Prognostic Value of Uric Acid in Patients With Acute Coronary Syndromes

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The association between uric acid and cardiovascular disease is incompletely understood. In particular, the prognostic value of uric acid in patients with acute coronary syndromes who undergo percutaneous coronary intervention has not been studied. This study included 5,124 patients with acute coronary syndromes who underwent percutaneous coronary intervention: 1,629 with acute ST-segment elevation myocardial infarction, 1,332 with acute non–ST-segment elevation myocardial infarction, and 2,163 with unstable angina. The primary end point was 1-year mortality. Patients were divided into quartiles according to uric acid level as follows: quartile 1, 1.3 to <5.3 mg/dl; quartile 2, 5.3 to <6.3 mg/dl; quartile 3, 6.3 to <7.5 mg/dl; and quartile 4, 7.5 to 18.4 mg/dl. There were 450 deaths during follow-up: 80 deaths in quartile 1, 77deaths in quartile 2, 72 deaths in quartile 3, and 221 deaths in quartile 4 of uric acid (Kaplan-Meier estimates of 1-year mortality 6.4%, 6.2%, 5.6%, and 17.4%, respectively; unadjusted hazard ratio 3.05, 95% confidence interval 2.54 to 3.67, p <0.001 for fourth vs first quartile of uric acid). After adjustment for traditional cardiovascular risk factors, renal function, and inflammatory status, the association between uric acid and mortality remained significant, with a 12% increase in the adjusted risk for 1-year mortality for every 1 mg/dl increase in the uric acid level. Uric acid improved the discriminatory power of the predictive model regarding 1-year mortality (absolute integrated discrimination improvement 0.008, p = 0.005). In conclusion, elevated levels of uric acid are an independent predictor of 1-year mortality across the whole spectrum of patients with acute coronary syndromes treated with percutaneous coronary intervention. **(Am J Cardiol 2012;109:1260–1265)**

Acute coronary syndromes (ACS) remain a leading cause of morbidity and mortality worldwide.[1–3] Despite the application of various risk stratification schemes,[4] ACS remain poorly characterized in terms of risk prediction. Uric acid is the end product of purine catabolism in humans and is readily tested in routine clinical practice. Although the possibility of an association between elevated uric acid level and cardiovascular disease has been recognized for >130 years,[5,6] the role of acid uric as a risk factor or a risk marker for cardiovascular disease remains a debatable issue. The association between elevated uric acid and increased risk for mortality has been investigated in the general population,[7,8] and in patients with congestive heart failure,[9] hypertension,[10] diabetes,[11] angiographically confirmed coronary artery disease,[12] and acute myocardial infarction.[13–16] No studies have addressed the prognostic value of this biomarker across the whole spectrum of patients with ACS. Thus, the aim of this study was to investigate whether there is an association between acid uric level and mortality across the whole spectrum of patients with ACS who undergo percutaneous coronary intervention (PCI).

Methods

This study included 5,124 patients with ACS who underwent PCI at the German Heart Center in Munich from March 2000 to December 2009. Of these, 1,629 patients had acute ST-segment elevation myocardial infarction (STEMI), 1,332 had acute non–ST-segment elevation acute myocardial infarction (NSTEMI), and 2,163 had unstable angina. The diagnosis of STEMI was based on the presence of chest pain lasting ≥20 minutes associated with typical changes on surface electrocardiography (ST-segment elevation ≥0.1 mV in ≥2 limb leads or ≥0.2 mV in ≥2 contiguous precordial leads or complete left bundle branch block of new onset). Unstable angina was diagnosed using Braunwald's criteria[17] plus documentation of significant coronary artery disease on coronary angiography. Diagnosis of NSTEMI required clinical and electrocardiographic criteria similar to those of unstable angina plus elevated troponin T (>0.03 μg/L) or creatine kinase or creatine kinase-myocardial band. In all included patients, the diagnosis of ACS was confirmed by coronary angiography. Weight and height were measured with patients wearing light clothing without shoes, and body mass index was calculated. The estimated glomerular filtration rate was calculated using the Cockcroft-Gault formula.[18] Detailed criteria of the diagnosis of cardiovascular risk factors are given in another publication from our group.[19] Patients with acute inflammatory states, known malignancies, or advanced kidney disease were not

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Table 1
Baseline demographic and angiographic characteristics

Variable	Quartile 1 (n = 1,271)	Quartile 2 (n = 1,261)	Quartile 3 (n = 1,300)	Quartile 4 (n = 1,292)	p Value
Age (years)	67.7 (59.2, 76.4)	67.0 (58.8, 74.5)	68.1 (59.1, 75.2)	69.7 (61.2, 77.5)	<0.001
Women	546 (43.0%)	293 (23.2%)	250 (19.2%)	273 (21.1%)	<0.001
Body mass index (kg/m^2)	25.7 (23.4, 28.1)	26.3 (24.5, 29.0)	27.4 (25.0, 29.8)	27.7 (25.0, 30.5)	<0.001
Diabetes mellitus	352 (27.7%)	303 (24.0%)	346 (26.6%)	430 (33.3%)	<0.001
Arterial hypertension	785 (61.8%)	802 (63.6%)	826 (63.5%)	742 (57.4%)	0.003
Current smoker	295 (23.2%)	281 (22.3%)	272 (20.9%)	235 (18.2%)	0.011
Hypercholesterolemia (≥240 mg/dl)	758 (59.6%)	817 (64.8%)	816 (62.8%)	810 (62.7%)	0.062
Previous myocardial infarction	268 (21.1%)	284 (22.5%)	344 (26.5%)	394 (30.5%)	<0.001
Previous coronary artery bypass surgery	156 (12.3%)	156 (12.4%)	171 (13.2%)	189 (14.6%)	0.261
Clinical presentation					<0.001
Unstable angina	525 (41.3%)	550 (43.6%)	604 (56.5%)	484 (37.5%)	
NSTEMI	281 (22.1%)	323 (25.6%)	299 (23.0%)	429 (33.2%)	
STEMI	465 (36.6%)	388 (30.8%)	397 (30.5%)	379 (29.3%)	
Cardiogenic shock	38 (3.0%)	42 (3.3%)	51 (3.9%)	146 (11.3%)	<0.001
Number of coronary artery narrowed					<0.001
1	310 (24.4%)	272 (21.5%)	258 (19.8%)	197 (15.2%)	
2	342 (26.9%)	340 (27.0%)	360 (27.7%)	314 (24.3%)	
3	619 (48.7%)	649 (51.5%)	682 (52.5%)	781 (60.4%)	
Multivessel disease	961 (75.6%)	989 (78.5%)	1,042 (80.2%)	1,095 (84.8%)	<0.001
Left ventricular ejection fraction (%)	54.0 (45.0, 61.0)	55.0 (45.0, 61.0)	54.0 (44.0, 61.0)	49.0 (37.0, 58.0)	<0.001
Uric acid (mg/dl)	4.6 (4.0, 5.0)	5.8 (5.5, 6.0)	6.8 (6.5, 7.1)	8.5 (7.9, 9.5)	<0.001
Serum creatinine (mg/dl)	0.9 (0.7, 1.0)	0.9 (0.8, 1.1)	1.0 (0.9, 1.3)	1.2 (1.0, 1.5)	<0.001
Glomerular filtration rate (ml/min)	79.2 (61.1, 100.4)	82.6 (63.4, 105.1)	79.8 (59.3, 102.0)	63.2 (44.4, 88.1)	<0.001
C-reactive protein (mg/L)	3.4 (1.2, 11.7)	3.2 (1.2, 9.6)	3.6 (1.4, 11.2)	5.8 (1.9, 17.7)	<0.001

Data are expressed as median (25th percentile, 75th percentile) or number of patients (percentage).

included in the present study. Written informed consent was obtained from all patients. The study was carried out in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee.

Angiographic data were analyzed in the quantitative angiographic core laboratory. Coronary artery disease was confirmed by the presence of coronary stenoses ≥50% luminal obstruction in ≥1 of the 3 main coronary arteries. Offline analysis of digital angiograms was performed in the core laboratory using an automated edge detection system (CMS; Medis Medical Imaging Systems, Leiden, The Netherlands). The global left ventricular ejection fraction was determined by left ventricular angiography using the area-length method. The diagnosis of stroke required confirmation by computed tomography or magnetic resonance imaging of the head. Stent implantation and periprocedural care were performed according to standard criteria. Postinterventional antiplatelet therapy consisted of clopidogrel (300 or 600 mg as a loading dose followed by 75 mg/day for ≥4 weeks to 6 months) and aspirin (200 mg/day administered orally and continued indefinitely). Drug-eluting stents were implanted in 3,366 patients (66%).

Blood samples were obtained before angiography in all patients. The uric acid concentration in plasma was determined with an enzymatic colorimetric test on a Cobas Integra 800 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Uricase cleaves uric acid to form allantoin and hydrogen peroxide, which reacts to form a quinoneimine dye. The measuring range in plasma is 0.20 to 25 mg/dl (11.9 to 1,500 μmol/L). The lower detection limit of the test is 0.20 mg/dl (11.9 μmol/l). The reference range for men is 3.4 to 7.0 mg/dl (202.3 to 416.5 μmol/L) and for women is 2.4 to 5.7 mg/dl (142.8 to 339.2 μmol/L).

The primary end point of the study was all-cause mortality. Nonfatal myocardial infarction, stroke, and target lesion revascularization were also evaluated. The follow-up protocol after discharge consisted of a phone interview at 1 month after the procedure, a visit at 6 months, and a phone interview at 12 months. Information about death was obtained from hospital records, death certificates, or phone contact with relatives of the patient or the referring physician. Patients who had cardiac symptoms underwent complete clinical, electrocardiographic, and laboratory evaluations. Follow-up information was obtained and adjudication of adverse events was performed by medical staff members unaware of clinical diagnosis, therapy received, or uric acid levels.

The normality of data distribution was assessed using a 1-sample Kolmogorov-Smirnov test. Data are presented as medians with 25th and 75th percentiles or as counts and proportions (percentages). Categorical data were compared using chi-square test. Continuous data were compared using Kruskal-Wallis rank-sum tests. A multiple linear regression model was used to identify the independent correlates of uric acid level. All variables listed in Table 1 were entered into the model. Survival analysis was performed by applying the Kaplan-Meier method. Univariate and multivariate Cox proportional-hazards models were used to assess the association between uric acid (entered into the model as a continuous variable) and 1-year mortality. All variables listed in Table 1 and the interaction between gender and uric acid level were entered into the model. The discrim-

Table 2
Correlates of uric acid concentration obtained by multiple linear regression model

Variable	β	p Value
Age	0.025	<0.001
Female gender	−0.974	0.001
Body mass index	0.138	<0.001
Diabetes mellitus	−0.115	0.035
Clinical presentation (STEMI vs angina)	−0.200	<0.001
Cardiogenic shock	0.655	<0.001
Previous coronary artery bypass surgery	−0.178	0.020
Left ventricular ejection fraction	−0.016	<0.001
Glomerular filtration rate	−0.025	<0.001

inatory power of the model regarding mortality with and without the inclusion of uric acid was assessed by calculating the C statistic in the Cox proportional-hazards model and the integrated discrimination improvement according to Pencina et al.[20] All analyses were performed using S-plus (Insightful Corporation, Seattle, Washington). Two-tailed p values <0.05 were considered to indicate statistical significance.

Results

A total of 5,124 patients with ACS were included in the study. Quartiles of uric acid concentrations were as follows: quartile 1, 1.3 to <5.3 mg/dl; quartile 2, 5.3 to <6.3 mg/dl; quartile 3, 6.3 to <7.5 mg/dl; and quartile 4, 7.5 to 18.4 mg/dl.

Table 1 lists baseline characteristics according to quartiles of uric acid. Patients with uric acid levels in the upper quartile were older, were less often women, and had higher body mass indexes. The upper quartile included higher proportions of those with previous myocardial infarction, diabetes, and multivessel disease and lower proportions of those with arterial hypertension and current smoking. These patients presented more often with cardiogenic shock, had lower left ventricular ejection fractions, had lower glomerular filtration rates, and had higher creatinine and C-reactive protein levels. There were also differences among patients of various uric acid quartiles with regard to clinical presentation (Table 1). Only 137 patients (2.7%) were receiving allopurinol on admission, with no difference among the groups (p = 0.11).

Independent determinants of uric acid level were identified using multivariate linear regression (see "Methods" for the variables entered into the model). The following variables were identified by the model as independently associated with elevated levels of uric acid: elderly age, male gender, higher body mass index, absence of diabetes, clinical presentation, cardiogenic shock, lack of previous coronary artery bypass surgery, left ventricular ejection fraction, and glomerular filtration rate (Table 2).

There were 450 deaths within the first year of follow-up. Deaths according to quartile of uric acid were as follows: 80 deaths in quartile 1, 77 in quartile 2, 72 in quartile 3, and 221 in quartile 4 (Kaplan-Meier estimates of 1-year mortality 6.4%, 6.2%, 5.6%, and 17.4%, respectively; unadjusted hazard ratio [HR] 3.05, 95% confidence interval [CI] 2.54 to 3.67, p <0.001 for fourth quartile vs first quartile; Figure 1). The other univariate associates of 1-year mortality are listed in Table 3.

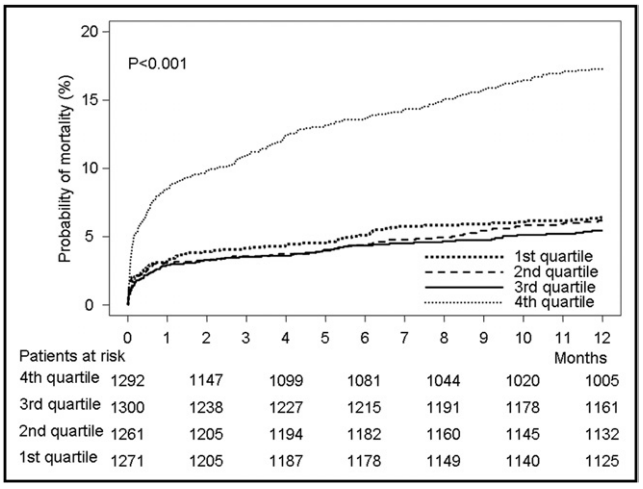

Figure 1. Kaplan-Meier curves of 1-year mortality in various quartiles of uric acid level.

Table 3
Correlates of 1-year mortality and hazard ratios calculated by univariate Cox proportional-hazards model

Variable	Unadjusted HR (95% CI)	p Value
Uric acid (1 mg/dl increase)	1.31 (1.26–1.36)	<0.001
Age (10-year increase)	1.89 (1.72–2.07)	<0.001
Male gender	1.45 (1.20–1.77)	<0.001
Diabetes mellitus	1.83 (1.52–2.21)	<0.001
Body mass index (5 kg/m^2 increase)	0.69 (0.60–0.78)	<0.001
Smoking	0.68 (0.52–0.87)	0.002
Hypercholesterolemia	0.56 (0.46–0.67)	<0.001
Arterial hypertension	0.43 (0.36–0.52)	<0.001
Previous myocardial infarction	1.30 (1.06–1.59)	0.010
Clinical presentation (STEMI, NSTEMI, unstable angina)	2.08 (1.85–2.34)	<0.001
Cardiogenic shock	12.49 (10.21–15.29)	<0.001
Glomerular filtration rate (30 ml/min decrease)	3.33 (2.94–3.85)	<0.001
Baseline C-reactive protein (1 mg/L increase)	1.02 (1.01–1.03)	<0.001
Left ventricular ejection fraction (10% decrease)	1.87 (1.73–2.01)	<0.001
Multivessel disease (vs single-vessel disease)	2.93 (2.10–4.11)	<0.001

The association between uric acid and 1-year mortality was assessed also according to clinical presentation of the patients. There were 234 deaths among patients with STEMI (n = 1,629) within the first year after PCI: 113 among those in quartile 4 (n = 379) and 121 among those in quartiles 1 to 3 (Kaplan-Meier estimates of 1-year mortality 30.7% and 9.8%, respectively; HR 3.56, 95% CI 2.80 to 4.52, p <0.001). There were 153 deaths among patients with NSTEMI (n = 1,332) within the first year after PCI: 85 in quartile 4 (n = 429) and 68 in quartiles 1 to 3 (Kaplan-Meier estimates of 1-year mortality 21.1% and 7.0%, respectively; HR 2.80, 95% CI 2.06 to 3.80, p <0.001). There

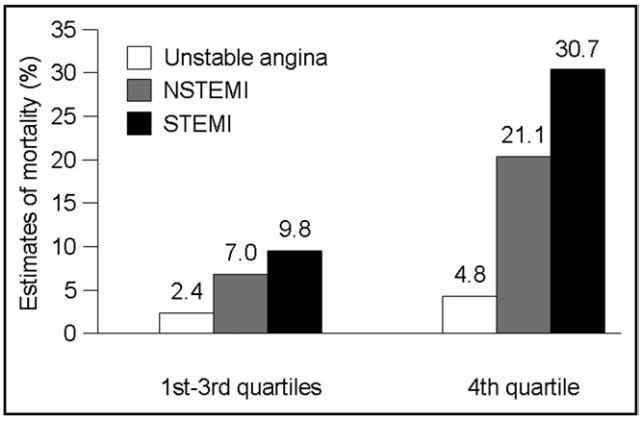

Figure 2. Estimates of 1-year mortality in patients in the lower 3 quartiles versus quartile 4.

Table 4
Correlates of 1-year mortality and hazard ratios calculated by multivariate Cox proportional-hazards model

Variable	Adjusted HR (95% CI)	p Value
Uric acid (1 mg/dl increase)	1.12 (1.06–1.18)	<0.001
Age (10-year increase)	1.30 (1.12–1.51)	<0.001
Diabetes mellitus	1.42 (1.12–1.80)	0.003
Clinical presentation (STEMI vs unstable angina)	1.41 (1.19–1.67)	<0.001
Cardiogenic shock	4.66 (3.44–6.31)	<0.001
Multivessel disease (vs single-vessel disease)	2.06 (1.35–3.14)	<0.001
Glomerular filtration rate (30 ml/min decrease)	1.68 (1.34–2.09)	<0.001
Left ventricular ejection fraction (10% decrease)	1.37 (1.25–1.51)	<0.001
Baseline C-reactive protein (1 mg/L increase)	1.01 (1.00–1.02)	0.009

were 63 deaths in patients with unstable angina (n = 2,163) within the first year after PCI: 23 in quartile 4 (n = 484) and 40 in quartiles 1 to 3 (Kaplan-Meier estimates of 1-year mortality 4.8% and 2.4%, respectively; HR 1.99, 95% CI 1.20 to 3.30, p = 0.007). Mortality estimates according to clinical presentation are listed in Figure 2.

Nonfatal myocardial infarction occurred in 205 patients: 60 in quartile 1, 42 in quartile 2, 49 in quartile 3, and 54 in quartile 4 (Kaplan-Meier estimates of nonfatal myocardial infarction 4.8%, 3.4%, 3.8%, and 4.5%, respectively; p = 0.306). Stroke occurred in 58 patients: 12 in quartile 1, 18 in quartile 2, 16 in quartile 3, and 12 in quartile 4 (Kaplan-Meier estimates of stroke 1.0%, 1.5%, 1.2%, and 1.0%, respectively; p = 0.635). Target lesion revascularization was required in 982 patients: 243 in quartile 1, 238 in quartile 2, 280 in quartile 3, and 221 in quartile 4 (Kaplan-Meier estimates of target lesion revascularization 20.5%, 20.1%, 23.0%, and 20.1%, respectively; p = 0.261).

The multivariate Cox proportional-hazards model (see "Methods" for the variables entered into the model) identified uric acid, age, diabetes, presentation pattern, cardiogenic shock, multivessel disease, glomerular filtration rate, the left ventricular ejection fraction, and C-reactive protein level as independent correlates of 1-year mortality (Table 4). Of note, for every 1 mg/dl increase in the uric acid concentration, the adjusted risk for 1-year mortality increased by 12%. There was no interaction between gender and uric acid regarding 1-year mortality (p for interaction = 0.792). This demonstrates no difference according to gender in the association between uric acid and 1-year mortality.

For the end point of all-cause mortality, the C statistic of the model without the inclusion of uric acid was 0.860. After adding uric acid to the model, the C statistic was 0.863. The inclusion of uric acid in the multivariate model was associated with a significant improvement of the discriminatory power of the model regarding the prediction of 1-year mortality (absolute integrated discrimination improvement 0.008, relative integrated discrimination improvement 4.0%, p = 0.005).

Discussion

The main findings of the present study can be summarized as follows. First, elevated levels of uric acid in patients with ACS treated with PCI are an independent correlate of 1-year mortality. For every 1 mg/dl increase in uric acid level, the adjusted risk for 1-year mortality was increased by 12%. Second, subgroup analyses in patients with STEMI, NSTEMI, and unstable angina showed that elevated levels of uric acid predict an increased risk for 1-year mortality across the whole spectrum of patients with ACS. Last, elevated levels of uric acid did not predict the occurrence of nonfatal myocardial infarction or stroke or the need for target lesion revascularization over the first year after PCI.

In a series of 1,124 patients with acute myocardial infarction, Kojima et al[13] showed that serum level of uric acid correlated closely with Killip class and predicted the development of congestive heart failure and short- and long-term mortality. In a recent study, Lazzeri et al[14] demonstrated in 466 patients with STEMI who underwent primary PCI <12 hours after the onset of symptoms that uric acid level was an independent predictor of in-hospital mortality. More recently, the same group showed in a larger series of patients with STEMI (856 patients) that uric acid predicted the occurrence of complications in the intensive cardiac care unit but not early mortality after adjustment for renal function and degree of myocardial necrosis.[15] In another recent study of patients with acute myocardial infarction and impaired renal function treated with PCI, elevated levels of uric acid predicted short-term and long-term mortality in all degrees of renal dysfunction.[16] Of note, elevated uric acid levels predicted death in patients who developed contrast-induced nephropathy.[16] The subgroup analysis from our study that included 1,629 patients with STEMI demonstrated that patients in quartile 4 of uric acid (7.5 to 18.4 mg/dl) had a 3.5-fold increase in the risk for 1-year mortality compared to patients in the lower 3 quartiles (uric acid concentration 1.3 to <7.5 mg/dl).

In the present study, we found that elevated levels of uric acid were associated with increased risk for 1-year mortality across the whole spectrum of patients with ACS. Mechanisms responsible for the increase in the risk for mortality with the increase in the uric acid level are not entirely clear. Analysis of the predictors of elevated uric acid level dem-

onstrated that elevated uric acid level is associated with factors that connote a more adverse cardiovascular risk profile. Expectedly, impaired renal function was an independent correlate of elevated uric acid level. Of note, impaired renal function is known to be a powerful independent predictor of short- and long-term mortality in patients with ACS treated with PCI.[21] Thus, the prognostic power of uric acid may be conveyed by cardiovascular risk accumulated in patients with increased levels of this biomarker. However, the preservation of an independent association between uric acid and mortality after adjustment for cardiovascular risk and other relevant clinical variables shows that uric acid offers prognostic information beyond that mediated by risk factors that are clustered in patients with elevated uric acid levels. Moreover, the inclusion of uric acid in the multivariate model alongside the other variables significantly improved the predictive power of the model regarding mortality, suggesting that uric acid per se may contribute to increased cardiovascular risk. A large body of evidence links uric acid with the promotion of atherosclerosis and vascular adverse events. It has been shown that increased levels of uric acid may be a marker of increased xanthine oxidase activity, which is a major source of oxygen free radicals.[22,23] Thus, elevated uric acid level may be a marker of increased oxidative stress. Furthermore, it has been reported that uric acid is linked with insulin resistance,[24] increased lipid peroxidation,[25] and increased platelet adhesiveness and activation.[26] The association of uric acid with proinflammatory states[27] or even a direct inflammatory role through the induction of cytokine secretion[28] has also been reported. Studies have also shown that elevated uric acid levels cause endothelial dysfunction, leading to reduced nitric oxide levels,[29,30] known to have a pivotal role in the promotion of atherosclerosis and the genesis of acute vascular events. Nevertheless, in the present study, we did not find any significant association between the occurrence of nonfatal myocardial infarction, stroke, or the need for repeat revascularization after PCI and uric acid level. It may be hypothesized that myocardial infarctions occurring in the setting of hyperuricemia may be more often fatal, and thus they are accounted as deaths.

An interesting finding of the present study was the unequal distribution of mortality in different uric acid quartiles, with a significant steep increase in mortality in patients in quartile 4 (>7.5 mg/dl) compared to the lower 3 quartiles, suggesting a threshold effect. Kojima et al[13] also reported that the best cut-off of uric acid level regarding mortality prediction in patients with acute myocardial infarction was 447 μmol/L, which closely coincides with the fourth quartile cutoff (7.5 mg/dl) in the present study.

The present study had some limitations. Although the patients were prospectively collected, the analysis in essence is retrospective. Because of the very limited number of patients receiving allopurinol therapy, the impact of this drug on prognosis could not be assessed. Although 1-year follow-up is typical for interventional studies, a longer follow-up period would have been desirable.

1. Fox KA, Cokkinos DV, Deckers J, Keil U, Maggioni A, Steg G. The ENACT study: a pan-European survey of acute coronary syndromes. *Eur Heart J* 2000;21:1440–1449.
2. Fox KA, Goodman SG, Anderson FA Jr, Granger CB, Moscucci M, Flather MD, Spencer F, Budaj A, Dabbous OH, Gore JM; GRACE Investigators. From guidelines to clinical practice: the impact of hospital and geographical characteristics on temporal trends in the management of acute coronary syndromes. The Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2003;24:1414–1424.
3. Kolansky DM. Acute coronary syndromes: morbidity, mortality, and pharmacoeconomic burden. *Am J Manag Care* 2009;15(suppl):S36–S41.
4. de Araújo Gonçalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. *Eur Heart J* 2005; 26:865–872.
5. Mohamed FA. On Bright's disease, and its essential symptoms. *Lancet* 1879;1:399–401.
6. Haig A. On uric acid and arterial tension. *BMJ* 1889;1:288–291.
7. 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.
8. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study 1971-1992. *JAMA* 2000;283:2404–2410.
9. Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, Davos CH, Cicoira M, Shamim W, Kemp M, Segal R, Osterziel KJ, Leyva F, Hetzer R, Ponikowski P, Coats AJ. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. *Circulation* 2003;107:1991–1997.
10. Franse LV, Pahor M, Di Bari M, Shorr RI, Wan JY, Somes GW, Applegate WB. Serumuric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). *J Hypertens* 2000;18:1149–1154.
11. Lehto S, Niskanen L, Rönnemaa 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.
12. Bickel C, Rupprecht HJ, Blankenberg S, Rippin G, Hafner G, Daunhauer A, Hofmann KP, Meyer J. Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease. *Am J Cardiol* 2002;89:12–17.
13. Kojima S, Sakamoto T, Ishihara M, Kimura K, Miyazaki S, Yamagishi M, Tei C, Hiraoka H, Sonoda M, Tsuchihashi K, Shimoyama N, Honda T, Ogata Y, Matsui K, Ogawa H; Japanese Acute Coronary Syndrome Study (JACSS) Investigators. Prognostic usefulness of serum uric acid after acute myocardial infarction (the Japanese Acute Coronary Syndrome Study). *Am J Cardiol* 2005;96:489–495.
14. Lazzeri C, Valente S, Chiostri M, Sori A, Bernardo P, Gensini GF. Uric acid in the acute phase of ST elevation myocardial infarction submitted to primary PCI: its prognostic role and relation with inflammatory markers: a single center experience. *Int J Cardiol* 2010;138: 206–209.
15. Lazzeri C, Valente S, Chiostri M, Picariello C, Gensini GF. Uric acid in the early risk stratification of ST-elevation myocardial infarction. *Intern Emerg Med*. In press.
16. Kowalczyk J, Francuz P, Swoboda R, Lenarczyk R, Sredniawa B, Golda A, Kurek T, Mazurek M, Podolecki T, Polonski L, Kalarus Z. Prognostic significance of hyperuricemia in patients with different types of renal dysfunction and acute myocardial infarction treated with percutaneous coronary intervention. *Nephron Clin Pract* 2010;116: c114–c122.
17. Hamm CW, Braunwald E. A classification of unstable angina revisited. *Circulation* 2000;102:118–122.
18. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31–41.
19. Ndrepepa G, Braun S, Iijima R, Keta D, Byrne RA, Schulz S, Mehilli J, Schömig A, Kastrati A. Total leucocyte count, but not C-reactive protein, predicts 1-year mortality in patients with acute coronary syndromes treated with percutaneous coronary intervention. *Clin Sci (Lond)* 2009;116:651–658.
20. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;27:157–172.
21. Seyfarth M, Kastrati A, Mann JF, Ndrepepa G, Byrne RA, Schulz S, Mehilli J, Schömig A. Prognostic value of kidney function in patients with ST-elevation and non-ST-elevation acute myocardial infarction treated with percutaneous coronary intervention. *Am J Kidney Dis* 2009;54:830–839.

22. Landmesser U, Spiekermann S, Dikalov S, Tatge H, Wilke R, Kohler C, Harrison DG, Hornig B, Drexler H. Vascular oxidative stress and endothelial dysfunction in patients with chronic heart failure: role of xanthine-oxidase and extracellular superoxide dismutase. *Circulation* 2002;106:3073–3078.
23. Ogino K, Kato M, Furuse Y, Kinugasa Y, Ishida K, Osaki S, Kinugawa T, Igawa O, Hisatome I, Shigemasa C, Anker SD, Doehner W. Uric acid-lowering treatment with benzbromarone in patients with heart failure: a double-blind placebo-controlled crossover preliminary study. *Circ Heart Fail* 2010;3:73–81.
24. Baldwin W, McRae S, Marek G, Wymer D, Pannu V, Baylis C, Johnson RJ, Sautin YY. Hyperuricemia as a mediator of the proinflammatory endocrine imbalance in the adipose tissue in a murine model of the metabolic syndrome. *Diabetes* 2011;60:1258–1269.
25. De Scheerder IK, van de Kraay AM, Lamers JM, Koster JF, de Jong JW, Serruys PW. Myocardial malondialdehyde and uric acid release after short-lasting coronary occlusions during coronary angioplasty: potential mechanisms for free radical generation. *Am J Cardiol* 1991;68:392–395.
26. Alderman M, Aiyer KJ. Uric acid: role in cardiovascular disease and effects of losartan. *Curr Med Res Opin* 2004;20:369–379.
27. Ruggiero C, Cherubini A, Ble A, Bos AJ, Maggio M, Dixit VD, Lauretani F, Bandinelli S, Senin U, Ferrucci L. Uric acid and inflammatory markers. *Eur Heart J* 2006;27:1174–1181.
28. Sánchez-Lozada LG, Nakagawa T, Kang DH, Feig DI, Franco M, Johnson RJ, Herrera-Acosta J. Hormonal and cytokine effects of uric acid. *Curr Opin Nephrol Hypertens* 2006;15:30–33.
29. Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, Krotova K, Block ER, Prabhakar S, Johnson RJ. Hyperuricemia induces endothelial dysfunction. *Kidney Int* 2005;67:1739–1742.
30. Sánchez-Lozada LG, Tapia E, López-Molina R, Nepomuceno T, Soto V, Avila-Casado C, Nakagawa T, Johnson RJ, Herrera-Acosta J, Franco M. Effects of acute and chronic L-arginine treatment in experimental hyperuricemia. *Am J Physiol Renal Physiol* 2007;292:F1238–F1244.