Relation Between Serum Uric Acid and Risk of Cardiovascular Disease in Essential Hypertension

The PIUMA Study

Paolo Verdecchia, Giuseppe Schillaci, GianPaolo Reboldi, Fausto Santeusanio, Carlo Porcellati, Paolo Brunetti

Abstract—The question of serum uric acid as an independent risk factor in subjects with essential hypertension remains controversial. For up to 12 years (mean, 4.0) we followed 1720 subjects with essential hypertension. At entry, all subjects were untreated and all were carefully screened for absence of cardiovascular disease, renal disease, cancer, and other important disease. Outcome measures included total cardiovascular events, fatal cardiovascular events, and all-cause mortality. During 6841 person-years of follow-up there were 184 cardiovascular events (42 fatal) and 80 deaths from all causes. In the 4 quartiles of serum uric acid (division points: 0.268, 0.309, and 0.369 mmol/L [4.5, 5.2, and 6.2 mg/dL] in men; 0.190, 0.232, and 0.274 mmol/L [3.2, 3.9, and 4.6 mg/dL] in women), the rate (per 100 person-years) of cardiovascular events was 2.51, 1.48, 2.66, and 4.27, that of fatal cardiovascular events was 0.41, 0.33, 0.38, and 1.23, and that of all-cause deaths was 1.01, 0.55, 0.93, and 2.01, respectively. The relation between uric acid and event rate was J-shaped in both genders. After adjustment for age, gender, diabetes, total cholesterol/HDL cholesterol ratio, serum creatinine, left ventricular hypertrophy, ambulatory blood pressure, and use of diuretics during follow-up, uric acid levels in the highest quartile were associated with increased risk for cardiovascular events (relative risk, 1.73; 95% CI, 1.01 to 3.00), fatal cardiovascular events (relative risk, 1.96; 95% CI, 1.02 to 3.79), and all-cause mortality (relative risk, 1.63; 95% CI, 1.02 to 2.57) in relation to the second quartile. In untreated subjects with essential hypertension, raised uric acid is a powerful risk marker for subsequent cardiovascular disease and all-cause mortality. (Hypertension. 2000;36:1072-1078.)

Key Words: uric acid ■ blood pressure ■ cardiovascular disease ■ hypertension, essential ■ blood pressure monitoring ■ hypertrophy, left ventricular

Several cohort studies conducted over the past 5 decades showed a link between serum uric acid (SUA) and subsequent cardiovascular (CV) disease.1–15 However, in some of these studies such association did not remain significant after adjustment for concomitant risk factors for CV disease2,4,5,12,15 or it was detected only in women.6,8,10 Thus, the role of SUA as an independent risk marker remains controversial.16 An increase in SUA might be simply a marker of obesity, hyperinsulinemia and glucose intolerance,17,18 hypertension,5 hyperlipidemia19 and renal disease.20,21

The assessment of the independent prognostic value of SUA is clinically relevant in the specific setting of essential hypertension, in which hyperuricemia is frequent22 and cardiovascular risk stratification is of utmost importance. In a recent cohort study in subjects with hypertension,14 the association between SUA and future CV events remained significant after adjustment for concomitant diuretic therapy, previous CV events, and other risk factors including office blood pressure (BP). In contrast, pretreatment SUA was not an independent predictor of CV events in the setting of the European Working Party on High Blood Pressure in the Elderly trial.23

Because of the discrepancy between these findings, we analyzed the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) database to clarify the independent prognostic value of SUA in a large cohort of initially untreated and apparently healthy subjects with essential hypertension.

Methods

PIUMA Study

The design of the PIUMA study has been reported previously.24,25 Office BP had to be ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic on ≥3 visits, and all of the subjects fulfilled the following inclusion criteria: no previous antihypertensive treatment or treat-
ment withdrawn from ≥4 weeks; no clinical or laboratory evidence of heart failure, coronary artery disease, significant valvular defects, secondary causes of hypertension, or other concomitant important disease; ≥1 valid BP measurement per hour over the 24 hours.

**Procedures**

The present analysis involved 1720 subjects enrolled from June 1986 to December 1996, for whom SUA levels were available. An additional group of 429 PIUMA subjects, who were excluded from the study because SUA levels were not available for technical or administrative reasons, did not differ by age, gender distribution, body mass index, prevalence of diabetes and left ventricular (LV) hypertrophy, office and ambulatory BP, total cholesterol (TC), HDL cholesterol (HDL-C) and LDL cholesterol (LDL-C), triglycerides, and creatinine (all $P=NS$) from the study population. BP was measured by a physician with a calibrated mercury sphygmomanometer in the outpatient clinic, with the subject sitting and relaxed for ≥10 minutes. The average of 3 measurements was used for analysis. Ambulatory BP was recorded with an oscillometric device (SpaceLabs 5200, 90202, and 90207, SpaceLabs), and measurements were automatically taken every 15 minutes throughout the 24 hours. Data editing was done as previously described.$^{20}$ Standard 12-lead ECG was recorded in all subjects at 25 mm/s and 1 mV/cm calibration. LV hypertrophy was diagnosed by using a score recently developed in our laboratory$^{26}$ and prognostically validated.$^{27}$

**Follow-Up**

Subjects were followed by their family doctors in cooperation with the colleagues of the outpatient clinic of the referring hospital and treated with the aim of reducing office BP <140/90 mm Hg, with standard lifestyle and pharmacological measures used. There were frequent contacts with family doctors and telephone interviews with patients to ascertain the vital status and the occurrence of major cardiovascular complications. All interviews were conducted without knowledge of the patient’s data.

**End Point Evaluation**

Hospital record forms and other source documents of patients who had an end point event were reviewed in conference by the authors of this study. CV events included myocardial infarction, unstable angina with concomitant ischemic ECG changes, stroke, transient cerebral ischemia, symptomatic aortoiliac occlusive disease verified at angiography, congestive heart failure requiring hospitalization, renal failure requiring dialysis, and death from all causes. The international standard criteria used to diagnose outcome events in the PIUMA study have been described elsewhere.$^{24,25,27}$

**Data Analysis**

Statistical analyses were performed with SAS/STAT (SAS Institute) release 6.12. Parametric data are reported as mean±SD. Standard descriptive and comparative statistical analyses were undertaken. In 2-tailed tests, probability values $<0.05$ were considered statistically significant. For the subjects who had multiple events, survival analysis was based on the first event. Survival curves were estimated by means of the Kaplan-Meier product-limit method$^{28}$ and compared by the Mantel (log-rank) test.$^{29}$ The effect of prognostic factors on survival was evaluated by means of the Cox model.$^{30}$ We tested the following variables: age (years), gender (women, men), diabetes (no, yes), serum cholesterol (mmol/L), serum creatinine (mmol/L), smoking habits (current smokers, previous smokers, never-smokers), body mass index (kg/m²), LV hypertrophy at ECG$^{29,27}$ (no, yes), and diuretic therapy during the follow-up (yes, no). Diabetes mellitus was defined by a fasting blood glucose level ≥140 mg/dL, a random nonfasting blood glucose level ≥200 mg/dL, or the use of an oral hypoglycemic agent or insulin. Diastolic BP and pulse pressure (PP) were tested as average 24-hour values because their predictive value is superior to that of office BP.$^{31}$ Because the rate of CV events and all-cause mortality did not increase linearly with SUA (Figure 1), it was not tested as a continuous variable in the Cox model.$^{30}$ Consequently, subjects were grouped according to the gender-specific quartile of SUA distribution (division points: 0.268, 0.309, and 0.369 mmol/L [4.5, 5.2, and 6.2 mg/dL]) in men; 0.190, 0.232, and 0.274 mmol/L [3.2, 3.9, and 4.6 mg/dL] in women).

**Results**

**Patient Characteristics**

Table 1 presents demographic and clinical characteristics for the study population. Several baseline characteristics differed among the 4 quartiles of distribution of SUA. Subjects in the highest quartile showed a cluster of demographic, biochemical, and BP features potentially associated with increased CV risk. The prevalence of subjects with concomitant diabetes showed a J-shaped distribution, with higher values in the first than in the second quartile ($P<0.01$), and another rise in the third and fourth quartile. SUA showed a direct association with serum creatinine ($r=0.31, P<0.001$), TC/HDL-C ($r=0.23, P<0.001$), and body mass index ($r=0.28; P<0.001$) and a weaker although significant direct association with glucose ($r=0.07; P<0.01$) and average 24-hour systolic ($r=0.11; P<0.01$) and diastolic ($r=0.11; P<0.01$) BP. There was also an inverse association between SUA and HDL-C ($r=-0.22; P<0.001$).

**Antihypertensive Therapy**

At the follow-up contact, 38.8% of the subjects were receiving lifestyle measures alone, 11.4% β-blockers alone or combined with other agents, 22.3% ACE inhibitors or calcium antagonists alone or combined, and 27.5% other drug combinations. Such distribution did not differ among the 4 quartiles of SUA ($P=NS$). However, the proportion of subjects treated with diuretics, alone or combined with other agents, during follow-up, was 13.0%, 14.2%, 16.4%, and 19.4%, respectively, in the 4 quartiles of pretreatment SUA ($P=0.008$).

**Prognostic Value of SUA**

The subjects who developed a first CV event during follow-up were 184 (10.7%). In the 429 subjects excluded from the study because SUA determination was not available, there were 46 CV events (10.7%; $P=NS$ versus the study group). There were 48 subjects with stroke, 36 with myocardial infarction, 10 with sudden cardiac death, 5 with cardiac death from other causes, 20 with transient cerebral ischemia, 21 with unstable angina, 5 with aortocoronary bypass sur-

![Figure 1](https:// hyper.ahajournals.org/)

**Figure 1.** Unadjusted rate of total CV events, fatal CV events, and all-cause deaths in the 4 quartiles of the distribution of serum uric acid. Division points for quartiles: 0.268, 0.309, and 0.369 mmol/L [4.5, 5.2, and 6.2 mg/dL] in men; 0.190, 0.232, and 0.274 mmol/L [3.2, 3.9, and 4.6 mg/dL] in women.
15 with heart failure requiring hospitalization, 19 with new-onset aortoiliac occlusive disease, and 5 with renal failure requiring dialysis. Fifteen of the 42 fatal CV events were preceded by a nonfatal event, and the others occurred as first clinical manifestation. In detail, there were 8 cases of fatal stroke, 5 cases of fatal myocardial infarction, 13 cases of sudden cardiac death, and 16 cases of non–sudden cardiac death. Overall, there were 80 deaths from any cause.

As shown in Table 2, the subjects who had a CV event were older that the subjects who did not. Moreover, diabetes and LV hypertrophy were more common among the subjects with future CV events, who also showed a higher BP (both office and ambulatory) and higher levels of TC, TC/HDL-C, triglycerides, glucose, creatinine, and SUA. In the 4 quartiles of SUA distribution, the rate (per 100 person-years) of future CV events was 2.51, 1.48, 2.66, and 4.27; that of fatal CV events was 0.41, 0.05, 0.93, and 1.23; and that of all-cause deaths was 1.01, 0.55, 0.93, and 2.01, respectively (all \( P < 0.01 \); log-rank test). The rate of total CV events, fatal CV events, and all-cause deaths showed a J-shaped distribution in both genders (Figure 1), with the bottom level in the second quartile of SUA distribution (268 to 309 mmol/L [4.5 to 5.2 mg/dL] in men; 190 to 232 mmol/L [3.2 to 3.9 mg/dL] in women).

Results of multivariate survival analysis are reported in Table 3. After adjustment for age, gender, diabetes, TC/HDL-C, LV hypertrophy, and 24-hour BP, SUA levels in the highest quartile were associated with increased risk for total CV events (relative risk, 1.73; 95% CI, 1.01 to 3.00) in comparison with the second quartile. Furthermore, SUA levels in the highest quartile also predicted an increased risk of fatal CV events (relative risk, 1.96; 95% CI, 1.02 to 3.79) and all-cause deaths (relative risk, 1.63; 95% CI, 1.02 to 2.57) in relation to the second quartile. Serum creatinine, 24-hour diastolic BP, and diuretic treatment during follow-up did not enter the final model. The age-adjusted and TC/HDL-C–adjusted 4-year risk of CV disease, standardized to different levels of significant explanatory variables in either gender, is reported in Figure 2.

Discussion

In our large cohort of subjects with essential hypertension, pretreatment SUA showed an association with subsequent CV events and death from all causes. In the highest quartile of SUA (>0.369 mmol/L [6.2 mg/dL] in men; >0.274 mmol/L [4.6 mg/dL] in women), such association was clinically consistent and independent of many potential confounders including age, gender, body mass index, diabetes, TC/HDL-C, serum creatinine, LV hypertrophy, ambulatory BP, and diuretic treatment during follow-up. At entry into the study, when SUA was determined, all subjects were untreated, important concomitant disease were excluded, and,
in addition to traditional risk markers, ambulatory BP was available in all subjects. Consequently, the PIUMA database offered the unique opportunity to test the independent prognostic value of pretreatment SUA in a large, apparently healthy hypertensive population without the disturbing influence of several powerful confounding factors including diuretic therapy, race, and overt concomitant disease.

Comparison With Previous Studies

Our results are in agreement with the findings of a study by Alderman et al.,\(^{14}\) who found an association between SUA and subsequent CV events in a large multiracial population of subjects with essential hypertension. In that study, CV disease risk was better predicted by in-treatment than by pretreatment SUA, and such association persisted after adjustment for diuretic therapy, serum creatinine, and race in addition to traditional risk factors. However, the prognostic value of SUA was not significant in whites as well as in subjects without a history of CV disease.\(^{18–21}\) The Systolic Hypertension in the Elderly Program\(^ {32}\) and the Chicago Studies\(^ {6}\) included several individuals with previous CV events. Furthermore, the effect of diuretics on glucose and lipids,\(^ {33}\) in addition to that on SUA,\(^ {34}\) might lead to subtle interactions of potential prognostic value that could be difficult to control in a multivariate survival analysis.

An example of the difficulties that may arise when the conclusions of general population studies are applied to particular clinical conditions comes from a recent analysis of the Framingham Heart Study,\(^ {15}\) which did not detect any association between SUA and CV events after adjustment for age, office BP, total cholesterol, smoking, diabetes, and diuretic therapy. In that study, only one third of men and 30% of women were hypertensive, 5% of men and 10% of women were taking diuretics at the time of SUA determination, and renal function was not included among the potential con-
Therefore, the conclusions of that study that SUA should not be used as a predictor of CV risk might be more relevant to the general population than to the clinical context of untreated subjects with essential hypertension free of overt renal failure or CV disease. Conversely, the results of the present study can be applied to such a context, but possibly not to the general population.

In our study, the relation of SUA to CV events and mortality was J-shaped (figures), with a nadir in the second quartile. A similar J-shaped relation is also apparent from inspection of studies by Alderman et al in subjects with hypertension, Lehto et al in subjects with type 2 diabetes, and Bengtsson et al in a general population. In the Framingham Heart Study, the relation of SUA to coronary heart disease, CV mortality and all-cause mortality appeared to be J-shaped in men but not in women. In our study, prevalence of diabetes mellitus was J-shaped across the 4 quartiles of SUA, possibly reflecting clusters of diabetic patients with low and high levels of SUA, and this might be one reason for the nonlinear increase of CV risk with SUA.

The prognostic value of SUA in the general population is supported by results of the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. Subjects with history of myocardial infarction, stroke, or gout at entry were excluded from the study. SUA was a potent predictor of CV mortality over a 16-year follow-up period after adjustment for age, race, body mass index, smoking, alcohol consumption, cholesterol levels, diuretic use, and history of hypertension or diabetes.

**Increased SUA in Hypertension**

The mechanisms underlying the increase in SUA and its potential prognostic implications in patients with essential hypertension are listed in Table 3. Multivariate Survival Analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Comparison</th>
<th>Relative Risk (95% CI)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td><strong>Cardiovascular morbidity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>(5 y)</td>
<td>1.23 (1.12–1.34)</td>
<td>0.0001</td>
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<tr>
<td>Sex</td>
<td>(men vs women)</td>
<td>1.71 (1.17–2.50)</td>
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<tr>
<td>Diabetes</td>
<td>(yes vs no)</td>
<td>1.91 (1.21–2.99)</td>
<td>0.0050</td>
</tr>
<tr>
<td>LV hypertrophy</td>
<td>(yes vs no)</td>
<td>1.74 (1.18–2.57)</td>
<td>0.0052</td>
</tr>
<tr>
<td>24-h PP</td>
<td>(10 mm Hg)</td>
<td>1.37 (1.17–1.62)</td>
<td>0.0002</td>
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<tr>
<td>TC/HDL-C</td>
<td>(1 U)</td>
<td>1.24 (1.10–1.40)</td>
<td>0.0006</td>
</tr>
<tr>
<td>SUA</td>
<td>Quartile 1 vs 2</td>
<td>1.14 (0.62–2.06)</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>Quartile 3 vs 2</td>
<td>1.46 (0.84–2.52)</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Quartile 4 vs 2</td>
<td>1.73 (1.01–3.00)</td>
<td>0.0492</td>
</tr>
</tbody>
</table>

**Cardiovascular mortality**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Comparison</th>
<th>Relative Risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>(5 y)</td>
<td>1.81 (1.49–2.21)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>(men vs women)</td>
<td>1.94 (0.96–3.93)</td>
<td>0.060</td>
</tr>
<tr>
<td>Diabetes</td>
<td>(yes vs no)</td>
<td>1.92 (0.96–3.85)</td>
<td>0.066</td>
</tr>
<tr>
<td>24-h PP</td>
<td>(10 mm Hg)</td>
<td>1.41 (1.11–1.79)</td>
<td>0.0046</td>
</tr>
<tr>
<td>SUA</td>
<td>Quartile 1 vs 2</td>
<td>2.03 (0.61–6.81)</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>Quartile 3 vs 2</td>
<td>1.03 (0.30–3.62)</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>Quartile 4 vs 2</td>
<td>1.96 (1.02–3.79)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

**All-cause mortality**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Comparison</th>
<th>Relative Risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>(5 y)</td>
<td>1.68 (1.48–1.91)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>(men vs women)</td>
<td>2.66 (1.64–4.34)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>(yes vs no)</td>
<td>1.67 (1.02–2.72)</td>
<td>0.0401</td>
</tr>
<tr>
<td>24-h PP</td>
<td>(10 mm Hg)</td>
<td>1.28 (1.08–1.50)</td>
<td>0.0034</td>
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<tr>
<td>SUA</td>
<td>Quartile 1 vs 2</td>
<td>1.73 (0.77–3.89)</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Quartile 3 vs 2</td>
<td>1.43 (0.64–3.20)</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>Quartile 4 vs 2</td>
<td>1.63 (1.02–2.57)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

**Figure 2.** With multivariate Cox regression, age- and cholesterol-adjusted 4-year risk of CV disease was standardized to different levels of significant explanatory variables in either gender. See Table 1 for abbreviations.
proximal tubular sodium reabsorption could be mediated by insulin, elevated SUA levels may reflect both these mechanisms. Hyperinsulinemia may increase sympathetic nervous system activity, with reduction in cortical blood flow and depressed tubular secretion of urate caused by its reduced delivery to the tubular secretory sites. Longitudinal studies are needed to clarify the potential value of SUA to reflect and predict the vicious cycle leading to progressive renal damage and elevated blood pressure. Increased activity of the sympathetic nervous system has also been associated with reduced renal excretion of uric acid, but the basic mechanisms are unknown. Hyperinsulinemia may cause a reduction in urinary excretion of uric acid and sodium through a reduced tubular secretion, increased reabsorption, or both. Because hyperinsulinemia may increase sympathetic nervous system activity, elevated SUA levels may reflect both these mechanisms. Also, the direct association between SUA and proximal tubular sodium reabsorption could be mediated by insulin.

In the present study, the highest quartile of SUA was characterized by a cluster of powerful predictors of increased CV disease risk (Table 1). Nevertheless, the association between SUA and CV events, CV mortality and all-cause mortality persisted after adjustment for the influence of the above factors. Thus, our results indicate that SUA should not be necessarily viewed as a causative factor for CV disease but most likely as a valuable biological marker that reflects and integrates different risk factors and their possible interactions. It is worth noting that under the present experimental conditions, SUA was more accurate than other markers for prediction of CV disease risk and all-cause mortality.

Limitations of the Study
A strength of the present study was the statistical adjustment for ambulatory BP, which is more accurate than office BP for CV risk stratification, thereby allowing a more conservative estimate of the prognostic value of SUA and other covariates. The main limitation of this study is the absence of information regarding the prognostic value of SUA determined during treatment, previously reported by Alderman et al. Furthermore, caution is needed when applying the results of this study to nonwhite populations or different clinical settings.

Implications
The present study demonstrates a strong independent association between SUA and CV risk in initially untreated and asymptomatic adult subjects with essential hypertension, but it is unable to answer the question of whether SUA exerts direct toxic effects. As extensively reviewed by Puig and Ruiolope, both uric acid and superoxide radicals are produced for the effect of xanthine oxidase in the late phase of purine metabolism. Superoxide radicals, which may cause tissue and vascular damage, are increased in subjects with essential hypertension. It would be important to clarify whether such increase is due, at least in part, to enhanced xanthine oxidase activity and whether inhibition of this enzyme by allopurinol may reduce CV risk.

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References


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