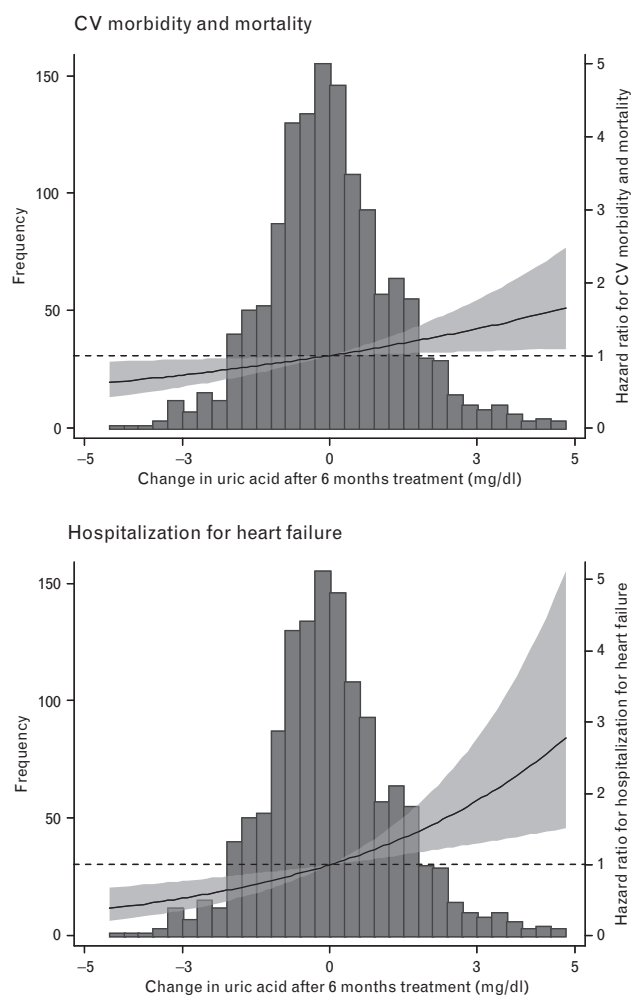


FIGURE 2 Histogram of the 6-month change in SUA in the RENAAL trial. The straight line in the upper graph represents the risk for CV outcomes as a function of the 6-month change in SUA. The straight line in the bottom graph shows the risk of hospitalization for heart failure as a function of the 6-month change in SUA. The grey area represents the 95% confidence interval. CV, cardiovascular; SUA, serum uric acid.

study of patients with type 2 diabetes showed that SUA is not an independent risk factor for cardiovascular mortality [15]. The reasons for the discrepant findings may be attributed to the different study populations with varying cardiovascular risk profiles and the different confounding cardiovascular risk factors considered in the data analyses.

There is some evidence that reductions in SUA, induced by drugs with varying indications, result in cardiovascular protection. In patients with hypertension and left-ventricular hypertrophy, treatment with losartan attenuated the increase in SUA as observed with atenolol treatment [13]. The effect of losartan on SUA contributed in turn to its ultimate cardiovascular-protective effect. Moreover, data from a prospective small-scale randomized controlled trial in patients with chronic kidney disease demonstrated that after 23 months of follow-up, treatment with allopurinol reduced SUA and decreased the incidence of cardiovascular events by more than 50% ($P=0.039$) [16]. On the contrary, some drugs increase SUA, of which diuretics are best known, which may dampen the cardiovascular-protective effect. Indeed, in the Systolic Hypertension in the Elderly

Program (SHEP) trial, the cardiovascular-protective effect of chlorthalidone was restricted to those individuals who did not develop hyperuricemia [17].

The hypouricemic effects of losartan are attributable to its action on the urate transporter 1 (URAT1) located on the brush border membranes of the renal proximal tubule [18]. URAT1 is the key component in the tubular reabsorption of SUA from lumen to cytosol. Time-course studies have indicated that the parent molecule of losartan itself, rather than its active metabolite, is responsible for the inhibition of URAT1 leading to uricosuria [19–21].

Serum uric acid increased in the placebo arm over time and started to increase in the losartan treatment arm after 6 months. A number of factors may explain the rise in SUA. Firstly, in the RENAAL trial, renal function declined with approximately 5 ml/min per 1.73 m² per year. It is possible that the fall in eGFR over time explains, at least in part, the rise in SUA during prolonged follow-up. Secondly, concomitant medication may have influenced SUA during follow-up. It could be possible that increased diuretic therapy during follow-up, required to achieve blood pressure targets, explains the rise in SUA. Indeed, the proportion of patients receiving a diuretic increased from 58% at baseline to 71% at 6 months and to 84% at the time of the primary renal endpoint in the RENAAL trial. However, it should be emphasized that the proportion of patients receiving diuretics was similar between the placebo and losartan group at baseline, 6 months, and at the end of the trial, which makes it unlikely that concomitant diuretic use has biased the data analyses. Finally, the increase in SUA could be explained by a diminished effect of losartan on SUA during prolonged therapy. A previous study has shown that the hypouricemic effects of losartan wane during prolonged treatment, suggesting that the hypouricemic effects of losartan are less pronounced once a new SUA steady state has been reached [22].

The association of change in uric acid after 6-month treatment seems stronger for heart failure than for cardiovascular morbidity and mortality. SUA has been associated with increased vascular stiffness and pulse wave velocity [23]. If a reduction in SUA would translate into decreases in vascular stiffness and pulse wave velocity, this could play a role in the stronger association of changes in SUA with heart failure. High SUA may also be a marker for asymptomatic heart failure with subclinical decreases in cardiac output resulting in less circulating volume perceived by the kidneys. To maintain adequate organ perfusion, there will be an increased tendency for renal tubular reabsorption of sodium, water, and uric acid which may result in a net increase in serum uric acid concentration [24,25]. In this regard, treatment-induced decreases in SUA may be more strongly associated with decreases in extracellular volume than with decrease in tendency for development of atherosclerosis and atherothrombosis, and thereby have a stronger association with benefit for heart failure than with benefit for cardiovascular outcome. It should be emphasized that the RENAAL and IDNT trials were not designed to study the mechanisms between changes in SUA and cardiovascular outcomes or hospitalization for heart failure and as a result our speculations cannot be substantiated by empirical data.

Strength of the present study was that analyses were not restricted to the effects of losartan, but also included a second ARB, irbesartan, which did not change SUA over time. By doing so, we confirmed that the hypouricemic effect of losartan is not a class-specific but instead is a drug-specific effect. A couple of limitations should be addressed as well. First of all, this is a post-hoc analysis of randomized controlled trial data. Since our analyses were not based on randomized data anymore we cannot exclude residual confounding despite our multivariable adjusted analyses. Baseline and 6-month SUA values were based on single measurements. Therefore, the change in SUA could be biased by regression to the mean. However, the fact that we adjusted our multivariate analyses for baseline uric acid and the fact that the 6-month uric acid (residual uric acid) remained a predictor for cardiovascular outcomes suggest that regression to the mean as an explanation for our findings is less likely. Moreover, initial changes in SUA in the IDNT trial were not associated with long-term cardiovascular complications which preclude the possibility of a regression to the mean phenomenon. Finally, by recruiting only patients with diabetes and nephropathy, the results cannot be extrapolated to other patient populations.

Losartan significantly lowers SUA compared to placebo in patients with type 2 diabetes and nephropathy. This effect was not observed with irbesartan in a similar patient population. The magnitude of the initial reduction in SUA during losartan treatment is linearly associated with a lower risk of cardiovascular complications and explains part of the cardiovascular effect of losartan. This supports the hypothesis that in patients with type 2 diabetes and nephropathy SUA may be a modifiable risk factor for cardiovascular disease.

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Conflicts of interest

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