Review Paper

Serum Uric Acid as a Risk Factor for Cardiovascular and Renal Disease: An Old Controversy Revived

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Hyperuricemia is commonly associated with traditional risk factors such as abnormalities in glucose metabolism, dyslipidemia, and hypertension. Recent studies have revived the controversy over the role of serum uric acid as an independent prognostic factor for cardiovascular mortality. The authors review clinical and experimental evidence concerning the role of serum uric acid in the development of cardiovascular and renal damage. Results of trials suggesting that serum uric acid variations over time may have a prognostic impact are also discussed. (J Clin Hypertens. 2006;8:510–518) ©2006 Le Jacq Ltd.

Considerable experimental evidence suggests a causal role for serum uric acid (SUA) in the pathogenesis of hypertension.[1–4] Furthermore, the link between SUA levels and traditional metabolic risk factors is well known, and several large clinical studies have shown that asymptomatic hyperuricemia is associated with cardiovascular (CV) and renal complications. Whether SUA is just an innocent bystander in proximity to unfavorable events or whether it plays a mechanistic role in the development of CV damage is still under debate.

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SUA AND CV EVENTS

Several reports indicate that SUA is independently associated with adverse events, especially in women (Table I). This finding has been confirmed by most, although not all,[11] studies among subjects at higher CV risk, such as those with hypertension[8] and diabetes.[6] Gueyffier et al.[21] analyzed the Individual Data Analysis of Antihypertensive Intervention Trials (INDANA) database and found that the prevalence of CV events associated with increased SUA levels is similar to what is attributable to blood pressure (BP) and total cholesterol. The association of SUA with cerebrocardiovascular disease is even stronger in well-treated hypertensive patients and endures after successful BP control.[8]

A relationship between SUA and events has been observed in patients with overt CV disease. Anker et al.[14] reported that high SUA levels predict unfavorable outcome in patients with moderate-to-severe chronic heart failure, a finding that has also been confirmed in patients with angiographically proven coronary artery disease[19,22] or with previous acute myocardial infarction[20] or stroke.[12,13] Although an increase in SUA could be at least partly due to a subtle impairment of renal function, the association between SUA and CV events seems to be independent of serum creatinine.[8,12–14,21] Preliminary observations suggest that, even in patients on hemodialysis therapy, increased CV risk has been observed in patients with higher SUA levels.[17]

On the other hand, several studies, especially those performed on the general population, have failed to prove the independent nature of these associations, further highlighting the complex relationship between SUA levels and CV outcome.[5,7,10]

Table I. Studies on the Association Between Serum Uric Acid (SUA) and Cardiovascular (CV) Events

Study	Population (M/W)	Age (yr)*	Follow-Up (yr)**	Events	Comparison	Adjusted Risk Estimate†	Independent Role of SUA
Wannamethee et al.[5]	7688 men	40–59	16.8	Fatal or nonfatal CHD	Highest vs. lowest quintile	1.55	No
Lehto et al.[6]	1017 patients with T2DM (551/466)	58	7.2	Fatal or nonfatal stroke	SUA >5.0 mg/dL	1.91	Yes
Culleton et al.[7]	6763 subjects from general population (3075/3688)	47	4 (c)	1) Overall mortality 2) CV diseases 3) CHD	Highest vs. lowest quintile	1) ns (M); 3.63 (W) 2) ns (M); 5.69 (W) 3) ns (M); 4.11 (W)	No
Liese et al. *Epidemiology*. 1999	1044 men from general population	45–64	8 (c)	1) All-cause mortality 2) CV mortality 3) Myocardial infarction	SUA >6.3 mg/dL vs. <5.4 mg/dL	1) 2.8 2) 2.2 (ns) 3) 1.7 (ns)	1) Yes 2) No 3) No
Alderman et al.[8]	7978 mild-to-moderate hypertensives (4883/3095)	53	6.6	CV events	SUA ≥7.6 mg/dL (M); ≥6.3 mg/dL (W) vs. lowest quartile	1.48	Yes
Moriarity et al. *Ann Epidemiol*. 2000	13,504 healthy subjects (5904/7600)	45–64	8 (c)	CHD	SUA ≥7.6 mg/dL (M); ≥6.3 mg/dL (W) vs. lowest quartile	1.02 (ns) (M) 1.18 (ns) (W)	No
Fang and Alderman. *JAMA*. 2000	5926 subjects from general population	48	16.4	CV mortality	SUA ≥7 mg/dL (M); ≥5.6 mg/dL (W) vs. lowest quartile	1.77 (M) 3.0 (W)	Yes
Franse et al.[9]	4327 patients with hypertension (1860/2467)	71	5 (c)	1) CV mortality 2) CHD 3) Stroke 4) All-cause mortality	SUA ≥6.7 mg/dL (M); ≥5.8 mg/dL (W) vs. lowest quartile	1) 1.32 2) 1.43 3) 0.85 (ns) 4) 1.05 (ns)	1) Yes 2) Yes 3) No 4) No
Verdecchia et al. *Hypertension*. 2000	1720 patients with primary hypertension (920/800)	51	4	1) CV events 2) Fatal CV events 3) All-cause mortality	SUA ≥6.2 mg/dL (M) ≥4.6 mg/dL (W) vs. second quartile	1) 1.73 2) 1.96 3) 1.63	Yes
Sakata et al.[10]	8172 subjects from general population (3596/4576)	49	14 (c)	All-cause mortality	SUA ≥6.6 mg/dL (M) ≥5.0 mg/dL (W) vs. lowest quartile	NS (M) 2.25 (W)	No
Mazza et al. *Eur J Epidemiol*. 2001	3282 elderly subjects from general population (1281/2001)	74	14 (c)	Stroke	SUA >6.5 mg/dL	1.61	Yes
Wang et al. *Hypertension*. 2001	1873 elderly Chinese patients with ISH (1207/666)	66	3	1) CV mortality 2) Fatal stroke	Per additional SUA 0.8 mg/dL	1) 1.14 2) 1.34	Yes

Table I. Studies on the Association Between Serum Uric Acid (SUA) and Cardiovascular (CV) Events *(continued)*

Study	Population (M/W)	Age (yr)*	Follow-Up (yr)**	Events	Comparison	Adjusted Risk Estimate†	Independent Role of SUA
De Leeuw et al.[11]	4556 elderly patients with ISH (1500/3056)	70	2	1) Overall mortality 2) CV mortality 3) CV events	Per additional SUA 0.8 mg/dL	1) ns 2) ns 3) 1.09	No
Bickel et al. *Am J Cardiol.* 2002	1017 patients with angiographically defined coronary artery disease (747/270)	62	2.2	Overall mortality	SUA >7.1 mg/dL vs. lowest quartile	2.71	Yes
Wong et al.[12]	354 stroke survivors	69	2.8	1) CV mortality 2) All-cause mortality	SUA >5.4 mg/dL	1) 3.1 2) ns	1) Yes 2) No
Weir et al.[13]	2498 stroke survivors (1199/1299)	72	2.7	Major vascular events	Per additional SUA 1.68 mg/dL	1.27	Yes
Anker et al.[14]	1) 112 patients with chronic HF (101/11) 2) 182 patients with chronic HF (149/33)	59	5 (c)	Overall mortality (in 12 months)	SUA ≥9.5 mg/dL	1) 3.9 2) 7.14	Yes
Niskanen et al. *Arch Intern Med.* 2004	1423 healthy Finnish men	52	11.9	CV mortality	SUA ≥5.9 mg/dL	4.77	Yes
Hoieggen et al.[15]	9193 hypertensive patients with LVH (4230/4963)	67	4.8 (c)	Major vascular events	Per additional SUA 0.17 mg/dL	1.006 (ns) (all) 1.006 (ns) (M) 1.013	Yes (W)
Athyros et al.[16]	1600 patients with established CHD (1256/344)	59	3	CV events	Per additional SUA 1 mg/dL	1.29	Yes
Hsu et al.[17]	146 hemodialysis patients (68/78)	60	1	All-cause mortality	≥80th percentile vs. lower levels	5.67	Yes
Hakoda et al. *J Rheumatol.* 2005	10615 Japanese atomic bomb survivors (3860/6755)	49	24.9	1) All-cause mortality 2) CV mortality	SUA ≥8.0 mg/dL (M) ≥7.0 mg/dL (W) vs. lower levels	1) 1.22 (M); 1.63 (W) 2) ns (M); 1.79 (W)	1) Yes 2) Yes (W)
Simon et al.[18]	2763 postmenopausal women	66	4.1 (c)	CHD	Per additional SUA 1.3 mg/dL	1.05	No
Madsen et al.[19]	1596 patients with angiographically defined coronary artery disease (1245/351)	65	2.6	All-cause mortality	Highest vs. lowest quintile	1.5	Yes: patients not using diuretics No: diuretics users
Kojima et al.[20]	1124 consecutive patients hospitalized within 48 hours of onset of symptoms of AMI (800/324)	67	30 days	All-cause mortality	SUA ≥6.8 mg/dL vs. lowest quartile	3.7	Yes

M=men; W=women; CHD=coronary heart disease; T2DM=type 2 diabetes mellitus; ISH=isolated systolic hypertension; HF=heart failure; LVH=left ventricle hypertrophy; AMI=acute myocardial infarction; *expressed as mean or range; **expressed as mean except where expressed as cumulative (c) years; †each report is statistically significant except when noted as non-significant (ns)

SUA AND RENAL EVENTS

Elevated SUA is a frequent finding in patients with kidney disease and may be the direct consequence of decreased renal clearance. However, hyperuricemia per se may be involved in the induction or aggravation of renal dysfunction.[23] Acute renal failure caused by marked hyperuricosuria, as observed in patients with tumor lysis syndrome, is a well recognized clinical entity. Moreover, subjects with recurrent gout attacks may develop chronic kidney disease, but the coexistence of vascular disease and age are better predictors of reduction in renal function.[24] A causal role for uric acid in renal disease is still under debate (Table II).

Recent epidemiologic studies have demonstrated that uric acid is an independent risk factor for the deterioration of glomerular filtration rate in the general population[27–29] as well as in patients with glomerulonephritis.[26,27] SUA levels proved to be a predictor of end-stage renal disease in a prospective cohort of 48,117 Japanese subjects, after adjusting for common confounding variables such as proteinuria, high BP, and dyslipidemia.[28] On the basis of multivariate analysis, Domrongkitchaiporn et al.[29] identified systolic hypertension, hyperuricemia (>6.3 mg/dL), and high body mass index as promoters of the development of chronic kidney disease over a 12-year follow-up period.[29] Increased uric acid levels are also believed to contribute to the deterioration of glomerular filtration rate in IgA nephropathy; hyperuricemia increased the risk of progression of kidney disease 4.6-fold after adjusting for proteinuria, hypertension, diabetes, dyslipidemia, age, gender, and body mass index.[26] At variance with these results, hyperuricemia was not found to predict renal deterioration in the Modification of Diet in Renal Disease (MDRD) study[30] or in other more recent studies in Japanese cohorts.[25,31]

Altogether these findings suggest, but do not offer definitive proof of, the role of SUA as an independent renal risk factor, especially in women and in patients who initially have normal renal function.[27,28]

IS SUA A PROMOTER OF CV AND RENAL DAMAGE?

The relationship between SUA and the development of subclinical CV and renal damage has been under investigation for several years. In several cross-sectional and prospective reports, SUA levels were found to be associated with carotid intima–media thickening and/or carotid plaque (Table III), but in some studies an independent correlation was observed only in a subset of patients[34,35] or could not be confirmed at all.[39]

As for cardiac end points, a link between SUA levels and electrocardiographic abnormalities,[32]

Table II. Studies on the Association Between Serum Uric Acid (SUA) and Renal Events

Study	Population (M/W)	Age (yr)*	Follow-Up (yr)**	Definition of Renal Events	Comparison	Adjusted Risk Estimate†	Independent Role of SUA
Tomita et al.[25]	49,413 Japanese workers (M)	25–60	5.4	Renal failure	SUA ≥8.5 mg/dL vs. <5.0–6.4 mg/dL	8.52	No
Syrjanen et al.[26]	1) 223 patients with IgAN (141/82) 2) Subgroup: 181 patients with IgAN with normal renal function	41	10 (c)	SCr ≥1.4 mg/dL (M); ≥1.2 mg/dL (W) at follow-up; >20% elevation from baseline	SUA >7.5 mg/dL (M); >5.7 mg/dL (W) vs. lower	1) 2.2 (ns) 2) 4.6	1) No 2) Yes
Iseki et al.[27]	6210 Japanese from general population with normal SCr levels (4047/2163)	48	2 (c)	SCr ≥1.4 mg/dL (M); ≥1.2 mg/dL (W) at follow-up	SUA ≥8 mg/dL vs. <5 mg/dL	2.91 (M) 10.39 (W)	Yes
Iseki et al.[28]	48,117 Japanese from general population (22,949/25,228)	52	7 (c)	End-stage renal disease	SUA ≥7 mg/dL (M); ≥6 mg/dL (W) vs. lower	2.0 (M) (ns) 5.8 (W)	Yes (W)
Domrongkitchaiporn et al.[29]	3499 Thai subjects	35–55	12 (c)	1) GFR <60 mL/min at follow-up 2) SCr ≥1.49 mg/dL (M); ≥1.13 mg/dL (W) at follow-up	SUA >6.3 mg/dL vs. <4.5 mg/dL	1) 1.82 2) 1.75	Yes

M=men; W=women; IgAN=IgA nephropathy; SCr=serum creatinine; GFR=glomerular filtration rate; *expressed as mean or range; **expressed as mean or cumulative (c) years; †each report is statistically significant except when noted as nonsignificant (ns)

Table III. Studies on the Association Between Serum Uric Acid (SUA) and Target Organ Damage (TOD)

Study	Population (M/W)	Age (yr)*	TOD	Correlation Between SUA and TOD	Independent Role of SUA
Persky et al.[32]	24,997 subjects	18–64	ECG abnormalities	Yes	Yes (W)
Mazza et al. *Metabolism*. 2000	130 T2DM patients (60/70)	53	Carotid abnormalities	Yes	Yes
Bo et al. *Eur J Clin Invest*. 2001	1186 T2DM patients (628/558)	65	1) Microalbuminuria by UAE 2) Macroalbuminuria by UAE	Yes	1) No 2) Yes
Tuttle et al.[33]	277 patients admitted for elective coronary angiography (195/82)	62	Angiographically defined coronary artery disease severity	Yes (W)	No
Ishizaka et al.[34]	8141 general population (5470/2671)	57	1) Carotid plaque 2) Carotid IMT	Yes	1) Yes (M without MS) 2) No
Kawamoto et al. *Intern Med*. 2005	919 elderly persons (398/521)	75	Carotid IMT	Yes	Yes
Tsioufis et al.[35]	842 patients with HTN (406/436)	53	1) LVH (echo) 2) Microalbuminuria by UAE	1) No 2) Yes	1) No 2) Yes
Viazzi et al.[36]	425 patients with HTN (265/160)	47	1) LVH (echo) 2) Carotid abnormalities 3) Microalbuminuria by ACR	1) Yes (W) 2) Yes (W) 3) No	1) Yes (W) 2) Yes (W) 3) No
Tseng *Kidney Int.* 2005	343 patients with T2DM (144/199)	63	Albuminuria by ACR	Yes	Yes (patients without HTN)
Wu et al.[37]	1005 IgA nephropathy	31	Arterial-arteriolar lesions (light microscopy semiquantitative scoring)	Yes	Yes
Myllymaki et al.[38]	202 patients with IgA nephropathy	41	Tubular atrophy (light microscopy semiquantitative scoring)	Yes	Yes
Iribarren et al.[39]	11,488 subjects free of cardiovascular disease (4966/6522)	45–64	Carotid abnormalities	Yes (W, white M)	No

M=men; W=women; ECG=electrocardiographic; T2DM=type 2 diabetes mellitus; UAE=urinary albumin excretion; IMT=intima–media thickness; MS=metabolic syndrome; HTN=hypertension; LVH (echo)=left ventricular hypertrophy assessed by echocardiogram; ACR=albumin/creatinine ratio; *expressed as mean or range

left ventricular hypertrophy,[28,35] and coronary artery disease[33] has been reported. It is noteworthy that this association was found to be stronger in women than in men.[32,33,36] The lack of relationship between left ventricular hypertrophy and SUA reported by Tsioufis et al.[35] may have been due to the failure to stratify patients by gender.

SUA has also been described as an independent correlate of the urinary albumin excretion rate both in patients with type II diabetes (Table III) and with primary hypertension.[35,36] Moreover, in patients with IgA nephropathy, the severity of intrarenal arterial lesions[37] and of tubular atrophy,[38] as assessed at biopsy, were closely correlated with SUA levels, regardless of other well known markers of adverse renal outcome.

In a recent cross-sectional study on untreated patients with primary hypertension,[36] we observed an independent association between the presence and degree of early signs of subclinical organ damage and SUA in women (Figure). These findings provide information relating to the association of SUA to CV events and renal progression. Subclinical organ damage represents an intermediate step between exposure to risk factors and occurrence of overt disease and has previously been shown to be a potent predictor of major CV and renal events. The correlation between SUA and target organ damage that we and others have observed in women compared with men (Table III) may account for the previously reported CV and renal predictive power of uric acid in women (Tables I and II).

Table IV. Drugs With Proven or Potential Serum Uric Acid-Lowering Effect

Drug(s)	Mechanism(s) of Action	Reference(s)	Effect*
Allopurinol	Xanthine oxidase inhibition	Johnson et al.[53] Rashid and William-Olsson[54] Tabayashi et al.[55]	Yes
		Gavin and Struthers[56]	No
Losartan	Uricosuric Insulin-sensitizing	Hoieggen et al.[15]	Yes
Estrogen + progestin	Uricosuric	Simon et al.[18]	No
Atorvastatin	Uricosuric Insulin-sensitizing	Athyros et al.[16] Milionis et al.[58]	Yes
Sulfinpyrazone (antiplatelet)	Uricosuric	The Anturane Reinfarction Trial. *N Engl J Med*. 1978	Yes
Cilostazol (antiplatelet)	Uricosuric	Mitsuhashi et al. *Endocr J*. 2004	Yes
Fenofibrate (PPAR-α)	Uricosuric PPAR agonist Insulin-sensitizing	Elisaf et al. *J Cardiovasc Pharmacol.* 1999 Seber et al. *Diabetes Res Clin Pract.* 2005	?
Rosiglitazone (PPAR-γ)	PPAR agonist Insulin-sensitizing	Tsunoda et al. *Am J Hypertens*. 2002	?
Metformin	Insulin-sensitizing	Gokcel et al. *Diabetes Obes Metab*. 2002	?
Sibutramine–orlistat (weight loss)	Insulin-sensitizing	Gokcel et al. *Diabetes Obes Metab*. 2002	?
Low-energy diet	Insulin-sensitizing	Tsunoda et al. *Am J Hypertens*. 2002	?
Amlodipine	Uricosuric	Sennesael et al. *Am J Kidney Dis*. 1996 Chanard et al. *Nephrol Dial Transplant*. 2003	?

PPAR=peroxisome proliferator-activated receptors; ?=potential, but still unproven; *attributed effect on renal and cardiovascular disease

ROLE OF SUA IN THE PATHOGENESIS OF VASCULAR DAMAGE

Although experimental evidence supports a role for SUA in the pathogenesis of vascular damage,[23] the issue remains controversial. SUA may exert its detrimental effects by entering vascular smooth muscle cells via an organic anion transport system,[40] and thus activating mitogen-activated protein kinases[3,41,42] and nuclear transcription factors.[3] Subsequently, cyclooxygenase-2,[37] platelet-derived growth factor,[3,43] and various inflammatory mediators, including C-reactive protein[42] and monocyte chemoattractant protein-1[44] are stimulated. The complex of these events may lead to vascular smooth muscle cell hypertrophy. Uric acid may also be implicated in the development of endothelial dysfunction and atherosclerosis by inactivating NO and arresting the proliferation of endothelial cells.[42,45] Hyperuricemic rats have been reported to show a decrease in serum nitrites, a reflection of NO production. The combination of a proliferative effect on vascular smooth muscle cells and an inhibitory effect on endothelial cells may account for the ability of SUA to induce small-vessel disease in experimental models.

Some human studies have investigated the relationship between SUA levels and endothelial damage. In high-risk patients with[46] or without[47] CV disease, some studies have shown a relationship between hyperuricemia and impaired flow-mediated vasodilation, a measurement of in vivo vascular NO activity. These findings, however, have not been confirmed in a recent study, which failed to show any effect of acute IV infusion of uric acid on endothelial function.[48] Thus, there is also some debate regarding the exact role of elevated SUA in the pathogenesis of renal and cardiac disease.[49]

Although renin is increased in the kidney of the hyperuricemic rat and angiotensin-converting enzyme inhibition ameliorates renal injury,[2] the mechanism by which uric acid increases renin–angiotensin system activity is not clear. It should be noted that uric acid may also act as an antioxidant,[50] due to its ability to preferentially react with peroxynitrite, thus leading to stabilization of endothelial NO synthase activity.[51] Uric acid has also been shown to stimulate the expression of extracellular superoxide dismutase, thereby conferring antioxidant activity.[52]

In summary, SUA plays several pathophysiologic roles both at the cellular and tissue level. The net balance of these contrasting mechanisms may result in adverse vascular effects.

SUA AS A POTENTIAL TARGET FOR TREATMENT

Available data on the prognostic impact of the pharmacologic lowering of SUA are scanty, and to date,

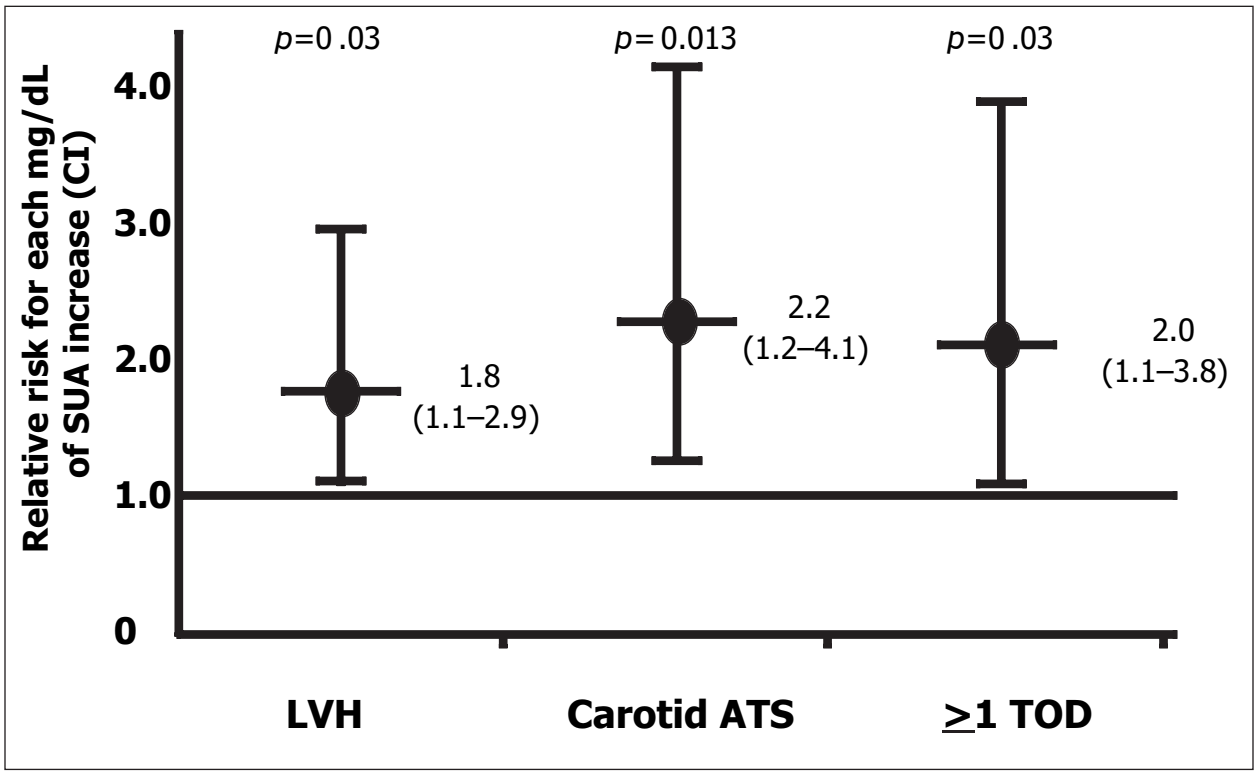

Figure. Relative risk in women (with 95% confidence interval [CI]) for left ventricular hypertrophy (LVH), carotid atherosclerosis (ATS), and early signs of subclinical target organ damage (TOD) in at least one organ, for each mg/dL rise in serum uric acid (SUA)

only a few randomized studies have described any CV benefits related to SUA changes (Table IV).

Allopurinol

Small studies have suggested that allopurinol, a widely used uric acid production blocker that inhibits xanthine oxidase activity, can improve endothelial function in patients with heart failure.[59,60] There are data suggesting that lowering uric acid levels did not result in improvement in outcome in patients with heart failure.[53–57]

Losartan

This angiotensin II receptor blocker lowers SUA by interfering with urate reabsorption in the renal proximal tubule.[61] This effect has been credited with at least some of the benefit in stroke outcome in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study,[15] which compared an angiotensin receptor blocker with an atenolol-based treatment program.

Hormones

Estrogens have been reported to lower SUA levels in hyperuricemic patients.[62] Although the exact mechanism is unclear, it has been suggested that they might increase uric acid renal clearance.[63] Recent studies with estrogen and progestin reported lowered SUA (–0.2 mg/dL) regardless of baseline levels, but lowering did not affect overall risk for CV events.[18] Thus, this issue cannot be considered settled.

Atorvastatin

In one study,[16] treatment with atorvastatin was associated with a 24% reduction in coronary heart disease-related events for each mg/dL decrease in SUA levels, regardless of changes in low- or high-density lipoprotein cholesterol.[16] The pathophysiologic mechanisms underlying the hypouricemic effect of atorvastatin are a matter of speculation; whether this effect is specific for this molecule or whether it is a class effect remains unclear. It has been hypothesized that uric acid production may be reduced by effects on carbohydrate metabolism; improvements in insulin sensitivity have been observed with atorvastatin in elderly patients with dyslipidemia and non–insulin-dependent diabetes.[64] It has been reported that the hypouricemic action of atorvastatin is, at least in part, mediated by an increase in the fractional excretion of uric acid.[58]

An interesting finding regarding the possible prognostic role of SUA comes from the Systolic Hypertension in the Elderly Program (SHEP).[9] After

1 year of treatment with 12.5–25 mg chlorthalidone, the benefits of the diuretic on coronary events were offset in patients who experienced an increase in SUA ≥1 mg/dL.[9] However, over a 5-year follow-up, diuretic treatment was associated with significantly fewer CV events compared with placebo.[65] To date, analyses of data on changes in SUA over the entire study period have not been published; the issue remains controversial. Furthermore, in the context of a decline in age-adjusted CV mortality, recent speculations about the effects of diuretic use and end-stage renal disease incidence are unproven.[66] Recent data[67] from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) indicate that CV events in diuretic-treated subjects were adversely affected in patients with varying degrees of renal impairment. Based on these data, there appears to be little reason to withhold the use of these agents in hypertensive patients if they are required to lower BP.

CONCLUSIONS

At present, there is insufficient evidence to recommend the routine use of SUA-lowering therapies in patients at high CV risk with asymptomatic hyperuricemia. Large-scale, prospective intervention trials are warranted, however, to ascertain the exact role that reducing SUA levels will play in reducing CV risk.

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