Is Serum Uric Acid Level an Independent Predictor of Heart Failure Among Patients With Coronary Artery Disease?

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ABSTRACT

Background: Uric acid (UA) is elevated in patients with the metabolic syndrome, and there is a possible association with coronary events. Its association with future risk of heart failure (HF) is not clear. Our objective was to evaluate the association between levels of UA and risk of HF in patients with stable coronary artery disease (CAD).

Hypothesis: Serum UA is associated with HF in CAD patients.

Methods: A retrospective cohort analysis among 2939 participants of the bezafibrate infarction prevention study, assessing long-term risk of HF incidence over an 8-year of follow-up in relation to baseline UA.

Results: Among patients with high levels of UA, there was a larger proportion of men, systolic hypertension, diabetes mellitus, metabolic syndrome, elevated total cholesterol, chronic renal failure, and previous coronary revascularization procedures. The rate of myocardial infarction during the follow-up was 10.9%, 10.3%, and 11.6% in the 1st, 2nd and 3rd tertiles of UA, respectively ($P = 0.68$). Age-adjusted hazard ratios for HF were 1.16 (95% confidence interval [CI]: 0.94–1.45) and 1.28 (95% CI: 1.04–1.59) in the 2nd and 3rd tertiles, respectively, as compared to the 1st tertile. After adjusting for multiple confounders and myocardial infarction, the hazard ratio for developing HF was 1.18 (95% CI: 0.95–1.47) and 1.25 (95% CI: 1.00–1.56) in the 2nd and 3rd tertiles of UA levels, respectively.

Conclusions: UA levels are associated with future risk of HF in patients with stable CAD, but this association is attenuated after adjusting for traditional CAD risk factors.

Introduction

Elevated serum uric acid (UA), or hyperuricemia, is associated with hypertension, abdominal obesity, insulin resistance, the metabolic syndrome, and renal failure.^{1–4} Several studies have demonstrated the association between serum UA and cardiovascular morbidity and mortality in the general population, as well as in patients with coexisting coronary artery disease (CAD), yet this issue remains controversial.^{5–7}

Elevated serum UA levels are common in patients with pre-existing heart failure (HF) and are associated with poor outcome in both patients with acute and chronic HF.^{8–11} There are limited data regarding the association between serum UA levels and subsequent incidence of HF in patients with stable CAD. We examined whether there is an association between serum UA level and risk of HF in a large group of patients with stable CAD.

Methods

Patients

A total of 3122 patients with chronic stable CAD (2854 men [91%]), age 45 to 74 years at baseline, participated in the Bezafibrate Infarction Prevention (BIP) study. BIP was a secondary prevention, placebo-controlled, randomized trial that evaluated the effect of bezafibrate on the risk of recurrent cardiovascular events and mortality.^{12,13} Among criteria for exclusion were: significant HF (New York Heart Association [NYHA] class III–IV) during the 3 months preceding the first screening visit, severe noncoronary heart disease (eg, cardiomyopathy), unstable angina pectoris during the 3 months before screening visit, life threatening arrhythmias within 3 months of screening, creatinine >1.5 mg/dL, and treatment with anticoagulation. Institutional ethics committees in each of the participating centers and the central national ethics committee approved the study. Follow-up included an interview and a physical examination by a cardiologist every 4 months for the study duration (5–7 years) and during an additional 2 years after study termination. A detailed description of the BIP study is published elsewhere.^{12,13}

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Among 3122 patients who participated in the BIP study, 171 patients with HF at baseline were excluded from the present analysis. Twelve patients for whom serum UA was not available were also excluded.

Variable Definition and Classification

HF incidence definition was based on clinical diagnosis reported by each study cardiologist on consecutive study visits, documentation of left or right HF as an adverse event, or report of a hospitalization for HF. All cases reported as an adverse event or hospitalization without indication of diagnosis on a follow-up visit were further adjudicated by a cardiologist and included as cases only if otherwise supported by additional data or labeled as noncases.

Body mass index (BMI) was calculated as the ratio between weight (in kilograms) and height squared (in meters). Obesity was defined as BMI >30 kg/m². Definition of hypertension was based on assessment by the screening physician or blood pressure above 140/90 mm Hg at screening. Diabetes was defined on the basis of report or treatment with an antidiabetic drug. Patients who quit smoking for at least a month before screening were categorized as past smokers. Patients who smoked at the time of screening or quit less than a month before screening were categorized as current smokers. Family history of CAD was defined as CAD in a first degree relative diagnosed under the age of 50 years. Functional capacity was classified according to NYHA classification. Metabolic syndrome was defined based on the Adult Treatment Panel III report (2002) classification.¹⁴ Coronary revascularization procedures included percutaneous transluminal coronary angioplasty and coronary artery bypass graft surgery.

Baseline serum uric acid was measured in blood samples taken at the screening visit prior to randomization or treatment allocation. Serum analysis was carried out in a central laboratory using standard automated procedures with commercially available diagnostic kits (Boehringer Mannheim, Mannheim, Germany). Due to differences in UA level distribution in men and women, UA level tertiles were determined for each sex separately (<5.29, 5.29–6.26, and ≥6.27 mg/dL for men; and <4.39, 4.39–5.38, and ≥5.39 mg/dL for women).

Statistical Methods

Data were analyzed using SAS 9.2 (SAS Institute, Cary, NC). Patients' characteristics are presented as frequencies or means ± SD unless otherwise specified and compared by χ^2 tests for categorical variables or analysis of variance for normally distributed continuous variables. Triglycerides and fibrinogen, which were not normally distributed, are presented as geometric means (with 95% confidence intervals [CI]) and compared by the Kruskal-Wallis test. Test of trend in mean was performed applying the CONTRAST statement with the SAS Generalized linear model (GLM) procedure. For geometric means, the test was performed on the log-transformed values. Trend in proportions was assessed by the Mantel-Haenszel χ^2 test.

Direct adjustment using the entire analysis group as the standard population was used for computation of

age-adjusted incidence rates/1000 person years. All tests were 2-sided.

Premature death may preclude HF onset. To account for this competing risk, HF onset probabilities over follow-up time according to UA tertiles were estimated by the cumulative incidence function using the method suggested by Gooley et al.¹⁵ Curves were compared by Gray's test¹⁶ using R (R Foundation for Statistical Computing, Vienna, Austria).

The age and multivariate adjusted HF hazards associated UA were estimated using the Cox proportional hazard model stratified on type of outcome (HF incidence or death before HF), which allowed the estimation of the association of UA level with HF in the presence of the competing risk of death, as suggested by Lunn and McNeil¹⁷ and described for SAS by Glynn et al.¹⁸

A fixed set of variables selected on the basis of previous knowledge and observed univariate associations in the current study was introduced into models. Variables included in the models were: age, diabetes, metabolic syndrome, GFR ≤60, smoking, and lipid profile. Two additional models were run to estimate the change in risk due to hypertension and number of myocardial infarctions (MIs) preceding HF.

The predictive discrimination ability of each model was evaluated using a C-statistic¹⁹ corresponding to the area under a receiver operating characteristics curve. The C-statistics ranged between 0.60 to 0.65 for all models.

The validity of the proportional hazard assumption was tested by running a model including a time-dependent explanatory variable for UA tertiles to test the assumption of no time-dependent effect. No significant deviation from the proportional hazard assumption was detected.

Results

A total of 2939 patients were followed for a median of 7.9 years (interquartile range: 7.1–8.7, corresponding to a total of 22317 person years). Uric acid level distribution in men and women is shown in Figure 1. Baseline characteristics of the patients by UA tertiles are listed in Table 1. Higher UA levels were associated with higher prevalence of systolic hypertension, past smoking, metabolic syndrome, elevated total cholesterol

Figure 1. Uric acid level distribution among study patients.

Table 1. Baseline Characteristics According to Serum Uric Acid Tertiles

	Uric Acid Tertiles			P Value
	1 (n = 974)	2 (n = 968)	3 (n = 997)	
Age (mean $\pm$ SD), y	60.1 $\pm$ 6.6	60.0 $\pm$ 6.8	60.2 $\pm$ 6.9	0.69
Men, n	893 (91.7%)	883 (91.2%)	991 (91.4%)	0.93
Previous MI	748 (76.8%)	735 (76.0%)	782 (78.6%)	0.38
Angina pectoris	565 (58.1%)	557 (57.6%)	537 (53.9%)	0.12
PVD	34 (3.5%)	33 (3.4%)	28 (2.8%)	0.65
Stroke	10 (1.0%)	9 (0.9%)	16 (1.6%)	0.32
Hypertension	388 (39.8%)	425 (43.9%)	460 (46.1%)	0.02
Diabetes	111 (11.4%)	96 (9.9%)	77 (7.7%)	0.02
HOMA, GM (range)	0.87 (0.82–0.92)	0.92 (0.86–0.97)	1.20 (1.13–1.27)	<0.0001
Anemia	45 (5.0%)	26 (2.8%)	33 (3.5%)	0.05
Family history of CHD	368 (41.1%)	377 (42.8%)	386 (43.1%)	0.66
COPD	29 (3.0%)	28 (2.9%)	24 (2.4%)	0.71
NYHA class				
1	738 (76.8%)	734 (76.9%)	756 (77.2%)	0.97
2+	223 (23.2%)	220 (23.1%)	223 (22.8%)	
MS	397 (40.9%)	421 (43.6%)	557 (56.1%)	<0.0001
BMI, mean $\pm$ SD	26.3 $\pm$ 3.2	26.5 $\pm$ 3.0	27.3 $\pm$ 3.4	<0.0001
Obesity, BMI $\geq$ 30	111 (11.4%)	110 (11.4%)	181 (18.2%)	<0.0001
GFR $\leq$ 60 mL/min/1.73m ²	102 (10.5%)	148 (15.3%)	289 (29.0%)	<0.0001
Smoking				
Past	519 (53.3%)	576 (59.5%)	619 (62.1%)	0.0003
Current	152 (15.6%)	103 (10.6%)	95 (9.5%)	<0.0001
Laboratory				
Total cholesterol	210.8 $\pm$ 17.3	211.8 $\pm$ 17.5	214.0 $\pm$ 17.7	0.0002
HDL-C	35.3 $\pm$ 5.4	34.8 $\pm$ 5.5	33.9 $\pm$ 5.5	<0.0001
Triglycerides, GM (range)	126.6 (123.8–129.5)	133.9 (130.9–137.0)	148.8 (145.8–151.9)	<0.0001
LDL-C	148.6 $\pm$ 16.2	148.5 $\pm$ 16.1	148.8 $\pm$ 17.1	0.91
WBC	6.8 $\pm$ 2.2	6.8 $\pm$ 1.7	6.9 $\pm$ 1.9	0.12
Fibrinogen, GM (range)	342.1 (337.6–346.7)	339.8 (335.5–344.2)	344.2 (339.7–348.7)	0.40
Treatment				
β -Blockers	347 (35.6%)	375 (38.7%)	438 (43.9%)	0.0007
ACE-I	91 (9.3%)	101 (10.4%)	137 (13.7%)	0.005
Digitalis	10 (1.0%)	25 (2.6%)	38 (3.8%)	0.0004
Diuretics	65 (6.7%)	106 (11.0%)	174 (17.5%)	<0.0001
Antidiabetics	59 (6.1%)	47 (4.9%)	36 (3.6%)	0.04
Nitrates	513 (52.7%)	471 (48.7%)	470 (47.1%)	0.04
CCBs	530 (54.4%)	486 (50.2%)	480 (48.1%)	0.02

Table 1. *Continued*

	Uric Acid Tertiles			<i>P</i> Value
	1 (n = 974)	2 (n = 968)	3 (n = 997)	
Lipid lowering drug	534 (54.8%)	540 (55.8%)	535 (53.7%)	0.64
Antiaggregants	650 (66.7%)	701 (72.4%)	728 (73.0%)	0.003
Blood pressure, mm Hg, mean $\pm$ SD				
Systolic	132.5 $\pm$ 15.2	133.6 $\pm$ 16.2	134.3 $\pm$ 16.2	0.04
Diastolic	80.8 $\pm$ 7.7	80.9 $\pm$ 8.1	81.6 $\pm$ 8.0	0.08
Pulse pressure	51.6 $\pm$ 11.4	52.7 $\pm$ 12.1	52.7 $\pm$ 12.1	0.08
Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blockers; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; GM, geometric mean; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostatic model assessment (insulin resistance); LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; MS, metabolic syndrome; NYHA, New York Heart Association; PVD, peripheral vascular disease; SD, standard deviation; WBC, white blood cell.				

Table 2. Coronary Revascularization and Myocardial Infarction Preceding Heart Failure Onset Among Study Patients According to Uric Acid Tertiles

	Uric Acid Tertiles						<i>P</i>
	1 (n = 974)		2 (n = 967)		3 (n = 995)		
Past revascularization	412	(42.5%)	449	(46.5%)	493	(49.3%)	0.006
Revascularization during follow-up							
PTCA	108	(11.1%)	115	(11.9%)	111	(11.1%)	0.81
CABG	170	(17.5%)	169	(17.5%)	148	(14.9%)	0.22
MI during follow-up							0.68
0	867	(89.0%)	868	(89.7%)	881	(88.4%)	
1	99	(10.1%)	90	(9.3%)	111	(11.1%)	
2+	8	(0.8%)	10	(1.0%)	5	(0.5%)	
Total MIs							0.69
0	206	(21.1%)	209	(21.6%)	191	(19.2%)	
1	583	(59.9%)	590	(61.0%)	599	(60.2%)	
2	157	(16.1%)	141	(14.6%)	169	(17.0%)	
3+	28	(2.9%)	27	(2.8%)	36	(3.6%)	
Median (IQR)	1.0	(1.0–1.0)	1.0	(1.0–1.0)	1.0	(1.0–1.0)	0.13
Abbreviations: CABG, coronary artery bypass graft surgery; IQR, interquartile range; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.							

and triglycerides, and chronic renal failure, increasing in a dose-response manner with increasing UA level (*P* for trend = 0.005 for hypertension; <0.0001 for the rest). Diabetes mellitus was inversely related to levels of UA (*P* = 0.02). There was also more use of β -blockers, diuretics, digitalis, and angiotensin-converting enzyme inhibitors in the 3rd tertile of UA levels (Table 1).

Patients with higher levels of UA had more previous coronary revascularization procedures before study entry as compared to patients with lower levels of UA (*P* = 0.006, Table 2). No difference between the groups was observed in coronary revascularization procedures during follow-up. There was no association between UA levels and history of

MI before the study (Table 1) or incidence of MI during the study period preceding HF onset (Table 2). The rate of MI during follow-up was 10.9%, 10.3%, and 11.6% in the 1st, 2nd, and 3rd tertiles of UA, respectively (*P* = 0.68). The same was true when the distribution of the total number of MIs (previous and incident MI, before and after inclusion in the BIP study) was examined (Table 2).

During the follow-up period, a total of 509 patients were diagnosed with HF. The age-adjusted HF incidence rates per 1000 person years were 21.5, 25.7, and 28.2 in the 1st, 2nd, and 3rd tertiles of UA, respectively. The cumulative incidence of HF by tertiles of UA, taking into account the competing risk of death is depicted in Figure 2. In

Figure 2. Age-adjusted Cumulative Incidence (CI) for heart failure during follow-up by tertiles of serum uric acid.

comparison to the lowest UA tertile, age-adjusted hazard ratios for HF were 1.16 (95% CI: 0.94–1.45) and 1.28 (95% CI: 1.04–1.59) in the 2nd and 3rd tertiles of UA, respectively.

Following adjustment for age, diabetes, metabolic syndrome, glomerular filtration rate <60 , smoking, lipid profile and past coronary revascularization, the hazard ratios of HF were 1.21 (95% CI: 0.97–1.50) and 1.30 (95% CI: 1.04–1.62) in the 2nd and 3rd tertiles of UA, respectively (Table 3, model I). When MI was added to the variables included in the first model (Table 3, model II), the hazard ratios of HF were slightly attenuated to 1.18 (95% CI: 0.95–1.47) and 1.25 (95% CI: 1.00–1.56) in the 2nd and 3rd tertiles of UA, respectively. On further adjustment for hypertension added to the variables included in model II (Table 3, model III), no significant change was noticed with similar hazard ratios for HF by UA level. We have repeated the analysis for patients free of any MI before or during the study period ($n = 606$). There were 66 events of HF in this subgroup of patients. By applying model I, the association between UA level and subsequent development of HF was of similar magnitude (HR in 3rd vs 1st tertile [1.49, 95% CI: 0.81–2.76]).

Subgroup analyses stratified for obesity, chronic kidney disease, diabetes mellitus, and hypertension revealed a

Figure 3. Subgroup analysis for the prediction of heart failure (hazard ratio [95% CI]) in the 3rd tertile of uric acid level. Abbreviations: CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension.

similar magnitude of risk for HF with the highest tertile of UA in different subgroups (Figure 3).

Discussion

The main finding of our study is that there is an apparent association between serum levels of UA and future risk of HF in patients with stable CAD, yet this association is attenuated when adjusting for other traditional CAD risk factors and for MI preceding HF onset.

Increased levels of UA in the general population are associated with hypertension, renal disease and CAD.^{1–4} Although still controversial, recent data suggest that elevated serum UA is associated with adverse cardiovascular outcome in the general population and in particular in patients with CAD.^{1–4}

Table 3. Incidence of Heart Failure in Study Patients According to Uric Acid Tertiles

	Uric Acid Tertiles		
	1 ($n = 974$)	2 ($n = 967$)	3 ($n = 995$)
HF incidence	149 (15.3%)	171 (17.7%)	189 (19.0%)
Age adjusted HF rate /1000 PY	21.5	25.7	28.2
Hazard ratio (95% CI)			
Age adjusted	1.0	1.16 (0.94–1.45)	1.28 (1.04–1.59)
Model I ^a	1.0	1.21 (0.97–1.50)	1.30 (1.04–1.62)
Model II ^b	1.0	1.18 (0.95–1.47)	1.25 (1.00–1.56)
Model III ^c	1.0	1.18 (0.94–1.46)	1.24 (0.99–1.55)

Abbreviations: CI, confidence interval; HF, heart failure; PY, person years. ^aModel I: multivariable hazard ratio (95% CI) adjusted for age, diabetes, metabolic syndrome, GFR ≤ 60 , smoking, lipid profile, past revascularization. ^bModel II: multivariable hazard ratio (95% CI) adjusted for age, diabetes, metabolic syndrome, GFR ≤ 60 , smoking, lipid profile, past revascularization and total MI. ^cModel III: multivariable hazard ratio (95% CI) adjusted for age, diabetes, metabolic syndrome, GFR ≤ 60 , smoking, lipid profile, past revascularization, total MI and hypertension.

Hyperuricemia is common among patients with HF and is associated with poor outcome.^{8,9} The pathophysiological link to HF is complex and not completely understood. Hyperuricemia is an index of oxidative stress and contributes to endothelial dysfunction by impairing nitric oxide production, thus possibly worsening HF.⁸ In addition, hyperuricemia is associated with higher levels of inflammatory mediators such as C-reactive protein, interleukin-6, and neutrophil count, which could be related to HF.⁹

There are some previous data on serum UA and risk of subsequent HF. Hyperuricemia was associated with subsequent HF in patients with hypertension.²⁰ In addition, among middle-age men from the general population, serum UA was associated with HF, but this relationship was no longer apparent on adjustment for established risk factors.²¹ In a study of elderly women, serum UA was an independent predictor for cardiovascular disease including death due to HF,⁴ and this relationship was also reported in 83683 Austrian men.²² However, these studies examined only the association of serum UA and fatal HF and did not examine the outcome of nonfatal HF. In the Apolipoprotein Mortality Risk (AMORIS) study, moderate levels of serum UA were associated with an increased incidence of acute myocardial infarction, stroke, and HF in middle-age subjects without CAD.¹ This risk increased as UA levels increased and was stronger in men compared to women. In another trial, it was demonstrated that hyperuricemia is an independent risk factor for HF in a group of young general community dwellers.²³

Our study is the first to our knowledge that reported the association between UA level and the development of HF in a large population of patients with stable CAD free of HF at baseline over a long-term follow-up period. After accounting for age, multiple confounders, and possible pathways, primarily MI, which is the leading cause of HF in CAD patients, this association was attenuated but still was significant in the 3rd tertile of UA.

Interestingly, although the association between UA and HF was attenuated after adjusting for MI, the incidence rates of MI in the 3 tertiles of UA during the study was similar. This observation implies that the association between UA and HF in this population is not mediated solely by MI, but rather that other mediators associated with MI might be involved. Suggested variables include MI size and effect on left ventricular function, variables which were not available in the present analysis. Another possible variable is the extent of CAD, demonstrated in this study by a higher rate of past coronary revascularization procedures in patients with higher levels of UA, and this too could account for the higher HF incidence in patients with elevated UA levels. Further mechanisms by which UA could be associated with HF in these patients include an increased oxidative burden, increased endothelial dysfunction, a pro inflammatory state, and subclinical atherosclerosis.^{3,9} Recently, it has been suggested that elevated serum UA is associated with greater risk of future incident atrial fibrillation. This by itself could also account for the association between UA and HF, yet these data were not available in our analysis.²⁴

Limitations

Some limitations apply to our analysis. First, we tested UA at baseline, and no data were available for the duration

of hyperuricemia, which could have changed over the years. Second, multivariate adjustment may not fully correct for differences detected between patients with different UA tertiles. Our definition of HF was based solely on clinical parameters and investigator's report, and no objective data, such as echocardiography reports or other imaging data of cardiac function, were available. Still, HF definition was clearly defined, and this was clinically assessed by a cardiologist on a clinical basis.

Conclusion

UA levels are associated with future risk of HF in patients with stable CAD, but whether this association is independent or is mainly driven by traditional CAD risk factors and severity of CAD is yet to be determined and deserves further investigation.

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