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Serum Uric Acid as an Independent Predictor of Early Death After Acute Stroke

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Background The prognostic significance of uric acid (UA) levels in acute stroke is unclear, so the objective of this study was to determine the association between levels of serum UA (SUA) and mortality in acute stroke.
Methods and Results Consecutive patients (n=435) presenting with ischemic stroke and intracerebral hemorrhage were included in the study. The length of stay in hospital and the occurrence of death were recorded. On univariate analysis, the occurrence of death was associated with older age, smoking, presence of congestive heart failure or atrial fibrillation, absence of hyperlipidemia, and intracerebral hemorrhage as the index event. Furthermore, glucose, urea, creatinine and SUA at admission were significantly higher in patients who died, whereas total and high-density-lipoprotein cholesterol were significantly lower. On multiple logistic regression analysis, the independent relationship between higher SUA levels and death was confirmed (odds ratio (OR), 1.37; 95% confidence interval (CI), 1.13–1.67; p=0.001). The only other variables independently associated with the occurrence of death were urea concentration and presence of atrial fibrillation. If urate was >7.8 mg/dl (0.47 mmol/L), then there would be a high probability of early death (87%).
Conclusions Elevated levels of SUA are independently associated with an increased risk of early death in acute stroke. (*Circ J* 2007; **71:** 1120–1127)

Key Words: Cardiovascular disease; Intracerebral hemorrhage; Ischemic stroke; Prognosis; Uric acid

The association between increased serum uric acid (SUA) levels and cardiovascular risk has been debated for over 50 years[1] Several large studies have provided conflicting results regarding the clinical significance of elevated SUA levels in cardiovascular or cerebrovascular disease. Some concluded that SUA is an independent risk factor for cardiovascular disease (CVD)[2–6] with an apparently stronger association in women than in men[7,8] in the elderly[9] and in patients with essential hypertension[10] congestive heart failure[11,12] and type 2 diabetes mellitus[13,14] In contrast, the Framingham Heart Study concluded that an association with CVD merely reflects the link between SUA and other risk factors, including hypertension, renal disease, elevated lipoprotein levels and the use of diuretics[15]

In vitro and in vivo studies have shown uric acid (UA) to be a powerful free radical scavenger and, paradoxically, these antioxidant properties would be expected to provide a number of benefits within the cardiovascular system[16] Furthermore, elevated SUA levels may induce renal disease[17] which seems to progress in parallel with CVD[18] Several mechanisms by which SUA could have a direct pathogenic role in CVD have also been suggested[16] Therefore, it is unclear whether high SUA promotes or protects against the development of CVD, or simply acts as a passive marker of increased risk.

In the present study we examined the association of UA concentrations with the clinical outcome and the fatality rate of patients with acute stroke.

Methods

Study Design

Consecutive patients presenting to the Second Propedeutic Department of Internal Medicine (Hippokration Hospital, Thessaloniki, Greece) between June 2001 and May 2005 with acute stroke were included in the study. We defined acute stroke as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with no apparent cause other than of vascular origin", according to the World Health Organization criteria.

At baseline, demographic data (age, sex), history of conventional vascular risk factors (hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia, smoking habit, alcohol abuse), and history of concomitant vascular diseases (ischaemic heart disease, congestive heart failure, previous stroke), were obtained. Diabetes mellitus was defined as fasting plasma glucose >126 mg/dl (7.0 mmol/L) on 2 occasions or prescribed antidiabetic medication. Atrial fibrillation was defined as the persistent replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in size, shape and timing, associated with an irregular ventricular response on the electrocardiogram; paroxymal atrial fibrillation was also included in this group. Hyper-

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Table 1 Demographics, Vascular Risk Factors and Vascular Diseases of the Study Population

	Ischemic stroke (n=380)	*Intracerebral hemorrhage (n=55)*	*p value**	*Overall (n=435)*
Age (years)	*75 (70–82)*	*76 (70–82)*	*0.69*	*75 (70–82)*
Males (%)	*47.9*	*50.9*	*0.78*	*48.3*
Hypertension (%)	*77.8*	*77.4*	*1.00*	*77.7*
Diabetes mellitus (%)	*31.6*	*24.5*	*0.38*	*30.7*
Atrial fibrillation (%)	*31.0*	*22.6*	*0.28*	*29.9*
Smoking (%)	*47.8*	*60.0*	*0.69*	*49.0*
Hyperlipidemia (%)	*58.1*	*56.9*	*0.99*	*57.9*
Alcohol abuse (%)	*13.6*	*11.1*	*1.00*	*13.3*
Ischemic heart disease (%)	*23.3*	*22.6*	*1.00*	*23.2*
Congestive heart failure (%)	*16.5*	*18.9*	*0.82*	*16.8*
Previous stroke (%)	*40.8*	*30.2*	*0.18*	*39.5*

**For the comparison between patients with ischemic stroke and those with intracerebral hemorrhage.*

lipidemia was defined as total cholesterol >200 mg/dl (5.17 mmol/L) and high-density lipoprotein-cholesterol (HDL-C) <40 mg/dl (1.03 mmol/l) for men and <50 mg/dl (1.29 mmol/L) for women or prescribed lipid-lowering medication. Individuals classified as smokers included current smokers (defined as those who smoked at least 10 cigarettes per day for 6 months or more and those who smoked daily for 1 year or more regardless of the number of cigarettes per day) and those who had been ex-smokers and had quit more than 1 year ago. Alcohol abuse was defined as drinking more than 5 drinks per day (1 drink defined as 12 g of alcohol). Coronary heart disease was defined as history of Q or non-Q myocardial infarction or percutaneous transluminal coronary angioplasty or coronary artery bypass graft. Congestive heart failure was defined as history of dyspnea on ordinary exertion, paroxysmal nocturnal dyspnea or acute pulmonary edema or the presence of distended neck veins (in other than the supine position and in absence of venous obstruction), bilateral ankle edema (not caused by a condition other than cardiac failure), hepatomegaly (not because of liver disease), rales in the absence of pulmonary disease, positive S_3, or chest radiographic evidence of pulmonary congestion (pleural fluid, pulmonary venous congestion, prominent pulmonary veins) with or without cardiomegaly. Previous stroke was defined as history of hospitalization for a syndrome of rapidly developing clinical signs of focal or global disturbance lasting for 24 h or longer, attributed to ischemic or hemorrhagic lesions in the brain and verified with computed tomography (CT) scan or MRI.

We recorded systolic and diastolic blood pressures, as well as pulse rate, on admission. Routine laboratory investigations were performed the first day after admission to hospital after overnight fasting, and included levels of glucose, total cholesterol, HDL-C and low-density lipoprotein-cholesterol (LDL-C) subfractions, triglycerides, urea, creatinine, UA, hemoglobin, hematocrit and erythrocyte sedimentation rate.

All patients underwent a CT brain scan. Stroke types were classified into ischemic stroke and intracerebral hemorrhage (ICH). All patients received treatment according to the current guidelines but none of them underwent thrombolysis or surgical treatment.[19–21] On discharge from hospital, the length of stay and the occurrence and causes of death were recorded.

The results are expressed as percentages for categorical variables and as mean ± standard deviation or as median and interquartile range (IQR) for continuous variables. The chi-square and Kruskal-Wallis tests were used to compare respective categorical and continuous variables between groups. Associations between continuous variables were explored using Spearman's rank order correlation coefficient. Using multiple logistic regression analysis, we assessed the effect of SUA concentration on acute stroke outcome after controlling for clinical variables that differed significantly between groups in the univariate analysis or that are already established as predictors of stroke.

Because in-hospital mortality has the weakness that it is not measured at a consistent time point following stroke onset, we also analyzed mortality via survival analysis. For the univariate analysis, we compared Kaplan-Meier survival curves using the log-rank test. Multiple Cox proportional-hazards analysis was then used to assess the association between SUA level and death rates after correction for factors known to influence acute stroke outcome. In all cases, a 2-tailed p-value less than 0.05 was considered significant. All statistical analyses were performed with the SPSS software (version 10.0; SPSS Inc, Chicago, IL, USA).

Results

A total of 435 patients with stroke, 210 (48.3%) men and 225 (51.7%) women, with a median age of 75 years (IQR, 70–82 years), were included in the present study. Three hundred and eighty (87.4%) of them experienced an ischemic stroke and 55 (12.6%) had an ICH.

Table 1 lists the demographics, the vascular risk factors and vascular diseases of the study population. The most prevalent vascular risk factors were hypertension and hyperlipidemia, which were present in 77.7% and 57.9%, respectively, of the patients. A significant proportion of the study population, rising up to 39.5%, had experienced another stroke in the past, and 23.2% of them also suffered from ischemic heart disease. There were no significant differences in the prevalence of vascular risk factors or concomitant vascular diseases between patients with ischemic stroke and those with ICH.

Table 2 lists the clinical and laboratory findings at admission. Patients with ICH had significantly higher systolic and diastolic blood pressures at admission compared with patients with ischemic stroke ($p<0.005$ and $p<0.01$, respectively). There were no other significant differences in the clinical or laboratory findings at admission between patients with ischemic stroke and those with ICH.

As shown in Table 3, a significantly higher concentration of SUA was associated with male sex and the presence of

Table 2 Clinical and Laboratory Findings at Admission

	Ischemic stroke (n=380)	Intracerebral hemorrhage (n=55)	p value*	Overall (n=435)
SBP (mmHg)	156.3±28.9	168.8±36.6	<0.005	157.9±30.3
DBP (mmHg)	85.9±14.2	93.0±20.1	<0.01	86.8±15.3
Pulse rate (beats/min)	79.7±19.9	83.2±22.5	0.52	80.1±20.3
Glucose (mg/dl)	128 (107–166)	136 (115–205)	0.07	129 (109–168)
TC (mg/dl)	221 (180–265)	236 (200–279)	0.25	224 (181–266)
LDL-C (mg/dl)	169.5 (120–202.5)	187.5 (152–223.5)	0.13	170.5 (127–205.7)
HDL-C (mg/dl)	42.5 (36–49)	44.5 (41–57)	0.13	43 (36–49.7)
TG (mg/dl)	127.5 (95.5–181)	112.5 (85.5–166)	0.22	126 (94–180)
Urea (mg/dl)	42 (32–58)	44 (33–65)	0.42	42 (32–59)
Creatinine (mg/dl)	1.0 (0.8–1.3)	1.0 (0.8–1.4)	0.75	1 (0.8–1.3)
Uric acid (mg/dl)	5.5 (4.4–7.1)	5.8 (4.0–6.9)	0.79	5.6 (4.3–7.1)
Hemoglobin (g%)	13.5 (12.5–14.8)	13.6 (12.5–14.5)	0.72	13.5 (12.5–14.8)
Hematocrit (%)	40.9 (37.5–44.5)	40.7 (37.6–43.5)	0.76	40.8 (37.5–44.4)
Erythrocyte sedimentation rate (mm/h)	24 (12–39)	28 (19–46)	0.29	24 (12–40)

*For the comparison between patients with ischemic stroke and those with intracerebral hemorrhage.
SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; TG, triglycerides.

Table 3 Uric Acid Concentration (in mg/dl) on Admission in Relation to Demographics and Risk Factors

	Yes	No	p value
Male sex	5.8 (4.6–7.4)	5.2 (4.2–7.0)	<0.05
Hypertension	5.6 (4.5–7.1)	5.2 (3.9–7.0)	0.12
Diabetes mellitus	5.2 (4.2–7.1)	5.6 (4.4–7.1)	0.32
Atrial fibrillation	5.8 (4.5–7.7)	5.4 (4.2–6.7)	0.06
Smoking	5.7 (4.7–7.8)	5.5 (4.1–6.9)	0.20
Hyperlipidemia	5.4 (4.3–6.7)	5.8 (4.5–7.7)	0.08
Alcohol abuse	6.3 (5.1–7.1)	5.5 (4.3–7.4)	0.40
Ischemic heart disease	5.7 (4.2–7.6)	5.5 (4.4–7.0)	0.79
Congestive heart failure	6.4 (4.8–8.3)	5.4 (4.3–6.7)	0.005
Previous stroke	5.4 (4.2–6.7)	5.7 (4.5–7.2)	0.25

congestive heart failure. SUA positively correlated with urea (r=0.26, p<0.001) and creatinine (r=0.36, p<0.001) and negatively with LDL-C (r=–0.20, p<0.05) and HDL-C (r=–0.23, p<0.01).

Median duration of hospitalization was 7 days (IQR, 5–9 days; range, 1–31 days). Duration of hospitalization was significantly longer for patients with ICH compared with patients with ischemic stroke (p=0.001).

Table 4 lists the outcomes of the study population. Overall fatality during hospitalization was 14.3%; case fatality for ischemic stroke was 11.6% and for ICH, 32.7% (p<0.001). Deaths were caused by incident stroke (n=28), cardiovascular causes (myocardial infarction and cardiac arrhythmia) (n=15), pneumonia (n=16) and other causes (n=3). Death occurred after a median of 4 days (IQR, 2–7 days; range, 1–25 days) after admission. As shown in Table 5, on

Table 4 Outcomes of the Study Population

	Ischemic stroke (n=380)	Intracerebral hemorrhage (n=55)	p value*	Overall (n=435)
Median duration of hospitalization (days) (IQR, minimum-maximum)	6 (5–8, 1–28)	11 (4–16, 1–31)	0.001	7 (5–9, 1–31)
Fatality rate (%)	11.6	32.7	<0.001	14.3

*For the comparison between patients with ischemic stroke and those with intracerebral hemorrhage.
IQR, interquartile range.

Table 5 Demographics, Vascular Risk Factors and Vascular Diseases of the Study Population According to Outcome

	Alive at discharge (n=373)	Death (n=62)	p value
Age (years)	74 (69–81)	80 (73–85)	<0.001
Males (%)	47.7	51.6	0.67
Hypertension (%)	79.0	70.0	0.17
Diabetes mellitus (%)	30.0	35.0	0.53
Atrial fibrillation (%)	25.7	55.0	<0.001
Smoking (%)	43.5	80.0	<0.05
Hyperlipidemia (%)	61.5	35.1	0.001
Alcohol abuse (%)	13.2	14.3	1.00
Ischemic heart disease (%)	22.4	28.3	0.39
Congestive heart failure (%)	14.4	31.7	<0.005
Previous stroke (%)	39.6	39.0	1.00
Index event (%) (ischemic stroke/intracerebral hemorrhage)	90.1/9.9	71.0/29.0	<0.001

Table 6 Admission Clinical and Laboratory Findings According to Outcome

	Alive at discharge (n=373)	*Death (n=62)*	*p value*
SBP (mmHg)	*157.9±29.3*	*157.6±35.9*	*0.95*
DBP (mmHg)	*87.0±14.6*	*85.5±18.9*	*0.24*
Pulse rate (beats/min)	*79.9±20.5*	*80.9±19.4*	*0.54*
Glucose (mg/dl)	*126.5 (107.0–163.5)*	*154 (124.5–191.5)*	*0.001*
TC (mg/dl)	*227.5 (184–273)*	*201 (155.5–243.5)*	*<0.01*
LDL-C (mg/dl)	*176 (129–207)*	*156 (99–171)*	*0.07*
HDL-C (mg/dl)	*44 (36–50)*	*39.5 (32–42)*	*<0.01*
TG (mg/dl)	*126 (94–180)*	*123 (93–173)*	*0.71*
Urea (mg/dl)	*40 (31–54)*	*74 (41.5–98.5)*	*<0.001*
Creatinine (mg/dl)	*1.0 (0.8–1.2)*	*1.4 (0.9–2.0)*	*<0.001*
Uric acid (mg/dl)	*5.4 (4.3–6.7)*	*7.9 (5.2–9.1)*	*<0.001*
Hemoglobin (g/dl)	*13.6 (12.5–14.8)*	*13.1 (12.3–14.5)*	*0.33*
Hematocrit (%)	*41.0 (37.5–44.4)*	*40.2 (37.3–43.7)*	*0.71*
Erythrocyte sedimentation rate (mm/h)	*24 (12–40)*	*28 (17–50)*	*0.36*

Abbreviations as in Table 2.

univariate analysis death was associated with older age, smoking, presence of congestive heart failure or atrial fibrillation, absence of hyperlipidemia, and ICH as the index event. As shown in Table 6, on univariate analysis, glucose, urea, creatinine and UA at admission were significantly higher in patients who died, whereas total cholesterol and HDL-C were significantly lower. Univariate survival analysis using the log-rank test yielded similar findings, except that the presence of hypertension also had a hazard ratio greater than 1, indicating an increased risk of death.

On multiple logistic regression analysis, the independent relationship between higher SUA levels on admission and death was confirmed (odds ratio (OR) 1.37; 95% confidence interval (CI), 1.13–1.67; p=0.001). In addition to SUA, the only other variables independently associated with death were urea level (OR, 1.03; 95% CI, 1.02–1.04; p<0.001) and the presence of atrial fibrillation (OR, 4.27; 95% CI, 1.62–11.23; p<0.005). Multiple Cox proportional-hazards analysis yielded similar relationships between death and SUA level (hazard ratio, 1.28; 95% CI, 1.11–1.48; p=0.001), urea level (hazard ratio, 1.02; 95% CI, 1.01–1.03; p<0.001), and presence of atrial fibrillation (hazard ratio, 2.69; 95% CI, 1.19–6.04; p<0.05).

In order to determine the sensitivity and specificity of SUA at predicting early mortality after stroke, a receiver-operator characteristics curve was plotted (area 0.700, 95% CI 0.607–0.792). Using a cut-off value of 4.95 mg/dl (0.29 mmol/L), the test was 78% sensitive, but only 39% specific. However, if the patient's urate was greater than or equal to 7.85 mg/dl (0.47 mmol/L), then there would be a high probability of early death from stroke (positive predictive value=87%), although the test's sensitivity would fall to 51%.

We also performed similar analyses in order to identify the variables that could predict each specific cause of death. On multiple logistic regression analysis, the only variables independently associated with death attributed directly to the initial stroke were SUA level (OR, 1.96; 95% CI, 1.46–2.64; p<0.001), urea level (OR, 1.02; 95% CI, 1.01–1.03; p<0.05) and presence of atrial fibrillation (OR, 3.58; 95% CI, 1.01–12.67; p<0.05). In contrast, there were no differences in SUA levels at admission between patients who died from cardiovascular causes, pneumonia or other causes and those who did not. However, when deaths from incident stroke and cardiovascular causes were analyzed together, these patients had higher SUA levels at admission. On multiple logistic regression analysis, SUA level was independently associated with this cause of death (OR, 1.81; 95% CI, 1.38–2.38; p<0.001) together with urea level (OR, 1.02; 95% CI, 1.01–1.04; p=0.005) and the presence of congestive heart failure (OR, 4.31; 95% CI, 1.30–14.30; p<0.05).

Finally, we evaluated the predictive value of SUA on the occurrence of death in the various ischemic stroke subtypes. Among the 380 patients with ischemic stroke, 117 (30.8%) had atrial fibrillation and were considered to have suffered a cardioembolic stroke and the remaining 263 patients with ischemic stroke (69.2%) were considered to have suffered a non-cardioembolic stroke. Case fatality for ischemic cardioembolic stroke was 23.1% and for ischemic non-cardioembolic stroke, 6.5% (p<0.001). Case fatality did not differ between ischemic cardioembolic stroke and ICH (23.1% vs 32.7%, p=0.25), but was significantly lower for ischemic non-cardioembolic stroke compared with ICH (6.5% vs 32.7%, p<0.001). There were no differences in SUA levels between patients with cardioembolic and non cardioembolic ischemic stroke. In patients with ischemic stroke (n=380), death was associated on multiple logistic regression analysis with the same variables as in the whole population [SUA (OR, 1.36; 95% CI, 1.10–1.68; p<0.005), urea level (OR, 1.03; 95% CI, 1.02–1.05; p<0.001) and presence of atrial fibrillation (OR, 5.53; 95% CI, 1.86–16.44; p<0.005)]. In patients with cardioembolic or non-cardioembolic ischemic stroke, death was associated on multiple logistic regression analysis only with urea level (OR, 1.04; 95% CI, 1.02–1.06; p<0.001 and OR, 1.02; 95% CI, 1.01–1.04; p<0.005 respectively). We did not perform multiple regression analysis in patients with ICH because there was only a small number of patients in this subgroup (n=55).

Discussion

In the present study elevated levels of SUA were independently associated with an increased risk of early death in patients with acute stroke, particularly death attributed to incident stroke or from cardiovascular causes. Although SUA has been found to be an independent predictor of stroke[22,23] there are few studies showing that SUA independently predicts poor outcome in stroke patients. Weir et al found in 2,498 patients admitted with acute stroke that the admission SUA level independently predicted worse outcome and a higher rate of repeated stroke or other cardio-

vascular events.[24] Others have also reported that elevated SUA levels in patients with acute stroke are strongly associated with poorer outcome.[25,26]

Experimental evidence could explain how UA may play a pathogenetic role in stroke. Hypertension is a powerful predictor of stroke,[27,28] and UA is commonly associated with hypertension.[29,30] Elevated SUA level is an independent predictor of hypertension and is present in 25% of patients with new-onset, untreated primary hypertension.[31] The increase in the SUA level may be caused by the decrease in renal blood flow that usually accompanies the hypertensive state, because a low renal blood flow stimulates urate reabsorption.[32] Experimentally-induced hyperuricemia also increased the blood pressure in rats by a renal mechanism linked to inhibition of nitric oxide (NO), activation of the renin–angiotensin system, and development of renal arteriosclerosis.[33] Once renal arteriosclerosis develops, the kidney plays a major role in the maintenance of hypertension, and lowering the UA level is no longer protective.[34] Prolonged hyperuricemia in rats also caused progressive renal injury via a crystalline-independent mechanism[33] and accelerated established renal disease.[35] Finally, UA stimulated synthesis of monocyte chemoattractant protein-1 by the rat vascular smooth muscle cells,[36] and this is known to stimulate macrophage infiltration of atherosclerotic vessels.[37]

Apart from the interactions between UA and other risk factors in CVD, there are several other plausible mechanisms whereby UA may directly affect atherogenesis or the clinical course of cerebrovascular disease. Cerebral infarction initiates a complex cascade of metabolic events in the surrounding tissue, and free-radical-mediated oxidative damage plays a key role in the pathogenesis of cerebral ischemia.[38] Free radicals are liberated from a variety of sources, including inflammatory cells, dysfunctional mitochondria and excitotoxic mechanisms stimulated by increased glutamate and aspartate concentrations.[39] Hydroxyl radicals, peroxynitrite and superoxide, are powerful radicals that can cause lipid peroxidation, a self-propagating chain reaction, that irreversibly damages plasma and mitochondrial membranes.[40] Products of lipid peroxidation irreversibly disrupt enzymes, receptors, and membrane transport mechanisms. The generation of local oxidants augments local injury and increases infarct size.[38] Stroke is associated with a rapid decrease in serum antioxidants,[41,42] and patients with lower plasma antioxidants at the time of acute stroke have a poorer outcome.[43] UA is the most abundant aqueous antioxidant in humans and contributes as much as two-thirds of all the free radical scavenging capacity of plasma. It is particularly effective in quenching hydroxyl, superoxide and penoxynitrite radicals, and may serve a protective physiological role by preventing lipid peroxidation.[44] It might therefore be expected that having an elevated SUA level during an acute stroke would be beneficial. However, only 1 study has reported that high SUA levels may be neuroprotective in patients with acute stroke, resulting in better functional outcome at discharge,[45] whereas 3 other large series[24–26] and our study found the opposite. One explanation would be that UA, being an aqueous antioxidant, can become a pro-oxidant under certain circumstances, particularly if other antioxidants such as ascorbate are low.[46] Thus, in patients with acute stroke the fall in ascorbate levels could predispose the SUA to take on pro-oxidant properties. Consistent with this hypothesis is the observation that in acute stroke, those with high SUA and low ascorbate levels have the worst outcome.[25]

Different studies support the hypothesis that hyperuricemia causes vascular disease via endothelial dysfunction. For example, direct infusion of UA into the human brachial artery caused endothelial dysfunction.[47] UA was also found to promote LDL-C oxidation in vitro[48] and to stimulate granulocyte adherence to the endothelium.[49] In addition, a consistent relationship between elevated SUA levels and circulating inflammatory markers has been reported.[50–52] Moreover, UA may accumulate as crystals within atherosclerotic plaques.[53]

It has also been speculated that SUA might increase the risk of developing CVD through its association with the metabolic syndrome (MetS).[54–56] SUA levels are often increased in subjects with MetS.[57–59] Insulin resistance (IR) is probably the underlying condition triggering the development of both hyperuricemia and MetS and is directly related to SUA levels.[54,60] In patients with MetS, IR and decreased insulin-induced UA excretion may account for the observed increase in UA levels.[54] In addition, IR may also be linked to increased purine biosynthesis and turnover, with its attendant increase in SUA levels.[54,60] On the other hand, there is evidence that SUA may not only be a consequence of IR, but it may actually promote or worsen IR and thus play an important role in the pathogenesis of MetS,[61] possibly through its ability to disturb endothelial function and thus inhibit NO bioavailability.[47] Because insulin requires NO to stimulate glucose uptake, it has been hypothesized that hyperuricemia may have a key role in the pathogenesis of IR.[61] In addition, a strong relationship between hyperuricemia and the risk factors of MetS has been shown in recent large epidemiologic studies.[55,58,62] The relationship between SUA levels and MetS is of considerable importance, because almost one-third of middle-aged men and women in the United States have MetS,[63] whereas in Greece, the respective percentage is 24.5%.[64] Furthermore, MetS has recently been shown to represent a strong independent risk factor for ischemic stroke.[65–68] In the present study, increased SUA levels strongly correlated with low HDL-C levels, one of the 5 diagnostic criteria of MetS.[69] Unfortunately, we cannot assess the prevalence of MetS in these patients because we did not determine waist circumference, a principal diagnostic criterion of MetS.[69] However, the prognostic value of increased SUA levels was independent of all the other criteria of MetS, namely blood pressure and HDL-C, glucose and triglyceride levels, pointing to a direct link between SUA levels and adverse outcome in acute stroke.[69] It is clear that more studies are needed to determine whether the SUA level increases the risk for CVD directly, or indirectly through its association with MetS.

A rather unexpected finding of this study was that, in the univariate analysis, lower levels of total cholesterol and the absence of hyperlipidemia was associated with the occurrence of death, particularly death from incident stroke and cardiovascular causes. In contrast, several prospective studies have showed that higher levels of total cholesterol increase the risk of ischemic stroke.[70,71] Furthermore, a meta-analysis of 90,000 patients showed that administration of statins reduces the risk of stroke among patients with coronary heart disease and those at increased risk for CVD and that this risk reduction is primarily related to the extent to which LDL-C levels are lowered.[72] However, in the acute stroke setting, several studies have shown the opposite; that is, low cholesterol levels are associated with short-term mortality or worse functional outcome in patients with ischemic stroke, particularly in those who are older.[73–75] Several pos-

sible explanations have been proposed to explain this apparent paradox, mainly the idea of selective mortality, which is a hypothesis that many individuals with high levels of total cholesterol might experience an earlier onset of severe coronary heart disease, leading to disproportionately greater mortality before reaching an advanced age.[76–78] It has also been argued that low cholesterol levels may reflect an underlying serious disease or poor nutritional status, which could predispose to a poor outcome after stroke.[76,79–81] Indeed, previous studies have shown a graded negative relationship between serum cholesterol levels and the risk of nosocomial infections.[82] Finally, serum levels of total cholesterol are known to be negative acute phase reactants, and decrease after ischemic and hemorrhagic stroke, and might therefore reflect the severity of stroke.[76,83,84] However, in the present multivariate analysis, there was no association between low total cholesterol levels and increased mortality. Even more importantly, these findings in the acute stroke setting should not be misinterpreted as indicating that elevated cholesterol levels also confer long-term survival benefit in these patients. On the contrary, in patients with prior cerebrovascular disease, high levels of total cholesterol increase the risk of myocardial infarction,[85] whereas treatment with a statin reduces the incidence of major cardiovascular events in this population.[86,87]

In conclusion, this study demonstrated that a raised SUA level is an independent predictor of early death after acute stroke. Although traditional risk factors such as hypertension, diabetes mellitus and hyperlipidaemia are nowadays treated aggressively after stroke, there is a need to identify additional modifiable risk factors that can affect morbidity and mortality. In this context, it is noteworthy that, beyond allopurinol and the well-established uricosuric drugs, several other agents can decrease the SUA level, such as losartan and fenofibrate.[88] More importantly, we have shown that administration of statins significantly reduces SUA levels[89] and preserves renal function,[90] and these actions independently protect against vascular events in high-risk patients.[59] Thus, a reduction in SUA level could also partially contribute to the beneficial effects of statins against stroke.[72,87] However, further prospective studies are required to identify the precise role of hyperuricemia in cerebrovascular disease before routine treatment of this potential risk factor can be recommended.

References

1. Gertler MM, Garn SM, Levine SA. Serum uric acid in relation to age and physique in health and in coronary heart disease. *Ann Intern Med* 1951; **34:** 1421–1431.
2. Lehto S, Ronnemaa T, Pyorala K, Laakso M. Predictors of stroke in middle-aged patients with non-insulin-dependent diabetes. *Stroke* 1996; **27:** 63–68.
3. Liese AD, Hense HW, Lowel H, Doring A, Tietze M, Keil U. Association of serum uric acid with all-cause and cardiovascular disease mortality and incident myocardial infarction in the MONICA Augsburg cohort: World Health Organization Monitoring Trends and Determinants in Cardiovascular Diseases. *Epidemiology* 1999; **10:** 391–397.
4. Niskanen LK, Laaksonen DE, Nyyssonen K, Alfthan G, Lakka TA, Salonen JT. Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: A prospective cohort study. *Arch Intern Med* 2004; **164:** 1546–1551.
5. Kawamoto R, Tomita H, Oka Y, Kodama A, Ohtsuka N, Kamitani A. Association between uric acid and carotid atherosclerosis in elderly persons. *Intern Med* 2005; **44:** 787–793.
6. Bos MJ, Koudstaal PJ, Hofman A, Witteman JC, Breteler MM. Uric acid is a risk factor for myocardial infarction and stroke: The Rotterdam study. *Stroke* 2006; **37:** 1503–1507.
7. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971–1992: National Health and Nutrition Examination Survey. *JAMA* 2000; **283:** 2404–2410.
8. Hoieggen A, Alderman MH, Kjeldsen SE, Julius S, Devereux RB, de Faire U, et al. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. *Kidney Int* 2004; **65:** 1041–1049.
9. Mazza A, Pessina AC, Pavei A, Scarpa R, Tikhonoff V, Casiglia E. Predictors of stroke mortality in elderly people from the general population: The CArdiovascular STudy in the ELderly. *Eur J Epidemiol* 2001; **17:** 1097–1104.
10. Verdecchia P, Schillaci G, Reboldi G, Santeusanio F, Porcellati C, Brunetti P. Relation between serum uric acid and risk of cardiovascular disease in essential hypertension: The PIUMA study. *Hypertension* 2000; **36:** 1072–1078.
11. Leyva F, Anker SD, Godsland IF, Teixeira M, Hellewell PG, Kox WJ, et al. Uric acid in chronic heart failure: A marker of chronic inflammation. *Eur Heart J* 1998; **19:** 1814–1822.
12. Sakai H, Tsutamoto T, Tsutsui T, Tanaka T, Ishikawa C, Horie M. Serum level of uric acid, partly secreted from the failing heart, is a prognostic marker in patients with congestive heart failure. *Circ J* 2006; **70:** 1006–1011.
13. Lehto S, Niskanen L, Ronnemaa T, Laakso M. Serum uric acid is a strong predictor of stroke in patients with non-insulin-dependent diabetes mellitus. *Stroke* 1998; **29:** 635–639.
14. Newman EJ, Rahman FS, Lees KR, Weir CJ, Walters MR. Elevated serum urate concentration independently predicts poor outcome following stroke in patients with diabetes. *Diabetes Metab Res Rev* 2006; **22:** 79–82.
15. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: The Framingham Heart Study. *Ann Intern Med* 1999; **131:** 7–13.
16. Nieto FJ, Iribarren C, Gross MD, Comstock GW, Cutler RG. Uric acid and serum antioxidant capacity: A reaction to atherosclerosis? *Atherosclerosis* 2000; **148:** 131–139.
17. Iseki K, Ikemiya Y, Inoue T, Iseki C, Kinjo K, Takishita S. Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. *Am J Kidney Dis* 2004; **44:** 642–650.
18. Daskalopoulou SS, Athyros VG, Elisaf M, Mikhailidis DP. Uric acid levels and vascular disease. *Curr Med Res Opin* 2004; **20:** 951–954.
19. Broderick JP, Adams HP Jr, Barsan W, Feinberg W, Feldmann E, Grotta J, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 1999; **30:** 905–915.
20. Adams HP Jr, Adams RJ, Brott T, del Zoppo GJ, Furlan A, Goldstein LB, et al. Guidelines for the early management of patients with ischemic stroke: A Scientific Statement from the Stroke Council of the American Stroke Association. *Stroke* 2003; **34:** 1056–1083.
21. Adams H, Adams R, Del Zoppo G, Goldstein LB. Guidelines for the early management of patients with ischemic stroke: 2005 Guidelines update: A Scientific Statement from the Stroke Council of the American Heart Association/American Stroke Association. *Stroke* 2005; **36:** 916–923.
22. Milionis HJ, Kalantzi KJ, Goudevenos JA, Seferiadis K, Mikhailidis DP, Elisaf MS. Serum uric acid levels and risk for acute ischaemic non-embolic stroke in elderly subjects. *J Intern Med* 2005; **258:** 435–441.
23. Daskalopoulou SS, Athyros VG, Elisaf M, Mikhailidis D. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. *Kidney Int* 2004; **66:** 1714–1715.
24. Weir CJ, Muir SW, Walters MR, Lees KR. Serum urate as an independent predictor of poor outcome and future vascular events after acute stroke. *Stroke* 2003; **34:** 1951–1956.
25. Cherubini A, Polidori MC, Bregnocchi M, Pezzuto S, Cecchetti R, Ingegni T, et al. Antioxidant profile and early outcome in stroke patients. *Stroke* 2000; **31:** 2295–2300.
26. Wong KY, MacWalter RS, Fraser HW, Crombie I, Ogston SA, Struthers AD. Urate predicts subsequent cardiac death in stroke survivors. *Eur Heart J* 2002; **23:** 788–793.
27. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360:** 1903–1913.
28. Asia Pacific Cohort Studies Collaboration. Blood pressure indices and cardiovascular disease in the Asia pacific region: A pooled analysis. *Hypertension* 2003; **42:** 69–75.
29. Sundström J, Sullivan L, D'Agostino RB, Levy D, Kannel WB, Vasan RS. Relations of serum uric aid to longitudinal blood pressure tracking and hypertension incidence in the Framingham Heart Study.

Hypertension 2005; **45:** 28–33.
30. Masuo K, Kawaguchi H, Mikami H, Ogihara T, Tuck ML. Serum uric acid and plasma norepinephrine concentrations predict subsequent weight gain and blood pressure elevation. *Hypertension* 2003; **42:** 474–480.
31. Cannon PJ, Stason WB, Demartini FE, Sommers SC, Laragh JH. Hyperuricemia in primary and renal hypertension. *N Engl J Med* 1966; **275:** 457–464.
32. Messerli FH, Frohlich ED, Dreslinski GR, Suarez DH, Aristimuno GG. Serum uric acid in essential hypertension: An indicator of renal vascular involvement. *Ann Intern Med* 1980; **93:** 817–821.
33. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, et al. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension* 2001; **38:** 1101–1106.
34. Watanabe S, Kang DH, Feng L, Nakagawa T, Kanellis J, Lan H, et al. Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. *Hypertension* 2002; **40:** 355–360.
35. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, et al. A role for uric acid in the progression of renal disease. *J Am Soc Nephrol* 2002; **13:** 2888–2897.
36. Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T, et al. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. *Hypertension* 2003; **41:** 1287–1293.
37. Gu L, Okada Y, Clinton SK, Gerard C, Sukhova GK, Libby P, et al. Absence of monocyte chemoattractant protein-1 reduces atherosclerosis in low density lipoprotein receptor-deficient mice. *Mol Cell* 1998; **2:** 275–281.
38. Love S. Oxidative stress in brain ischemia. *Brain Pathol* 1999; **9:** 119–131.
39. Sun AY, Chen YM. Oxidative stress and neurodegenerative disorders. *J Biomed Sci* 1998; **5:** 401–414.
40. Maxwell SR, Lip GY. Free radicals and antioxidants in cardiovascular disease. *Br J Clin Pharmacol* 1997; **44:** 307–317.
41. Gariballa SE, Hutchin TP, Sinclair AJ. Antioxidant capacity after acute ischaemic stroke. *Q J Med* 2002; **95:** 685–690.
42. Spranger M, Krempien S, Schwab S, Donneberg S, Hacke W. Superoxide dismutase activity in serum of patients with acute cerebral ischemic injury: Correlation with clinical course and infarct size. *Stroke* 1997; **28:** 2425–2428.
43. Leinonen JS, Ahonen JP, Lonnrot K, Jehkonen M, Dastidar P, Molnar G, et al. Low plasma antioxidant activity is associated with high lesion volume and neurological impairment in stroke. *Stroke* 2000; **31:** 33–39.
44. Squadrito GL, Cueto R, Splenser AE, Valavanidis A, Zhang H, Uppu RM, et al. Reaction of uric acid with peroxynitrite and implications for the mechanism of neuroprotection by uric acid. *Arch Biochem Biophys* 2000; **376:** 333–337.
45. Chamorro A, Obach V, Cervera A, Revilla M, Deulofeu R, Aponte JH. Prognostic significance of uric acid serum concentration in patients with acute ischemic stroke. *Stroke* 2002; **33:** 1048–1052.
46. Abuja PM. Ascorbate prevents prooxidant effects of urate in oxidation of human low density lipoprotein. *FEBS Lett* 1999; **446:** 305–308.
47. Waring WS, Webb DJ, Maxwell SRJ. Effect of local hyperuricaemia on endothelial function in the human forearm vascular bed. *Br J Clin Pharmacol* 2000; **49:** 511P.
48. Bagnati M, Perugini C, Cau C, Bordone R, Albano E, Bellomo G. When and why a water-soluble antioxidant becomes pro-oxidant during copper-induced low-density lipoprotein oxidation: A study using uric acid. *Biochem J* 1999; **340:** 143–152.
49. Boogaerts MA, Hammerschmidt DE, Roelant C, Verwilghen RL, Jacob HS. Mechanisms of vascular damage in gout and oxalosis: Crystal induced, granulocyte mediated, endothelial injury. *Thromb Haemost* 1983; **50:** 576–580.
50. Duff GW, Atkins E, Malawista SE. The fever of gout: Urate crystals activate endogenous pyrogen production from human and rabbit mononuclear phagocytes. *Trans Assoc Am Physicians* 1983; **96:** 234–245.
51. Nakanishi N, Shiraishi T, Wada M. C-reactive protein concentration is more strongly related to metabolic syndrome in women than in men: The Minoh Study. *Circ J* 2005; **69:** 386–391.
52. Kondo N, Nomura M, Nakaya Y, Ito S, Ohguro T. Association of inflammatory marker and highly sensitive C-reactive protein with aerobic exercise capacity, maximum oxygen uptake and insulin resistance in healthy middle-aged volunteers. *Circ J* 2005; **69:** 452–457.
53. Patetsios P, Rodino W, Wisselink W, Bryan D, Kirwin JD, Panetta TF. Identification of uric acid in aortic aneurysms and atherosclerotic artery. *Ann NY Acad Sci* 1996; **800:** 243–245.
54. Tsouli SG, Liberopoulos EN, Mikhailidis DP, Athyros VG, Elisaf MS. Elevated serum uric acid levels in metabolic syndrome: An active component or an innocent bystander? *Metabolism* 2006; **55:** 1293–1301.
55. Ishizaka N, Ishizaka Y, Toda EI, Nagai R, Yamakado M. Association between serum uric acid, metabolic syndrome, and carotid atherosclerosis in Japanese individuals. *Arterioscler Thromb Vasc Biol* 2005; **25:** 1038–1044.
56. Rathmann W, Funkhouser E, Dyer AR, Roseman JM. Relations of hyperuricemia with the various components of the insulin resistance syndrome in young black and white adults: The CARDIA study [Coronary Artery Risk Development in Young Adults]. *Ann Epidemiol* 1998; **8:** 250–261.
57. Schmidt MI, Duncan BB, Watson RL, Sharrett AR, Brancati FL, Heiss G. A metabolic syndrome in whites and African-Americans: The Atherosclerosis Risk in Communities baseline study. *Diabetes Care* 1996; **19:** 414–418.
58. Yoo TW, Sung KC, Shin HS, Kim BJ, Kim BS, Kang JH, et al. Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome. *Circ J* 2005; **69:** 928–933.
59. Athyros VG, Mikhailidis DP, Liberopoulos EN, Kakafika AI, Karagiannis A, Papageorgiou AA, et al. Effect of statin treatment on renal function and serum uric acid levels and their relation to vascular events in patients with coronary heart disease and metabolic syndrome: A subgroup analysis of the GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) Study. *Nephrol Dial Transplant* 2007; **22:** 118–127.
60. Modan M, Halkin H, Karasik A, Lusky A. Elevated serum uric acid: A facet of hyperinsulinaemia. *Diabetologia* 1987; **30:** 713–718.
61. Nakagawa T, Hu H, Zharikov S, Tuttle KR, Short RA, Glushakova O, et al. A causal role for uric acid in fructose-induced metabolic syndrome. *Am J Physiol Renal Physiol* 2006; **290:** 625–631.
62. Onat A, Uyarel H, Hergenc G, Karabulut A, Albayrak S, Sarı I, et al. Serum uric acid is a determinant of metabolic syndrome in a population-based study. *Am J Hypertens* 2006; **19:** 1055–1062.
63. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: Findings from the third National Health and Nutrition Examination Survey. *JAMA* 2002; **287:** 356–359.
64. Athyros VG, Ganotakis ES, Elisaf M, Mikhailidis DP. The prevalence of the metabolic syndrome using the National Cholesterol Educational Program and International Diabetes Federation definitions. *Curr Med Res Opin* 2005; **21:** 1157–1159.
65. Milionis HJ, Rizos E, Goudevenos J, Seferiadis K, Mikhailidis DP, Elisaf MS. Components of the metabolic syndrome and risk for first-ever acute ischemic nonembolic stroke in elderly subjects. *Stroke* 2005; **36:** 1372–1376.
66. Kurl S, Laukkanen JA, Niskanen L, Laaksonen D, Sivenius J, Nyyssönen K, et al. Metabolic syndrome and the risk of stroke in middle-aged men. *Stroke* 2006; **37:** 806–811.
67. Chen HJ, Bai CH, Yeh WT, Chiu HC, Pan WH. Influence of metabolic syndrome and general obesity on the risk of ischemic stroke. *Stroke* 2006; **37:** 1060–1064.
68. Koren-Morag N, Goldbourt U, Tanne D. Relation between the metabolic syndrome and ischemic stroke or transient ischemic attack: A prospective cohort study in patients with atherosclerotic cardiovascular disease. *Stroke* 2005; **36:** 1366–1371.
69. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel Ⅲ). *JAMA* 2001; **285:** 2486–2497.
70. Zhang X, Patel A, Horibe H, Wu Z, Barzi F, Rodgers A, et al; Asia Pacific Cohort Studies Collaboration. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. *Int J Epidemiol* 2003; **32:** 563–572.
71. Horenstein RB, Smith DE, Mosca L. Cholesterol predicts stroke mortality in the Women's Pooling Project. *Stroke* 2002; **33:** 1863–1868.
72. Amarenco P, Labreuche J, Lavallée P, Touboul P-J. Statins in stroke prevention and carotid atherosclerosis: Systematic review and meta-analysis. *Stroke* 2004; **35:** 2902–2909.
73. Zuliani G, Cherubini A, Atti AR, Ble A, Vavalle C, Di Todaro F, et al. Low cholesterol levels are associated with short-term mortality in older patients with ischemic stroke. *J Gerontol A Biol Sci Med Sci* 2004; **59:** 293–297.
74. Vauthey C, de Freitas GR, van Melle G, Devuyst G, Bogousslavsky J. Better outcome after stroke with higher serum cholesterol levels. *Neurology* 2000; **54:** 1944–1949.
75. Dyker AG, Weir CJ, Lees KR. Influence of cholesterol on survival

after stroke: Retrospective study. *BMJ* 1997; **314:** 1584–1588.
76. Onder G, Landi F, Volpato S, Fellin R, Carbonin P, Gambassi G, et al. Serum cholesterol levels and in-hospital mortality in the elderly. *Am J Med* 2003; **115:** 265–271.
77. Brescianini S, Maggi S, Farchi G, Mariotti S, Di Carlo A, Baldereschi M, et al, for the ILSA Group. Low total cholesterol and increased risk of dying: Are low levels clinical warning signs in the elderly?: Results from the Italian Longitudinal Study on Aging. *J Am Geriatr Soc* 2003; **51:** 991–996.
78. Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: A cohort study. *Lancet* 2001; **358:** 351–355.
79. Iribarren C, Reed DM, Chen R, Yano K, Dwyer JH. Low serum cholesterol and mortality: Which is the cause and which is the effect? *Circulation* 1995; **92:** 2396–2403.
80. Abbott RD, Sharp DS, Burchfiel CM, Curb JD, Rodriguez BL, Hakim AA, et al. Cross-sectional and longitudinal changes in total and high-density-lipoprotein cholesterol levels over a 20-year period in elderly men: The Honolulu Heart Program. *Ann Epidemiol* 1997; **7:** 417–424.
81. Manolio TA, Ettinger WH, Tracy RP, Kuller LH, Borhani NO, Lynch JC, et al. Epidemiology of low cholesterol levels in older adults. *Circulation* 1993; **87:** 728–737.
82. Iribarren C, Jacobs DR Jr, Sidney S, Claxton AJ, Feingold KR. Cohort study of serum total cholesterol and in-hospital incidence of infectious diseases. *Epidemiol Infect* 1998; **121:** 335–347.
83. Woo J, Lam CWK, Wong HY, Teoh R, Nicholls MG. Acute and long-term changes in serum lipids after acute stroke. *Stroke* 1990; **21:** 1407–1411.
84. Lindgren A, Nilsson-Ehle P, Norrving B, Johansson BB. Plasma lipids and lipoproteins in subtypes of stroke. *Acta Neurol Scand* 1992; **86:** 572–578.
85. Patel A, Woodward M, Campbell DJ, Sullivan DR, Colman S, Chalmers J, et al. Plasma lipids predict myocardial infarction, but not stroke, in patients with established cerebrovascular disease. *Eur Heart J* 2005; **26:** 1910–1915.
86. Collins R, Armitage J, Parish S, Sleight P, Peto R; Heart Protection Collaborative Study Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20,536 people with cerebrovascular disease or other high-risk conditions. *Lancet* 2004; **363:** 757–767.
87. Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, et al; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006; **355:** 549–559.
88. Daskalopoulou SS, Tzovaras V, Mikhailidis DP, Elisaf M. Effect on serum uric acid levels of drugs prescribed for indications other than treating hyperuricaemia. *Curr Pharm Des* 2005; **11:** 4161–4175.
89. Athyros VG, Elisaf M, Papageorgiou AA, Symeonidis AN, Pehlivanidis AN, Bouloukos VI, et al; GREACE Study Collaborative Group. Effect of statins versus untreated dyslipidemia on serum uric acid levels in patients with coronary heart disease: A subgroup analysis of the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Am J Kidney Dis* 2004; **43:** 589–599.
90. Athyros VG, Mikhailidis DP, Papageorgiou AA, Symeonidis AN, Pehlivanidis AN, Bouloukos VI, et al. The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease: A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. *J Clin Pathol* 2004; **57:** 728–734.