Implications of Hyperuricemia in Severe Coronary Artery Disease

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Hyperuricemia has been associated with mortality in patients with coronary artery disease (CAD). However, its prognostic value remains unknown in the context of severe CAD with heavy atherosclerotic burden in all 3 vessels. We used data from a large cohort of consecutive patients with severe CAD. The primary end point was all-cause death. Propensity score matching was used to identify 2 cohorts of patients with similar baseline characteristics. A total of 8,529 patients with available serum uric acid data were included in the study. Hyperuricemia was present in 1,207 (14.2%) patients. At baseline, hyperuricemic patients had more co-morbidities, and more often received medical therapy alone. During the median follow-up of 7.5 years, significantly more deaths occurred in hyperuricemic patients compared with normouricemic patients (22.5% vs 13.7%; $p < 0.001$). Multivariable analyses showed that hyperuricemia was associated with an increased risk of mortality (hazard ratio 1.33; 95% confidence interval 1.15 to 1.53; $p < 0.001$). Propensity score matching yielded similar results (hazard ratio 1.33; 95% confidence interval 1.11 to 1.61; $p = 0.003$). The association was relatively consistent across subgroups, except for an interaction between age and hyperuricemia. Addition of uric acid to SYNTAX score II provided significant improvements of reclassification and discrimination for mortality prediction. In conclusion, hyperuricemia is relatively common among patients with severe CAD and is independently associated with mortality. Moreover, uric acid can improve the predictability of a well-established risk score. **(Am J Cardiol 2019;123:558−564)**

Accurate risk stratification is essential for evaluation of patients with coronary artery disease (CAD), especially those with severe CAD in the presence of advanced atheroma burden in all 3 vessels. In this regard, the SYNTAX score (SS) and SYNTAX score II (SSII) have been developed to predict long-term mortality in patients with severe CAD.[1,2] Serum uric acid (UA) is a low-cost biomarker applicable to routine clinical practice. Emerging evidence indicates that an elevated UA level can independently predict mortality in patients with stable CAD,[3,4] or acute coronary syndrome.[5−10] However, other studies failed to confirm these associations.[11,12] The prognostic significance of hyperuricemia also remains unclear in the context of severe CAD. To address these issues, we conducted the present study to evaluate the prognostic value of hyperuricemia in patients with severe CAD.

Methods

The study evaluated data from a large cohort involving 8,943 consecutive patients with severe CAD at Fuwai Hospital (Beijing, China) between 2004 and 2011. Eligible patients had severe CAD which was defined as angiographically confirmed stenosis of ≥50% in all 3 main epicardial coronary arteries (left anterior descending, left circumflex, and right coronary arteries), with or without involvement of the left main artery, and were willing to undergo follow-up. Patients received medical therapy alone, percutaneous coronary intervention, or coronary artery bypass grafting (CABG) according to contemporary practice guidelines[13,14] and their preferences. Baseline and procedural data for all participants were collected in a database by independent clinical research coordinators. Outcome data were obtained by telephone interview, follow-up letter, or clinic visit. The last follow-up was completed in 2016, with a response rate of 80.6%. In the present analyses, patients with a history of CABG were excluded, because the SS could not be calculated in these subjects. The primary endpoint was all-cause death. Secondary end points included cardiac death and major adverse cardiac and cerebrovascular events (MACCE), a composite of all-cause death, myocardial infarction (MI), stroke, or unplanned revascularization. All deaths were considered

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See page 563 for disclosure information.

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cardiac unless an unequivocal noncardiac cause could be established. The study complied with the principles of the Declaration of Helsinki and was approved by the Review Board of Fuwai Hospital. Written informed consent was obtained from all participants.

Serum UA was defined as the first value documented in the medical record after admission for coronary angiography. Hyperuricemia was defined as serum UA of >416 mmol/L (7 mg/dl) in men and >357 mmol/L (6 mg/dl) in women.

Propensity score (PS) matching was used to identify a normouricemic cohort with similar baseline and procedural characteristics to the hyperuricemic patients. The PS was estimated by a multivariable logistic regression model. The covariates included in the model were age, gender, body mass index, hypertension, previous MI, hyperlipidemia, history of stroke, diabetes, chronic kidney disease (CKD), peripheral arterial disease, clinical presentation (stable angina pectoris, unstable angina pectoris, or acute myocardial infarction), left main coronary artery involvement, left ventricular ejection fraction (<40 or ≥40), serum creatine, creatinine clearance, procedure (medical therapy, percutaneous coronary intervention, or CABG), aspirin, and statins. PS matching was performed with a ratio of 1:1 and a caliper of 0.1 using R software version 3.4.3 (R Core Team, Vienna, Austria).

Continuous variables were presented as median and interquartile range, and categorical variables were expressed as number and proportion. Comparisons were performed using an independent-sample Student's *t* test or the Mann−Whitney U test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. Univariable and multivariable Cox proportional hazards models were used to calculate the hazard ratio and 95% confidence interval. The covariates for the multivariable model were identical to those in the logistic regression model for PS estimation. Survival curves were constructed by the Kaplan−Meier method, and compared by the log-rank test. Exploratory subgroup analyses of the primary outcome were performed using the Cox regression models with tests for interaction. To assess the added information of UA beyond SSII, C-index, continuous net reclassification improvement, and integrated discrimination improvement were calculated using R software. Two-sided p values of <0.05 were considered statistically significant. Analyses were performed using SPSS software version 22.0 (IBM, Armonk, New York) unless otherwise stated.

Table 1
Baseline characteristics of the study population before and after propensity score matching

Variable	Before matching			After matching		
	Hyperuricemia (n = 1,207)	Normouricemia (n = 7,322)	p value	Hyperuricemia (n = 1,163)	Normouricemia (n = 1,163)	p value
Age (year)	62.0 (53.0–70.0)	61.0 (54.0–69.0)	0.117	62.0 (53.0–70.0)	62.0 (54.0–69.0)	0.894
Male	901 (74.6%)	5879 (80.3%)	<0.001	877 (75.4%)	879 (75.6%)	0.923
Body mass index (kg/m^2)	26.0 (24.1–28.1)	25.8 (23.9–27.5)	<0.001	26.0 (24.1–28.1)	26.0 (24.3–28.0)	0.295
Hypertension	894 (74.1%)	4886 (66.7%)	<0.001	853 (73.3%)	861 (74.0%)	0.706
Diabetes mellitus	358 (29.7%)	2627 (35.9%)	<0.001	339 (29.1%)	341 (29.3%)	0.927
Previous myocardial infarction	486 (40.3%)	2478 (33.8%)	<0.001	458 (39.4%)	451 (38.8%)	0.766
Hyperlipidemia	738 (61.1%)	4005 (54.7%)	<0.001	704 (60.5%)	712 (61.2%)	0.734
Stroke	134 (11.1%)	716 (9.8%)	0.155	125 (10.7%)	127 (10.9%)	0.894
Peripheral artery disease	111 (9.2%)	563 (7.7%)	0.072	106 (9.1%)	104 (8.9%)	0.885
Chronic kidney disease	33 (2.7%)	38 (0.5%)	<0.001	26 (2.2%)	20 (1.7%)	0.457
Smoker	667 (55.3%)	4081 (55.7%)	0.758	651 (56.0%)	652 (56.1%)	0.967
Stable angina pectoris	437 (36.2%)	2958 (40.4%)	0.006	428 (36.8%)	444 (38.2%)	0.493
Unstable angina pectoris	478 (39.6%)	2702 (36.9%)	0.072	458 (39.4 %)	425 (36.5%)	0.159
Acute myocardial infarction	292 (24.2%)	1662 (22.7%)	0.253	277 (23.8%)	294 (25.3%)	0.413
Left main disease	268 (22.2%)	1688 (23.1%)	0.515	259 (22.3%)	273 (23.5%)	0.489
Left ventricular ejection fraction <40%	158 (13.1%)	397 (5.4%)	<0.001	141 (12.1%)	143 (12.3%)	0.899
Serum uric acid (μmol/L)	451.8 (425.4–494.6)	305.6 (255.2–339.3)	<0.001	450.5 (424.7–492.8)	318.7 (267.1–349.7)	<0.001
Creatinine (μmol/L)	92.4 (79.2–109.0)	81.3 (70.9–90.0)	<0.001	91.6 (79.0–106.0)	88.6 (80.1–105.0)	0.307
Creatinine clearance (ml/min)	71.4 (56.4–91.1)	84.4 (68.7–102.7)	<0.001	72.2 (57.9–91.9)	74.2 (59.6–91.7)	0.298
SYNTAX score						
≤22	459 (38.0%)	2820 (38.5%)	0.748	443 (38.1%)	441 (37.9%)	0.932
23-32	454 (37.6%)	2786 (38.0%)	0.773	438 (37.7%)	443 (38.1%)	0.831
≥33	294 (24.4%)	1716 (23.4%)	0.485	282 (24.2%)	279 (24.0%)	0.884
Angiotensin II receptor blockers	395 (32.7%)	1814 (24.8%)	<0.001	371 (31.9%)	351 (30.2%)	0.370
Percutaneous coronary intervention	475 (39.4%)	3189 (43.6%)	0.006	465 (40.0%)	460 (39.6%)	0.832
Coronary artery bypass grafting	337 (27.9%)	2319 (31.7%)	0.009	327 (28.1%)	352 (30.3%)	0.254
Aspirin	1137 (94.2%)	7013 (95.8%)	0.014	1098 (94.4%)	1100 (94.6%)	0.856
Clopidogrel	630 (52.2%)	3829 (52.3%)	0.949	606 (52.1%)	575 (49.4%)	0.199
Beta-blockers	1047 (86.7%)	6441 (88.0%)	0.229	1008 (86.7%)	1022 (87.9%)	0.384
Statins	833 (69.0%)	4806 (65.6%)	0.022	798 (68.6%)	794 (68.3%)	0.858
Angiotensin converting enzyme inhibitors	460 (38.1%)	2658 (36.3%)	0.226	447 (38.4%)	431 (37.1%)	0.494
Angiotensin II receptor blockers	197 (16.3%)	1089 (14.9%)	0.193	189 (16.3%)	194 (16.7%)	0.780

Results

After excluding patients with previous CABG, a total of 8,529 (95.4%) patients with available serum UA data were included in the present analyses. The median UA level was significantly higher in male patients than in female patients (322.0 μmol/L vs 281.1 μmol/L, $p < 0.001$, Figure S1 in supplementary material).

The baseline and procedural characteristics are shown in Table 1. Compared with normouricemic patients, hyperuricemic patients were more likely to be male and to have higher body mass index, blood pressure, serum lipid level, and serum creatinine, and lower creatinine clearance and left ventricular ejection fraction. Higher rates of diabetes, previous MI, and CKD were observed in hyperuricemic patients. Managements also differed between the 2 groups. After PS matching, the baseline and procedural characteristics were similar between the 2 groups.

During the median follow-up of 7.5 years, 1,276 (15.0%) patients experienced all-cause deaths, and 653 (7.7%) patients died from cardiac causes. Serum UA was significantly higher in patients who died during follow-up than in those who survived (451.8 [425.4 to 494.6] μmol/L vs 305.6 [255.2 to 339.3] μmol/L, $p < 0.001$). Significantly more all-cause deaths, cardiac deaths, and MACCE were observed in patients with hyperuricemia than in those with normouricemia (all $p < 0.001$; Table 2). Univariable and multivariable analyses identified that hyperuricemia was significantly associated with increased risks of all-cause death, cardiac death, and MACCE, but not MI, stroke, or unplanned revascularization (Table 2). Similar results were also found in the PS-matched cohorts (Table 3). Cumulative

Table 2
Risks of primary and secondary outcomes before propensity score matching

Outcome	No. of patients with event	Crude hazard ratio (95% confidence interval)	Crude p value	Adjusted hazard ratio (95% confidence interval)	Adjusted p value
All-cause death					
Hyperuricemia	271 (22.5%)	1.72 (1.50–1.96)	<0.001	1.33 (1.15–1.53)	<0.001
Normouricemia	1005 (13.7%)	Reference		Reference	
Cardiac death					
Hyperuricemia	154 (12.8%)	1.96 (1.64–2.35)	<0.001	1.47 (1.21–1.80)	<0.001
Normouricemia	499 (6.8%)	Reference		Reference	
Major adverse cardiac and cerebrovascular events					
Hyperuricemia	461 (38.2%)	1.32 (1.19–1.46)	<0.001	1.17 (1.05–1.30)	0.004
Normouricemia	2215 (30.3%)	Reference		Reference	
Myocardial infarction					
Hyperuricemia	68 (5.6%)	1.02 (0.79–1.31)	0.907	0.95 (0.73–1.25)	0.719
Normouricemia	429 (5.9%)	Reference		Reference	
Stroke					
Hyperuricemia	82 (6.8%)	0.98 (0.78–1.24)	0.883	1.01 (0.79–1.28)	0.967
Normouricemia	530 (7.2%)	Reference		Reference	
Unplanned revascularization					
Hyperuricemia	104 (8.6%)	1.04 (0.85–1.28)	0.703	1.01 (0.82–1.26)	0.904
Normouricemia	622 (8.5%)	Reference		Reference	

Table 3
Risks of primary and secondary outcomes after propensity score matching

Outcome	No. of patients with event	Hazard ratio (95% confidence interval)	p value
All-cause death			
Hyperuricemia	255 (21.9%)	1.33 (1.11–1.61)	0.003
Normouricemia	193 (16.6%)	Reference	
Cardiac death			
Hyperuricemia	142 (12.2%)	1.43 (1.11–1.85)	0.006
Normouricemia	100 (8.6%)	Reference	
Major adverse cardiac and cerebrovascular events			
Hyperuricemia	442 (38.0%)	1.22(1.06–1.40)	0.005
Normouricemia	370 (31.8%)	Reference	
Myocardial infarction			
Hyperuricemia	68 (5.8%)	0.98 (0.70–1.36)	0.885
Normouricemia	71 (6.1%)	Reference	
Stroke			
Hyperuricemia	80 (6.9%)	1.13 (0.83–1.56)	0.438
Normouricemia	72 (6.2%)	Reference	
Unplanned revascularization			
Hyperuricemia	100 (8.6%)	1.12 (0.84–1.49)	0.427
Normouricemia	90 (7.7%)	Reference	

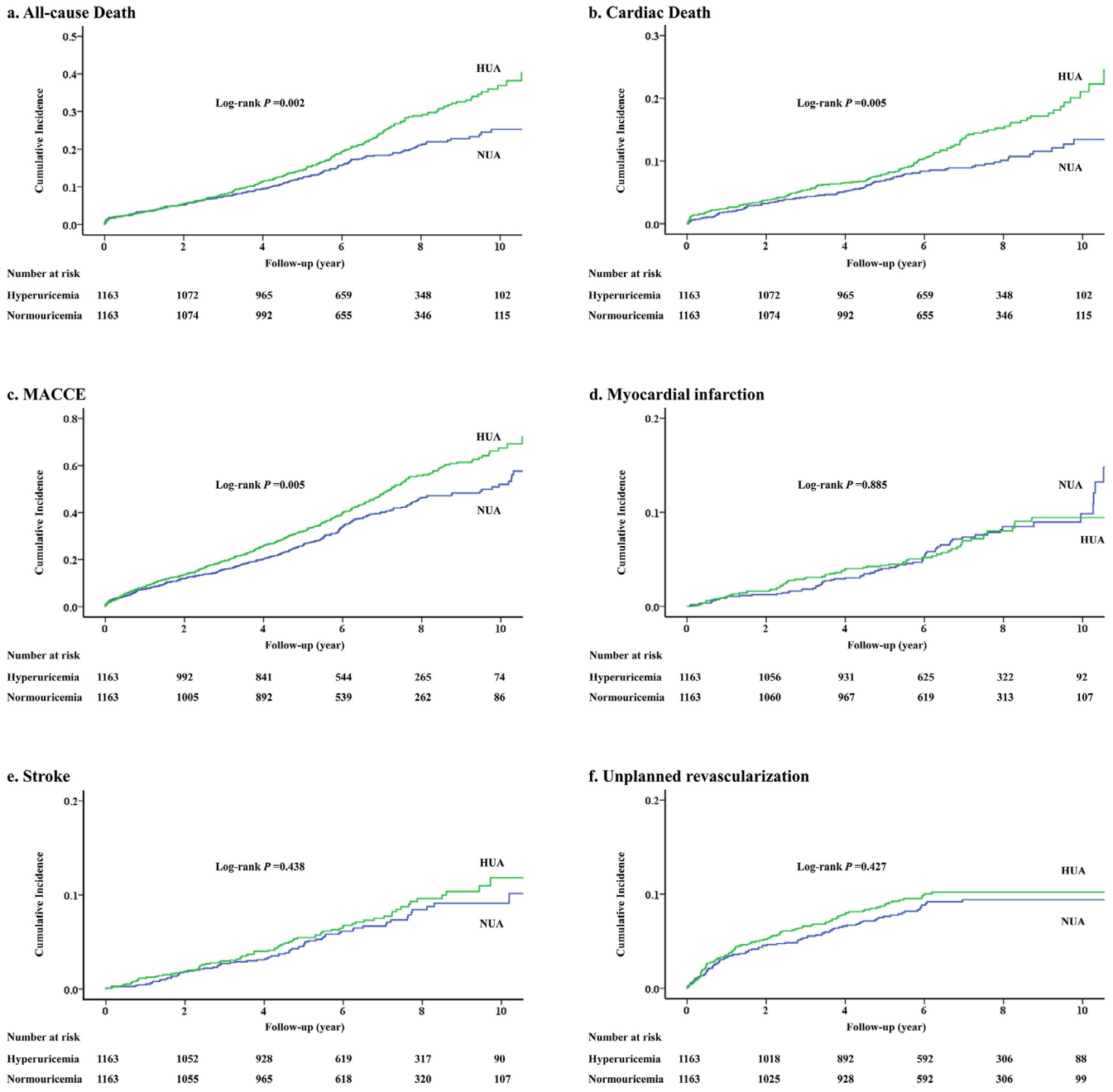

Figure 1. Cumulative incidence curves for primary and secondary outcomes in the propensity score-matched cohorts. (*a*–*f*) Cumulative incidences of all-cause death (*a*), cardiac death (*b*), MACCE (*c*), myocardial infarction (*d*), stroke (*e*), and unplanned revascularization (*f*). MACCE, major adverse cardiac and cerebrovascular events.

incidence curves for the primary and secondary endpoints are shown in Figure 1.

The effect of hyperuricemia on the primary end point was consistent across subgroups except for age, in which a significant interaction was found (p = 0.038; Figure 2). In patients aged <65 years, mortality risk was significantly higher in those with hyperuricemia than in those with normouricemia. However, among patients aged ≥65 years, there was only a trend toward an increased risk of mortality in those with hyperuricemia (Figure 2).

Addition of hyperuricemia to SSII was associated with a modest improvement in the C-index for prediction of MACCE, but not for prediction of all-cause or cardiac death (Table S1 in supplementary material). A significant improvement in the net reclassification improvement was also observed for all-cause death or MACCE, but not for cardiac death. Significant improvement of the integrated discrimination improvement was found for prediction of all-cause death, cardiac death, or MACCE (Table S1 in supplementary material).

Subgroup	Hyperuricemia	Normouricemia	Hazard ratio (95% confidence interval) *	*P*-value for interaction †
	no. of patients with all-cause death/total no.			
Overall	271/1207 (22.5%)	1005/7322 (13.7%)	1.31 (1.05–1.64)	
Age				0.038
<65 years	108/687 (15.7%)	342/4447 (7.7%)	1.59 (1.25–2.02)	
⩾65 years	163/520 (31.3%)	663/2875 (23.1%)	1.18 (0.98–1.41)	
Sex				0.115
Male	186/901 (20.6%)	804/5879 (13.7%)	1.28 (1.08–1.52)	
Female	85/306 (27.8%)	201/1443 (13.9%)	1.39 (1.04–1.87)	
Diabetes				0.400
Yes	104/358 (29.1%)	432/2627 (16.4%)	1.32 (1.04–1.69)	
No	167/849 (19.7%)	573/4695 (12.2%)	1.31 (1.10–1.58)	
Chronic kidney disease				0.436
Yes	19/33 (57.6%)	19/38 (50.0%)	1.46 (0.59–3.62)	
No	252/1174 (21.5%)	986/7284 (13.5%)	1.30 (1.12–1.52)	
Presentation				0.865
SAP	82/437 (18.8%)	337/2958 (11.4%)	1.40 (1.07–1.83)	
UAP	111/478 (23.2%)	401/2702 (14.8%)	1.27 (1.01–1.60)	
AMI	78/292 (26.7%)	267/1662 (16.1%)	1.33 (1.00–1.77)	
Left main disease				0.214
Yes	77/268 (28.7%)	272/1688 (16.1%)	1.71 (1.29–2.27)	
No	194/939 (20.7%)	733/5634 (13.0%)	1.23 (1.04–1.46)	
Ejection fraction				0.244
<40%	73/158 (46.2%)	116/397 (29.2%)	1.70 (1.21–2.39)	
⩾40%	198/1049 (18.9%)	889/6925 (12.8%)	1.25 (1.06–1.47)	
SYNTAX score				0.178
0-22	76/459 (16.6%)	310/2820 (11.0%)	1.12 (0.85–1.46)	
23-32	91/454 (20.0%)	376/2786 (13.5%)	1.23 (0.96–1.58)	
⩾33	104/294 (35.4%)	319/1716 (18.6%)	1.73 (1.34–2.21)	
Procedure				0.060
MT	138/395 (34.9%)	457/1814 (25.2%)	1.28 (1.03–1.58)	
PCI	69/475 (14.5%)	338/3189 (10.6%)	1.09 (0.83–1.44)	
CABG	64/337 (19.0%)	210/2319 (9.1%)	1.56 (1.15–2.12)	

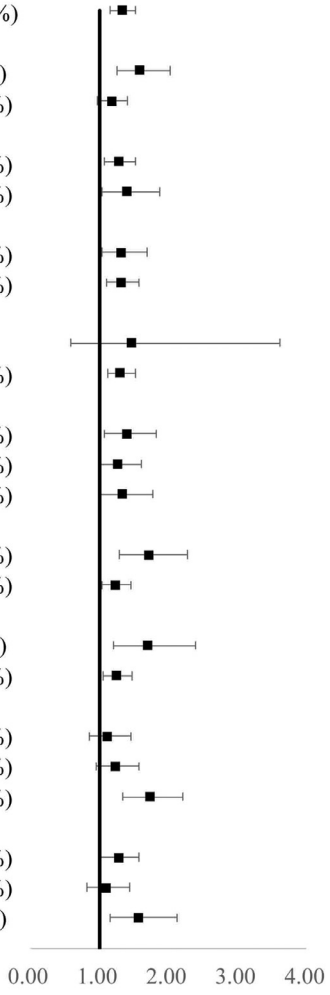

Figure 2. Subgroup analyses for the primary outcome. AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; MT, medical therapy; PCI, percutaneous coronary intervention; SAP, stable angina pectoris; UAP, unstable angina pectoris. *Hazard ratios and 95% confidence intervals were calculated by reference to patients with normouricemia. †The interaction between hyperuricemia and each covariate was tested by a multivariable Cox proportional hazards regression model.

Discussion

In patients with severe CAD, hyperuricemia was found to be independently associated with an increased risk of all-cause death, cardiac death, and MACCE after multivariable analyses or PS matching for adjustment. The association was relatively consistent across subgroups, except for an interaction between age and hyperuricemia. After adding UA to SSII, there were significant improvements of reclassification and discrimination for mortality prediction.

Although many studies found that an elevated UA level was associated with mortality in CAD patients,[3–10,15] some other studies argued that such an association might be confounded by renal functions or statins.[11,16] Limitations pertaining to small sample sizes and incomplete adjustment for confounders may have contributed to the above controversies. With these considerations, we used data from a large cohort with relatively complete information on potential confounders such as diabetes status, CKD status, and statin treatment. Two robust methods were used to adjust for these confounders and yielded similar results. Moreover, subgroup analyses were performed to further reduce confounding. The association was also relatively consistent in subgroups for diabetes, CKD status, CAD types, or treatments.

The interaction between hyperuricemia and age suggested a stronger association between hyperuricemia and mortality in patients aged <65 years than in those aged ≥65 years. Individual increments in serum UA have been shown to increase mortality risk in patients with CAD, suggesting a dose effect between UA and mortality.[15] In patients with hyperuricemia in this study, UA was significantly lower in patients aged ≥65 years than in patients aged <65 years ($p = 0.029$), indicating a relatively mild elevation of UA in elderly patients. Therefore, the contribution of hyperuricemia to the mortality risk was weaker in

patients aged ≥65 years. This interaction between UA and age should be noted and investigated in more detail in future studies.

Most previous studies categorized participants into quantiles according to UA levels,[3,4,6–9] which can notably hamper comparability and clinical applicability. In contrast, we defined hyperuricemia using a gender-specific cut-off value which was commonly adopted in analyses. Thus, the present findings can be easily compared with those in other studies and implemented in clinical practice.

Three-vessel disease is present in up to 30% of patients with obstructive CAD.[17,18] It confers an almost twofold higher risk of mortality compared with single-vessel disease and is considered as a severe type of CAD.[19] In this study, we found, for the first time, hyperuricemia was associated with adverse events in the context of 3-vessel disease. Several possible mechanisms may be involved in this association. First, UA can penetrate the endothelium and myocytes and result in endothelial dysfunction and vasoconstriction.[20] Indeed, atherosclerotic plaques contain more urate than normal artery walls,[21] and serum UA is associated with coronary endothelial dysfunction in humans.[22] Second, UA can stimulate chemokines and inflammatory markers.[23] During the production of UA, reactive oxygen species are generated, which can induce oxidative stress.[20] Third, UA can promote the development of insulin resistance and metabolic syndrome.[24,25] All these processes are involved in the development and progression of atherosclerosis. Taken together, elevated UA can exacerbate the originally heavy coronary atherosclerotic burden and lead to a higher risk of coronary events in patients with severe CAD.

Risk stratification has been challenging for patients with severe CAD. For example, SSII showed only a moderate discrimination ability for long-term mortality prediction in patients with multivessel disease.[26] It has been shown that adding UA to conventional risk factors can improve predictability.[27] In this regard, we combined hyperuricemia with SSII to evaluate its prognostic value and found that it could improve reclassification and discrimination of SSII for mortality prediction.

Besides risk stratification, it is important to clarify the implications of hyperuricemia also because UA levels can be modified by drug therapy.[28] Allopurinol has been shown to have an anti-ischemic effect in patients with stable CAD,[29] and be associated with a reduced risk of MI.[30] Further studies with UA-lowering therapies are needed to prove whether modulation of serum UA can improve clinical outcomes in patients with severe CAD and hyperuricemia.

There are some limitations to our study. First, this was a real-world observational study which might suffer from residual confounding. Second, all participants were from a single center, which may limit the generalization of the results. Third, medication information on diuretics or allopurinol, which could influence UA levels, was not recorded in the database.

Disclosures

The investigators have no conflicts of interest to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.11.027.

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