Serum Uric Acid and Cardiovascular Events in Successfully Treated Hypertensive Patients

Michael H. Alderman, Hillel Cohen, Shantha Madhavan, Salah Kivlighn

Abstract—To determine whether pretreatment and/or in-treatment serum uric acid (SUA) is independently and specifically associated with cardiovascular events in hypertensive patients, we examined the 20-year experience of 7978 mild-to-moderate hypertensive participants in a systematic worksite treatment program. Clinical evaluation and treatment were protocol-directed. SUA was measured at entry and annually thereafter. Subjects were stratified according to gender-specific quartile of baseline SUA. Blood pressures at entry and in-treatment were, respectively, 152.5/95.6 and 138.9/85.4 mm Hg. SUA was normally distributed with a mean of 0.399±0.0893 and 0.321±0.0833 mmol/L for men and women, respectively. Subjects with highest SUA were heavier, had greater evidence of cardiovascular disease (CVD), higher systolic blood pressure, higher creatinine, more frequent diuretic use, and lower prevalence of diabetes. During an average follow-up of 6.6 years (52,751 patient-years), 548 CVD events (183 mortal) and 116 non-CVD events occurred. In bivariate analysis, the association of SUA to CVD was more robust in nonwhites than whites and in patients at low versus high CVD risk. In multivariate analysis, CVD incidence was significantly associated with SUA with a hazard ratio of 1.22 (95% confidence interval 1.11 to 1.35), controlling for other known cardiovascular risk factors, including serum creatinine, body mass index, and diuretic use. Despite blood pressure control, SUA levels increased during treatment and were significantly and directly associated with CVD events, independently of diuretic use and other cardiovascular risk factors. (Hypertension. 1999;34:144-150.)

Key Words: uric acid, serum • blood pressure • cardiovascular disease • hypertension, essential

The association of elevated serum uric acid (SUA) with cardiovascular disease (CVD) has been recognized for more than a century. During the last 50 years, a substantial body of clinical and epidemiological research has convincingly defined a positive association of SUA with myocardial infarction, stroke, and all cardiovascular events in both the general population1–7 and, more particularly, among hypertensive patients.8,9 Despite long-standing awareness of this association, little attention has been paid to its potential significance. This is particularly true with regard to hypertensive patients, of whom ≈1 in 4 have elevated levels of uric acid.10 The existence of a large, long-term, and systematically treated hypertensive cohort has made it possible to determine whether an independent relationship of SUA levels to stroke, heart attack, and total CVD events exists and whether this relationship persists after normalization of blood pressure (BP).

Methods

Subjects
Study subjects were patients with mild-to-moderate hypertension identified through screening for high BP who entered a union-sponsored treatment program in New York City between 1973 and 1996. Entry criteria, evaluation, and treatment methods of this worksite-based prospective cohort study have been previously described.11,12 Baseline information included demographic data, personal medical history, cigarette smoking status, physical examination by a nurse and physician, ECG findings, routine clinical chemistry, and qualitative urine protein. At each annual reexamination, intervening history was recorded. All clinical data were obtained and treatment decisions were made according to a protocol approved by the institutional review committee.

SUA levels were available from entry examinations and annual reexaminations for 7978 patients. These examinations yielded nearly 48,000 measurements during 52,751 patient-years of follow-up. SUA was measured in commercial laboratories using enzymatic spectrophotometry by automated techniques. In this long-term study, the SUA estimations were performed in 2 laboratories over different periods of time. There were minor variations in yearly mean SUA over the 23 years not related to changes in laboratory. In-treatment SUA was computed for each patient as the mean of all available SUA values recorded at annual examination during follow-up. The number of values ranged from 1 to 20, and averaged 4.7 per patient.

Eligibility Criteria
Eligibility criteria included a systolic BP≥160 mm Hg or diastolic BP≥95 mm Hg at screening and 2 consecutive follow-up visits or the taking of antihypertensive medication at the time of screening.

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These criteria were changed to systolic \( \geq 140 \) mm Hg or diastolic \( \geq 90 \) mm Hg in 1993 in accordance with the recommendation of the Joint National Committee (JNC V) on Detection, Evaluation, and Treatment of high BP.\(^ {13} \)

### Antihypertensive Drug Therapy

Before 1988, treatment generally began with either hydrochlorothiazide or propranolol or, less commonly, \( \alpha \)- and/or \( \beta \)-adrenergic blockers. After the 1988 report of JNC IV, calcium channel blockers and angiotensin-converting enzyme inhibitors were available as first-line drug choices. In 1993, after JNC V, first drug preference again returned to diuretics or \( \beta \)-blockers.\(^ {13} \)

At each clinic visit, prescriptions for antihypertensive drugs were provided. For each patient, the percentage of clinic visits in which diuretics or \( \beta \)-blockers were prescribed (singly or in combination with other drugs) was computed separately for the 2 drugs, irrespective of dose or the total number of antihypertensive medications prescribed. Based on this percentage, patients were classified into 1 of the following 3 categories of diuretic use: 0% to 10% \((n=2949)\), 11% to 89% \((n=3962)\), and 90% \((n=1067)\) of all clinic visits.

### Morbidity and Mortality

Illnesses and deaths were classified according to the International Classification of Disease, Ninth Revision, Clinical Modification. CVD events of interest in this study were myocardial infarction (code 410), including angioplasty or coronary bypass surgery procedure (procedure code 36); cerebrovascular disease (codes 430 to 434 and 436 to 438, henceforth referred to as strokes); unstable angina (code 411.1); congestive heart failure (code 428); and deaths from all other CVD causes (codes 390 to 459). For patients with \( >1 \) event during follow-up, the first incident CVD event was included as the end point in the present analysis. All non-CVD deaths and hospitalizations for cancer were defined as major non-CVD events. The following 3 categories of diuretic use in-treatment SUA

### TABLE 1. Baseline Characteristics of Men by Quartile of SUA

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>I (( &lt;0.333 ))</th>
<th>II (0.334 – 0.387)</th>
<th>III (0.388 – 0.446)</th>
<th>IV (( \geq 0.447 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.9±9.9</td>
<td>53.5±9.8</td>
<td>52.6±10.2</td>
<td>52.7±10.4</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>23.7</td>
<td>24.1</td>
<td>26.2</td>
<td>29.9</td>
</tr>
<tr>
<td>White</td>
<td>39.9</td>
<td>44.4</td>
<td>44.1</td>
<td>45.0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>33.5</td>
<td>28.7</td>
<td>26.4</td>
<td>22.7</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>26.8±3.7</td>
<td>27.8±3.8</td>
<td>28.0±3.8</td>
<td>28.7±4.3</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.61±1.086</td>
<td>5.79±1.267</td>
<td>5.84±1.138</td>
<td>6.05±1.241</td>
</tr>
<tr>
<td>SUA, mmol/L</td>
<td>0.292±0.0363</td>
<td>0.292±0.0363</td>
<td>0.292±0.0363</td>
<td>0.292±0.0363</td>
</tr>
<tr>
<td>Serum creatinine, ( \mu )mol/L</td>
<td>101.7±17.68</td>
<td>105.2±21.22</td>
<td>107.0±17.68</td>
<td>113.15±25.64</td>
</tr>
<tr>
<td>Blood sugar, mmol/L</td>
<td>6.16±2.664</td>
<td>5.88±1.721</td>
<td>5.88±1.554</td>
<td>5.94±1.499</td>
</tr>
<tr>
<td>LVH by ECG, %</td>
<td>13.7</td>
<td>11.7</td>
<td>14.0</td>
<td>16.9</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>26.1</td>
<td>26.6</td>
<td>24.9</td>
<td>24.4</td>
</tr>
<tr>
<td>History of CVD, %</td>
<td>13.6</td>
<td>14.8</td>
<td>16.1</td>
<td>19.6</td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>10.3</td>
<td>6.1</td>
<td>5.9</td>
<td>5.2</td>
</tr>
<tr>
<td>Prior treatment, %</td>
<td>40.9</td>
<td>42.4</td>
<td>46.6</td>
<td>56.6</td>
</tr>
<tr>
<td>Diuretic use, ( \geq 90)%†</td>
<td>11.2</td>
<td>11.5</td>
<td>12.5</td>
<td>12.9</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>152.9±19.8</td>
<td>152.6±19.8</td>
<td>153.1±20.6</td>
<td>154.1±23.1</td>
</tr>
<tr>
<td>Diastolic</td>
<td>96.3±10.5</td>
<td>97.0±11.1</td>
<td>97.5±12.5</td>
<td>97.8±12.5</td>
</tr>
</tbody>
</table>

\(^*\)Differences between quartiles are highly significant \((P<0.001)\) for all characteristics except smoking and systolic BP.

\(^†\)Percent of prescriptions for diuretics.

### Statistical Analysis

Baseline characteristics were assessed according to gender-specific quartile of SUA. Differences between the quartile groups were tested for statistical significance by \( \chi^2 \) test for categorical variables and ANOVA for continuous variables.

Unadjusted CVD and non-CVD event rates expressed per 1000 person-years were initially computed according to gender-specific SUA quartile. Further analysis included estimation of age- and gender-adjusted CVD incidence rates by SUA quartile. Also, age- and gender-adjusted relative risk and 95% confidence interval (CI) of CVD incidence were calculated to compare SUA quartiles with the lowest quartile as the reference group. In bivariate analysis, similar estimates of CVD incidence by SUA quartile were computed for patients with and without risk factors.

Cox proportional hazards regression models were constructed to determine the effect of baseline and in-treatment SUA on CVD while controlling for age at entry, gender, race, history of CVD, history of diabetes, prior treatment, smoking status, left ventricular hypertrophy (LVH) by ECG, blood sugar, cholesterol, serum creatinine, body mass index, and initial systolic BP.\(^ {14} \) Additional models were constructed to examine the association of SUA and CVD risk in patient groups stratified by race and gender.

All clinical chemistry measures are reported in SI units, using conversion factors. To convert SUA values from mmol/L to mg/dL, divide by 0.0595. All statistical analyses were performed with Statistical Package for Social Sciences (SPSS) software (SPSS Inc).

### Results

#### Patient Characteristics

Most baseline characteristics, including SUA (mmol/L), differed between men \((n=4883)\) and women \((n=3095)\). SUA

### Methods

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was fairly stable over the patient age range of 20 to 85 years and was roughly similar for whites and nonwhites. Nondiabetics (n = 7382) had higher values (0.369 versus 0.351, P < 0.001) than diabetics (n = 596). Because the mean SUA levels for men (0.399 mmol/L) and women (0.321 mmol/L) differed significantly (P < 0.001), patients were stratified by gender-specific quartile cut points (Tables 1 and 2). In general, those in the highest SUA quartile had greater body mass index, higher total cholesterol, higher serum creatinine, higher initial BP, more LVH, and prior antihypertensive treatment. Among women, the mean age at entry increased from the lowest to highest SUA quartile (consistent with population-based evidence that SUA increases with age after menopause) versus an inverse relation in men. Women with a history of diabetes were equally distributed across quartiles, whereas for men, the lowest SUA quartile had the highest concentration of diabetics.

Uric Acid and Incidence of CVD

During 52,751 patient-years of follow-up (average 6.6 years), there were 548 (365 morbid and 183 mortal) CVD events, and 116 non-CVD deaths. Of the 548 CVD events, 414 (75.5%) occurred in men. Overall, age- and gender-adjusted CVD rates (Figure 1) were positively related to baseline SUA, with a relative risk of 1.48 (95% CI, 1.18 to 1.86) for the highest versus the lowest quartile. Non-CVD events were not similarly distributed.

Exposure-specific CVD incidence rates per 1000 person-years, as adjusted for age and gender, in each SUA quartile (Table 3) revealed a positive relation of SUA to CVD for nonwhites with a threshold at the highest quartile (14.32/1000 person-years). This was not true for whites, who had higher CVD rates than nonwhites in all quartiles except the fourth (12.67 versus 14.32). The presence or absence of individual CVD risk factors did not generally alter the positive relation of SUA to CVD events (Table 3). As expected, incidence rates in patients with risk factors compared with those without, were higher in all SUA quartiles. SUA was not significantly associated with CVD in diabetics, patients with elevated cholesterol, smokers, or obese patients. The positive relation of SUA to CVD events was observed in patients with higher or lower serum creatinine as well as those with or without a history of CVD, although for the latter group, relative risk for highest versus lowest quartile did not differ.
Diuretic Use and SUA
Frequency of diuretic prescription was categorized as rare (0% to 10%), moderate (11% to 89%), and frequent (≥90%) use. The percentages of patients in these groups were 37%, 49.7%, and 13.4%, respectively. At the final clinic visit, 50% of frequent users were on diuretics alone. Mean in-treatment SUA increased with increasing diuretic exposure: 0.004 mmol/L for rare, 0.030 mmol/L for moderate, and 0.047 mmol/L for frequent users. There was no correlation of SUA with β-blocker use.

CVD incidence rates were 10.7, 9.2, and 16.3 for the rare, moderate, and frequent diuretic users, respectively. There was no significant difference in rates between rare and moderate users, but the relative risk of frequent users compared with the other 2 groups was 1.61 (95% CI 1.30, 2.00). A similar relation was observed for rates of myocardial infarction.

Multivariate Analysis
To determine whether pretreatment or average in-treatment SUA best predicted CVD events, separate multivariate Cox regression analyses for baseline and average in-treatment SUA as continuous variables were performed. In the separate models, both in-treatment (Table 4) and baseline (not shown) SUA were significantly and directly associated with CVD. However, a substantial difference was found between the 2 models. The standard deviation of SUA declined from 0.095 mmol/L at baseline, to 0.086 mmol/L for in-treatment. Moreover, the hazard ratio (1.11) for 1 SD of SUA at baseline.
TABLE 4. Proportional Hazards Cox Regression Model: Association of In-Treatment Uric Acid With Incidence of Cardiovascular Disease in Treated Hypertensive Patients

<table>
<thead>
<tr>
<th>Variable*</th>
<th>( \beta )</th>
<th>( P )</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid (mmol/L)†</td>
<td>0.2013</td>
<td>0.0001</td>
<td>1.22 (1.11–1.35)</td>
</tr>
<tr>
<td>Age, (y)</td>
<td>0.4313</td>
<td>&lt;0.0001</td>
<td>1.54 (1.40–1.69)</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.6885</td>
<td>&lt;0.0001</td>
<td>1.99 (1.58–2.51)</td>
</tr>
<tr>
<td>White race</td>
<td>0.2858</td>
<td>0.0015</td>
<td>1.33 (1.12–1.59)</td>
</tr>
<tr>
<td>History of CVD</td>
<td>0.7245</td>
<td>&lt;0.0001</td>
<td>2.06 (1.71–2.49)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>0.7006</td>
<td>&lt;0.0001</td>
<td>2.02 (1.53–2.65)</td>
</tr>
<tr>
<td>Diuretic use (≥90%)</td>
<td>0.3684</td>
<td>0.0017</td>
<td>1.45 (1.15–1.82)</td>
</tr>
<tr>
<td>Prior treatment</td>
<td>0.2317</td>
<td>0.0125</td>
<td>1.26 (1.05–1.51)</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.4258</td>
<td>&lt;0.0001</td>
<td>1.53 (1.27–1.85)</td>
</tr>
<tr>
<td>LVH</td>
<td>0.3912</td>
<td>0.0015</td>
<td>1.48 (1.16–1.88)</td>
</tr>
<tr>
<td>Blood sugar (mmol/L)</td>
<td>0.0955</td>
<td>0.0142</td>
<td>1.10 (1.02–1.19)</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>0.1678</td>
<td>0.0001</td>
<td>1.18 (1.09–1.29)</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>−0.0142</td>
<td>0.7805</td>
<td>0.99 (0.89–1.09)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.0434</td>
<td>0.3707</td>
<td>1.04 (0.95–1.15)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>0.0902</td>
<td>0.0400</td>
<td>1.09 (1.00–1.19)</td>
</tr>
</tbody>
</table>

*Abbreviations as in text and previous tables.
†In-treatment uric acid.

rose to 1.22 for in-treatment. All other risk factors had roughly similar hazard ratios in the 2 models. Similar point estimates were observed for coronary heart disease (CVD minus strokes) as the end point. SUA was not an independent predictor of stroke at baseline \( (P=0.612) \) or during treatment \( (P=0.301) \). In the presence of SUA, serum creatinine was not independently associated with CVD either at baseline \( (P=0.844) \) or in-treatment \( (P=0.973) \). Diuretic use (in this model ≥90% of the time) was an independent predictor of both CVD and coronary heart disease.

The effect size of the risk associated with 1 SD (0.086 mmol/L) of SUA was larger than that associated with 1 SD of either cholesterol (1.078 mmol/L) or systolic BP (21.3 mm Hg) (Table 4). When the population was restricted to those without prior CVD, the significant association of SUA with CVD persisted with an unchanged hazard ratio of 1.22 (1.10, 1.41).

Finally, Cox models were constructed for patients stratified by race and gender. In all patients, the hazard ratios for SUA (Figure 2) for the group as a whole and for each gender were significantly >1. Nonwhite men (1.39) had a slightly higher CVD risk than white men (1.13). In women, the risk of SUA was the same for nonwhites and whites (1.31). The hazard ratios for white men (1.13; range 0.98 to 1.33) and women (1.31; range 0.98 to 1.77) did not achieve statistical significance.

**Discussion**

In this study of hypertensive patients, both baseline and in-treatment SUA are independently, significantly, and specifically associated with myocardial infarction/revascularization, despite satisfactory control of BP. This relationship is continuous throughout the range of SUA values but is most pronounced among those in the highest quartile (men ≥0.452 mmol/L; women ≥0.375 mmol/L) of uric acid. This association applies to both racial/ethnic subgroups, but is generally more demonstrable in nonwhites than whites.

The important new finding here is that not only does hyperuricemia persist after successful BP control, but that its association with CVD endures. Indeed, among these 7978 systematically treated subjects studied for 52,751 patient years, changes in uric acid contribute at least as much to explaining the variation in vascular events as did other conventional risk markers. Specifically, a 0.086-mmol/L difference in SUA predicted a larger variation in total CVD (stroke, myocardial infarction/revascularization, and total fatal and nonfatal CVD events) than did a 1.078 mmol/L increase in cholesterol, or a 21.3 mm Hg increase in systolic BP. Those in the highest SUA quartile were nearly 50% more likely to experience a cardiovascular end point over an average follow-up of 6 years than were those in the lowest quartile. In sharp contrast, noncardiovascular mortality was not associated with SUA.

While the direction of the relationship of SUA to CVD events was consistent in most subgroups of exposure, it varied by risk status. Thus, nonsmokers, those without diabetes or hyperlipidemia, and less obese patients displayed a more pronounced increase in events with increasing SUA than did patients with those characteristics. By contrast, patients with LVH, history of CVD, or a wide pulse pressure showed a stronger SUA effect than did patients without those conditions.

Longstanding awareness of the link of SUA to CVD events in the general population is supplemented by a considerable body of literature specifically addressing the association of SUA to BP. Hypertensive patients have higher SUA levels than normotensive subjects. Not surprisingly, baseline SUA was significantly higher in previously treated hypertensive subjects, (0.371 mmol/L) than in untreated patients (0.362 mmol/L). However, in contrast to earlier findings after correction of renal artery stenosis, SUA levels did not...
decrease in this large group when BP was normalized over a prolonged period. Indeed, in-treatment SUA exceeded baseline values even for patients who did not receive diuretic therapy. Of interest, after BP control, in-treatment SUA had a more robust relation to CVD than did baseline values. This may have been due to the fact that the in-treatment SUA for each patient was an average of multiple (mean = 4.7) annual measurements, providing a more precise estimate of SUA than a single measurement. This would correct for regression dilution bias.

Frohlich\(^1\)\(^9\) has hypothesized that the frequent presence of hyperuricemia in hypertensive patients reflects underlying renal dysfunction or reduced renal perfusion. It certainly is possible that uric acid may be an earlier and more sensitive marker of decreased renal flow than serum creatinine. The available data do not allow us to rule out the possibility that it is underlying but clinically inapparent renal disease that is responsible for both elevated uric acid and increased CVD events. However, in this study, both in multivariate and stratified analysis the association of uric acid to CVD events was independent of serum creatinine.

The influence of diuretic therapy on SUA is of particular note and potential importance.\(^1\)\(^7\)\(^8\)\(^9\)\(^18\)\(^19\) The possibility that diuretic-based antihypertensive therapy may not have achieved the reduction in coronary heart disease morbidity predicted from epidemiological studies of BP remains unresolved. Some observers believe that adverse metabolic consequences associated with diuretic use detract from its hemodynamic benefits.\(^20\) In this large treated group, followed for many years, diuretic therapy did appear to modestly increase SUA. However, the SUA to CVD relation was independent of the effect of diuretics. These findings, nevertheless, suggest the hypothesis that among controlled hypertensive patients whose therapy included diuretics persistent elevation in SUA may have detracted from the benefit anticipated from the hemodynamic effects of the diuretics. In recent years, as the dose of diuretics has tended to lower, the impact on SUA may have declined.

The above possibility presumes that the relationship of SUA to cardiovascular events is causal.\(^21\) This observational cohort study does not provide a basis on which to make such a claim. It is not possible to determine here whether SUA is a marker, a comorbid or intervening factor, or a direct cause of CVD. Although SUA elevation is commonly found in patients with renal disease or in league with other risk factors, including hyperlipidemia, insulin resistance, hypertriglycerideremia, and obesity, no evidence exists to demonstrate that this particular characteristic produces vascular damage.\(^22\)\(^23\)\(^24\)

A variety of mechanisms has been suggested to explain a possible causal relation. These include increasing superoxide production, inflammation and direct vascular injury, and effects on platelet aggregation. None of these possibilities has been confirmed.\(^25\)\(^–\)\(^29\)

In any event, SUA meets conventional criteria for a cardiovascular risk factor. The association of SUA to CVD events is significant, is independent of other known confounders, is specific (no association with non-CVD events is shown), has a substantial effect size (similar to traditional risk factors), and is dose related. In even successfully treated hypertensive patients, most CVD events that would have occurred without treatment still occur. At the very least, knowledge of SUA improves the ability to stratify risk and, thus, enhances the efficiency and, perhaps, the efficacy of antihypertensive therapy. The possibility that reduction of uric acid might reduce CVD morbidity remains to be assessed.

In summary, this study demonstrates that the specific, continuous, strong, significant, and independent association of SUA to CVD events, described in the general as well as the untreated hypertensive population, is even more robust in well-treated hypertensive patients. Whether elevated SUA actually causes disease and, more importantly, whether a reduction in this risk factor would prevent CVD events, remains an open question.

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References


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