

# Serum Uric Acid As An Independent Predictor of Cardiovascular Event In Patients With Acute ST Elevation Myocardial Infarction

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## Abstract

**Background:** There is uncertainty whether uric acid level could be used as a prognostic marker in acute ST elevation myocardial infarction (STEMI) patients. Furthermore, there is a need to find a simple, less expensive but accurate marker that could be use in rural areas where fibrinolytic treatment is the first choice of acute reperfusion therapy. We studied the association of uric acid levels on cardiovascular event in patients with STEMI receiving fibrinolytic treatment.

**Methods:** Seventy-five patients with acute STEMI, eligible for fibrinolytic therapy, were enrolled in this cohort study. Over a night of fasting period, uric acid level was measured. One month clinical follow up was done. Re-infarction, heart failure, urgent revascularization, recurrent angina and death were defined as end point of the study.

**Results:** In STEMI patients with lowest uric acid levels (<4.8 mg/dl) compared with highest uric acid levels (>7.3 mg/dl), the cardiovascular event rate increased from 8% to 20%. From multivariate Cox regression analysis showed that elevated levels of uric acid (>7.3 mg/dl) demonstrated an independent, significant positive relation to cardiovascular events [Hazard Ratio 3.10 (95% Confidence Interval 1.16 to 8.29),  $p < 0.024$ ].

**Conclusion:** Serum uric acid is an independent predictor of cardiovascular event in patients with post fibrinolytic treatment in acute STEMI.

**Keywords:** Uric acid; Myocardial infarction; Predictor of cardiovascular event

## Introduction

Previous trials suggest that uric acid might be an independent predictor of major adverse cardiovascular events (MACE) in patients with coronary artery disease or only an indirect marker of adverse event due to the association between uric acid and other cardiovascular risk factors [1-5].

Several theories have been discussed, such as high serum uric acid has impact on increasing platelet reactivity [6], mediating inflammation, and stimulation of smooth muscle cell proliferation [7,8], which probably worsened the acute thrombosis complication. There is uncertainty about the role of uric acid in acute coronary syndrome and whether it could be used as a prognostic marker in STEMI patients.

Furthermore, there is a need to find a simple and accurate prognostic marker that could be used in a remote area where fibrinolytic therapy is the first choice of acute reperfusion therapy (as part of pharmacoinvasive strategy) in non PCI capable hospitals especially in developing countries.

To explore the relation between uric acid and myocardial infarction, we investigated the predictive role of uric acid on the risk of cardiovascular event from 75 consecutive patients with acute STEMI receiving fibrinolytic treatment.

## Methods

### Study design

Seventy-five consecutive patients were enrolled in this single center prospective cohort study. All patients were recruited in emergency department of National Cardiovascular Center Harapan Kita, Jakarta, Indonesia. The inclusion criteria were all acute STEMI patients with

less than 12 hours of onset, and eligible for fibrinolytic therapy. Fibrinolytic therapy was performed using intravenous streptokinase with the dose of 1.5 million unit, and given for 30 to 60 minutes. One month clinical follow-up was done by a dedicated medical practitioner by phone contact and medical record study, and blinded to the baseline characteristic of patients. Re-infarction, heart failure, urgent revascularization, recurrent angina and death were defined as the end point of the study.

Participation of all subjects was voluntary and written, informed consent was obtained from each subject. This study has been approved by institutional review committee and local medical ethical committee.

### Baseline measurements and definitions

In all 75 subjects, blood samples were drawn under standardized conditions after an overnight fasting period. Samples were centrifuged at 4,000 rpm for 10 minutes. Serum uric acid was determined by enzymatic calorimetric test (Roche, Germany). Diabetes mellitus was diagnosed in patients with a history of oral antidiabetic or insulin medication or fasting blood glucose >125 mg/dl at study entrance;

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**Received** March 09, 2012; **Accepted** March 23, 2012; **Published** March 25, 2012

**Citation:** Dharma S, Siswanto BB, Soerianata S, Wardeh AJ, Jukema JW (2012) Serum Uric Acid As An Independent Predictor of Cardiovascular Event In Patients With Acute ST Elevation Myocardial Infarction. J Clin Exp Cardiol S5:005. doi:10.4172/2155-9880.S5-005

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hypertension was diagnosed by the Joint National Committee VII criteria on hypertension or currently taking antihypertensive treatment; dyslipidemia was diagnosed in patients with a history of lipid lowering medication or a total cholesterol level >200 mg/dl, LDL >130 mg/dl, HDL<40 mg/dl, triglyceride >150 mg/dl, and a positive family history of premature coronary artery disease (CAD) in whom the CAD had developed before the age of 65 years in a first degree relative.

### Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and percentages were used for categorical variables. Uric acid levels were described as quartiles (first quartile range: <4.8mg/dl, second quartile range: 4.8 to 6.2 mg/dl, third quartile range: >6.2 to 7.3 mg/dl, fourth quartile range: >7.3 mg/dl).

Chi-square test was used to compare categorical variables and student's t-test or Mann-Whitney U-test were used to compare differences between the highest and lowest uric acid quartile. Univariate and multivariate regression analyses were performed to identify the independent predictor of cardiovascular event. Survival cumulative was assessed by Kaplan-Meier method. A p-value of < 0.05 was regarded as a statistically significant. All computations were performed using statistical package.

## Results

### Serum uric acid levels

Baseline characteristics of all patients are shown in table 1. The

mean uric acid level was  $6.28 \pm 1.68$  mg/dl. There was no significant difference between uric acid level in women and men ( $6.38 \pm 1.57$  mg/dl Vs  $6.26 \pm 1.71$  mg/dl,  $p=0.83$ ).

Compared with the lowest quartile of uric acid (Table 1), the highest quartile was associated with more use of diuretics (4% Vs 13%,  $p=0.027$ ), whereas there was only a trend toward a higher level of creatinine in the highest uric acid quartile ( $1.06 \pm 0.26$  mg/dl Vs  $1.22 \pm 0.32$  mg/dl,  $p=0.109$ ). No statistically differences were observed in location of MI (anterior myocardial infarction) (13% Vs 18%,  $p=0.329$ ), and in use of angiotensin converting enzyme inhibitor (13% Vs 20%,  $p=0.169$ ) between the lowest and the highest uric acid quartile.

### Cardiovascular events

During one month follow-up, cardiovascular events occurred in 43 patients (57%), of which 7 patients (17%) were women. Heart failure was the most common event (55%). In the lowest uric acid quartile (<4.8 mg/dl), the cardiovascular event rate was 8% while in the highest quartile (>7.3 mg/dl), the cardiovascular event rate increased to 20% ( $p=0.006$ ).

Patients in the highest uric acid quartile had an increased cardiovascular event compared to other quartile with HR of 3.24 (95% CI 1.25-8.41,  $p=0.016$ ) (Table 2) and multivariate Cox regression analysis (Table 3) showed that fourth quartile range of uric acid (>7.3 mg/dl) was the strongest independent predictor of cardiovascular event with HR of 3.10 (95% CI 1.16-8.29,  $p=0.024$ ).

Variables	All Patients (n=75)	Lowest Uric Acid Quartile Patients* (n=16)	Highest Uric Acid Quartile Patients* (n=18)	p Value
Age (years)	53.68 ± 7.72	53.12 ± 7.71	52.72 ± 6.95	0.873
Body mass index (kg/m <sup>2</sup> )	22.99 ± 2.76	22.38 ± 2.45	22.95 ± 1.73	0.442
Male, n (%)	63 (84)	15 (20)	15(20)	0.347
Prior myocardial infarction n (%)	4 (5)	2 (2)	0 (0)	0.122
Risk factor, n (%)				
Family history	18 (24)	6 (8)	3 (4)	0.169
Smoker	39 (52)	8 (10)	8 (10)	0.746
Hypertension	40 (53)	9 (12)	9 (12)	0.715
Diabetes mellitus	16 (21)	6 (8)	4 (5)	0.329
Dyslipidemia	52 (69)	13 (17)	12 (16)	0.336
Door to needle (minute)	57.88 ± 43.56	59.43 ± 41.43	51.88 ± 46.08	0.276
Time to reperfusion (minute)	297.28 ± 154.44	288.18 ± 173.43	264.38 ± 139.70	0.661
Anterior MCI, n (%)	47 (63)	10 (13)	14 (18)	0.329
Lipid Profile				
Total cholesterol (mg/dl)	209.70 ± 44.00	214.18 ± 54.25	217.16 ± 41.77	0.857
LDL cholesterol (mg/dl)	136.80 ± 40.08	144.25 ± 49.54	148.77 ± 33.35	0.754
HDL cholesterol (mg/dl)	42.93 ± 10.70	43.25 ± 12.05	43.55 ± 11.25	0.939
Triglyceride (mg/dl)	152.57 ± 69.95	134.06 ± 51.60	135.50 ± 41.58	0.769
Creatinine (mg/dl)	1.03 ± 0.28	1.06 ± 0.26	1.22 ± 0.32	0.109
Medication at enrollment, n (%)				
Diuretic	21 (28)	3 (4)	10 (13)	0.027
ACE Inhibitor	52 (69)	10 (13)	15 (20)	0.169
Statin	41(54)	9 (12)	8 (10)	0.492
Beta blocker	23 (30)	6 (8)	7 (9)	0.934
MACE, n (%)	43 (57)	6 (8)	15 (20)	0.006

\*Uric acid quartiles: first quartile range <4.8mg/dl, second quartile range 4.8 to 6.2 mg/dl, third quartile range >6.2 to 7.3 mg/dl, fourth quartile range >7.3 mg/dl. Data are expressed as percentages of patients or mean ± SD. The p value is given for the comparison of lowest versus highest uric acid quartile, for normally distributed, continuous variables by t test, for skewed continuous variables by Mann-Whitney U test, and for categorical variables by Pearson's chi-square test. MACE=Major Adverse Cardiac Event, MCI=myocardial infarction, ACE=angiotensin converting enzyme

**Table 1:** Baseline Characteristics between the lowest and highest uric acid levels in patients with acute STEMI.

Variables (n=75)	Univariate Predictors of Cardiovascular Event	
	HR (95% CI)	p Value
Age (>65 years)	1.00 (0.24-4.18)	0.990
Body mass index (>25kg/m <sup>2</sup> )	0.86 (0.41-1.81)	0.705
History of CAD	0.36 (0.05-2.68)	0.244*
History of MCI	0.79 (0.19-3.27)	0.748
Risk Factor		
Family History	0.76 (0.36-1.59)	0.477
Diabetes mellitus	1.25 (0.61-2.55)	0.524
Hypertension	0.69 (0.38-1.26)	0.238*
Dyslipidemia	0.80 (0.42-1.52)	0.500
Smoker	0.94 (0.52-1.72)	0.862
Heart rate >100X/minute	2.11 (1.08-4.14)	0.029*
Anterior location of Infarction	2.29 (1.15-4.57)	0.018*
Door to needle time >30 minute	0.56 (0.29-1.06)	0.078*
Time to reperfusion therapy >240 minute	1.00 (0.54-1.85)	0.977
Lipid Profile		
Total cholesterol >200 mg/dl	1.15 (0.61-2.16)	0.654
HDL <40mg/dl	1.09 (0.60-2.00)	0.763
LDL >130mg/dl	1.34 (0.72-2.50)	0.344
Triglyceride >150mg/dl	0.71 (0.37-1.36)	0.310
Creatinine >1.5mg/dl	0.98 (0.35-2.75)	0.976
Medication at enrollment		
Beta blocker	0.55 (0.27-1.13)	0.107*
ACE Inhibitor	1.67 (0.82-3.39)	0.154*
Statin	0.61 (0.33-1.12)	0.118*
Uric acid		
Second quartile (4.8-6.2 mg/dl)	1.34 (0.47-3.77)	0.575
Third quartile (>6.2-7.3 mg/dl)	1.79 (0.68-4.73)	0.234*
Fourth quartile (>7.3 mg/dl)	3.24 (1.25-8.41)	0.016*

\*Variables with p value <0.25 were entered in the multivariate Cox regression analysis; All uric acid quartile was entered in the multivariate Cox regression analysis. The variables were tested for presence or absence unless stated otherwise.

**Table 2:** Univariate Predictors of Cardiovascular Event.

Kaplan-Meier event-free survival curve clearly showed that patients with highest uric acid level (quartile 4) had a significantly lower cumulative survival than those with other quartile (log-rank test, p=0.026) (Figure 1).

## Discussion

This is the first study focusing the role of uric acid levels in patients with acute ST elevation myocardial infarction that were receiving fibrinolytic therapy. Uric acid levels can be measured at a low cost in almost all hospitals in the world, especially in developing countries, which have no facilities to measure other more expensive prognostic markers such as high sensitive C-Reactive Protein, Brain-type Natriuretic Peptide, Interleukin-6, and many others. This study documents and validates that high serum uric acid levels (>7.3 mg/dl) is a strong, independent predictor of cardiovascular events in post fibrinolytic patients with acute STEMI. The assessment of uric acid in this study provides information independently of, and better than other well established parameters such as age, prior MCI, history of hypertension or diabetes mellitus, heart rate, anterior STEMI and time to reperfusion [9].

Most epidemiologic studies have suggested that there is an association between serum uric acid and coronary artery disease [10,11]. Mandel, implicates urate, which is a byproduct from the lysosomal enzymatic degradation of glycoprotein-urate complexes. The urate links to the lysosomal membrane via hydrogen bond, causing membrane lysis. Another theory involves uric acid as a mediator of inflammation by directly activating complement factors. Xanthine

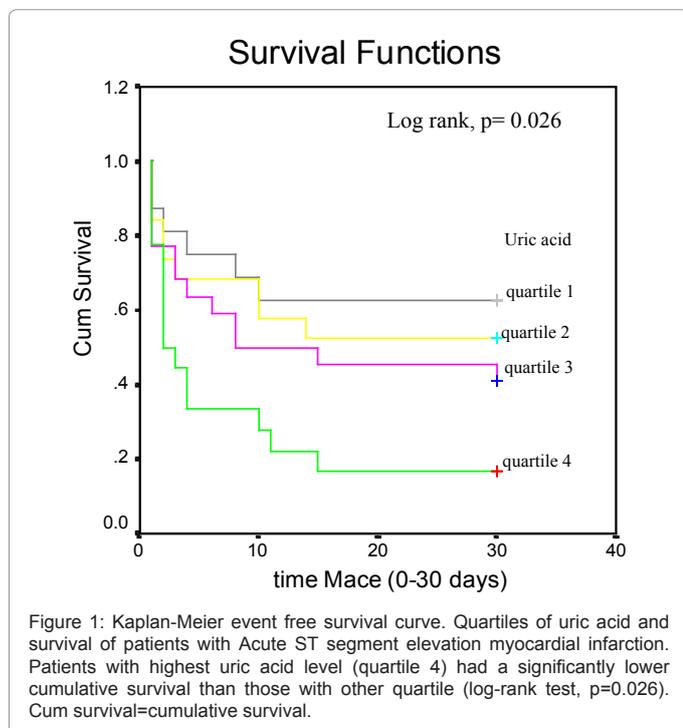
oxidase, the rate limiting enzyme for the formation of uric acid, has been found localized in endothelial cells and smooth muscle cells of arteries. The resultant uric acid may result in free radical injury to the vessel wall [7,12,13]. All of these actions are believed to contribute to the development of degenerative vascular disease [7], and might have role in worsening the acute thrombosis. Furthermore, uric acid is a general marker of cell death [14] and elevated serum uric acid is linked with obesity, dyslipidemia [15], hypertension, insulin resistance [16], male gender, aging, menopause [17], excessive alcohol intake and diuretic use [18]. Moreover, uric acid level may reflect xanthine oxidase pathway activity, which has the potential to contribute in to the progression of left ventricular dysfunction by interfering with myocardial energetics and myofilament calcium sensitivity [10].

Other trials showed the relation between serum levels of uric acid and cardiovascular disease is generally stronger in women than men [19,20], but Maxwell et al. [6], showed that man had a significantly higher serum uric acid than women (5.5 ± 1.3 mg/dl Vs 4.2 ± 1.4 mg/dl, p< 0.0001). Our study, consisting of 12 female patients (16%) did not show any difference compared to male (6.26 ± 1.71 mg/dl Vs 6.38 ± 1.57 mg/dl, p=0.83). Also, there were no any differences in traditional risk factors between high and low uric acid levels. Culleton et al. [4] reported in 1999 using data from the Framingham study concerning the role of uric acid as an independent risk factor in CAD. They found an increased risk for adverse outcome after age adjustment only in women, which was not independently associated with death from cardiovascular disease or from all causes after additional adjustment for cardiovascular disease risk factors. In a stepwise Cox model, they concluded that uric acid does not have a causal role in the development

Variables	Multivariate Cox Predictive Model for Cardiovascular Event	
	HR (95% CI)	p value
History of CAD	0.38 (0.04-3.23)	0.382
History of hypertension	1.00 (0.48-2.08)	0.985
Heart rate >100x/minute	2.31 (1.03-5.19)	0.041
Anterior location of infarction	2.93 (1.06-8.07)	0.038
Door to needle time >30 minute	0.70 (0.32-1.53)	0.377
Use of beta blocker	0.39 (0.17-0.92)	0.033
Use of ACE Inhibitor	0.66 (0.21-2.04)	0.472
Use of statin	0.89 (0.44-1.79)	0.759
Second quartile of uric acid	1.55 (0.51-4.63)	0.433
Third quartile of uric acid	2.10 (0.78-5.68)	0.141
Fourth quartile of uric acid	3.10 (1.16-8.29)	0.024

CAD= coronary artery disease

Table 3: Multivariate Analysis of Cardiovascular Event.



Variables	Univariate Hazard Ratio of Uric Acid in Low Risk Subgroup		
	n	HR (95% CI)	p value
Nonobese patients (BMI <27 kg/m <sup>2</sup> )	17	1.11 (0.14-8.72)	0.915
No family history	15	1.96 (0.43-8.79)	0.379
No history of hypertension	9	0.92 (0.33-2.55)	0.877
No history of diabetes	14	0.38 (0.11-1.29)	0.123
No history of smoking	10	1.94 (0.65-5.81)	0.231
No dyslipidemia	6	3.86 (1.06-14.04)	0.040
No renal failure (creatinine <1.5mg/dl)	14	1.55 (0.43-5.55)	0.496

Cox regression was performed entering only uric acid >7.3 mg/dl as 1 variable. The variables were tested for presence or absence unless stated otherwise. BMI=body mass index, n indicates number of patients

Table 4: Cardiovascular Event in Low Risk Subgroups.

of coronary heart disease and that any apparent association with these outcomes is probably due to the association of uric acid levels with other risk factors.

In contrast to those results, in our prospective observational study, we identified uric acid as an independent risk factor for adverse outcome in patients with STEMI, even among subjects with low cardiac risk (patients who were not having dyslipidemia) (Table 4).

Our study presents the results of an observational study in patients with clinically proven coronary artery disease (acute STEMI), whereas in the Framingham study and NHANES I epidemiologic follow-up studies, primarily healthy persons were included, which is a different approach and may explain some of the different results. Furthermore, recent study from Ndrepepa et al. [21] concluded that elevated levels of uric acid is an independent predictor of 1-year mortality in all spectrum of acute coronary syndrome patients treated with percutaneous coronary intervention, thus strengthening the prognostic value of uric acid, not only for short term, but also for a longer follow up period.

In some developing countries that are using pharmaco-invasive approach for their acute myocardial infarction system of care (fibrinolytic treatment in pre-hospital setting with an invasive procedure back up), this simple, inexpensive and accurate prognostic marker might be use for further risk stratification. Thus, the role of allopurinol in the treatment of hyperuricemia needs further evaluation in STEMI patients.

### Study Limitation

The role of uric acid from this small sample size needs to be confirmed by a larger study.

### Conclusion

Serum uric acid is an independent predictor of cardiovascular event in patients with post fibrinolytic treatment in acute STEMI.

### References

- Weir CJ, Muir SW, Walters MR, Lees KR (2003) Serum urate as an independent predictor of poor outcome and future vascular events after acute stroke. *Stroke* 34: 1951-1956.
- Freedman DS, Williamson DF, Gunter EW, Byers T (1995) Relation of serum uric acid to mortality and ischemic heart disease: The NHANES I epidemiologic follow up study. *Am J Epidemiol* 141: 637-644.
- Wannamethee SG, Shaper AG, Whincup PH (1997) Serum urate and the risk of major coronary heart disease events. *Heart* 78: 147-153.
- Culleton BF, Larson MG, Kannel WB, Levy B (1999) Serum uric acid and risk for cardiovascular disease and death:the Framingham Heart Study. *Ann Intern Med* 131: 7-13.
- Bickel C, Rupprecht HJ, Blankenberg S, Ripplin G, Hafner G, et al. (2002) Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease. *Am J Cardiol* 89: 12-17.
- Maxwell AJ, Bruinsma KA (2001) Uric acid is closely linked to vascular nitric oxide activity. Evidence for mechanism of association with cardiovascular disease. *J Am Coll Cardiol* 38: 1850-1858.
- Patetsios P, Song M, Shutze WP, Pappas C, Rodino W, et al. (2001) Identification of uric acid and xanthine oxidase in atherosclerotic plaque. *Am J Cardiol* 88: 188-191.
- Kanellis J, Watanabe S, Li JH, Kang DH, Li P, et al. (2003) Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen activated protein kinase and cyclooxygenase-2. *Hypertension* 41: 1287-1293.
- Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, et al. (2000)

- TIMI risk score for ST elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation. *Circulation* 102: 2031-2037.
10. Hare JM, Johnson RJ (2003) Uric acid predicts clinical outcomes in heart failure: Insights regarding the role of xanthine oxidase and uric acid in disease pathophysiology. *Circulation* 107: 1951-1953.
  11. Fang J, Alderman MH (2000) Serum uric acid and cardiovascular mortality. The NHANES I epidemiologic follow-up study, 1971-1992. National health and nutrition examination survey. *JAMA* 283: 2404-2410.
  12. Guthikonda S, Sinkey C, Barenz T, Haynes WG (2003) Xanthine oxidase inhibition reverses endothelial dysfunction in heavy smokers. *Circulation* 107: 416-421.
  13. Farquharson CA, Butler R, Hill A, Belch JJ, Struthers AD (2002) Allopurinol improves endothelial dysfunction in chronic heart failure. *Circulation* 106: 221-226.
  14. Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, et al. (2003) Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. *Circulation* 107: 1991-1997.
  15. Cappuccio FP, Strazzullo P, Farinara E, Trevisan M (1993) Uric acid metabolism and tubular sodium handling. Results from a population based study. *JAMA* 270: 354-359.
  16. Alderman M (1999) Uric acid in hypertension and cardiovascular disease. *Can J Cardiol* 15: 20F-22F.
  17. Lee J, Sparrow D, Vokonas PS, Landsberg L, Weiss ST (1995) Uric acid and coronary heart disease risk: evidence for a role of uric acid in the obesity-insulin resistance syndrome. The normative aging study. *Am J Epidemiol* 142: 288-294.
  18. Iribarren C, Sharp DS, Curb JD, Yano K (1996) High uric acid: a metabolic marker of coronary heart disease among alcohol abstainers. *J Clin Epidemiol* 49: 673-678.
  19. Tuttle KR, Short RA, Johnson RJ (2001) Sex differences in uric acid and risk factors for coronary artery disease. *Am J Cardiol* 87: 1411-1414.
  20. Alderman MH, Cohen H, Madhavan S, Kivlighn S (1999) Serum uric acid and cardiovascular events in successfully treated hypertensive patients. *Hypertension* 34:144-150.
  21. Ndrepepa G, Braun S, Haase HU, Schulz S, Ranftl S, et al. (2012) Prognostic value of uric acid in patients with acute coronary syndromes. *Am J Cardiol*.

This article was originally published in a special issue, **Myocardial Infarction and Protection** handled by Editor(s). Dr. Dayue Darrel Duan, University of Nevada, USA