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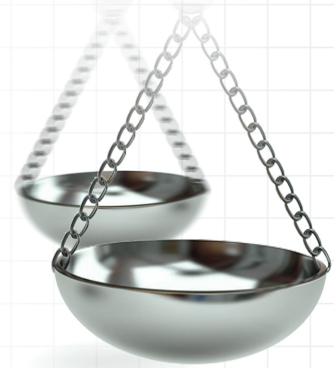

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Uricemia in the acute phase of myocardial infarction and its relation to long-term mortality risk

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Aim: Although uric acid has antioxidant effects, hyperuricemia has been established as an indicator of increased cardiovascular mortality in various patient populations. Treatment of asymptomatic hyperuricemia in patients with acute myocardial infarction (MI) is not routinely recommended, and the efficacy of such treatment in terms of cardiovascular risk reduction remains doubtful. **Materials & methods:** In a prospective cohort study, we followed 5196 patients admitted for a MI between 2006 and 2018. We assessed the relationship between baseline uricemia and the incidence of all-cause death and cardiovascular mortality and the effect of long-term allopurinol treatment. Hyperuricemia was defined as serum uric acid >450 μmol/l in men and >360 μmol/l in women. **Results:** In the entire cohort, the 1-year all-cause and cardiovascular mortality rates were 8 and 7.4%, and the 5-year rates were 18.3 and 15.3%, respectively. Using a fully adjusted model, hyperuricemia was associated with a 70% increased risk of both all-cause death and cardiovascular mortality at 1 year, and the negative prognostic value of hyperuricemia persisted over the 5-year follow-up (for all-cause death, hazard risk ratio = 1.45 [95% CI: 1.23–1.70] and for cardiovascular mortality, hazard risk ratio = 1.52 [95% CI: 1.28–1.80], respectively). Treatment of asymptomatic hyperuricemia with allopurinol did not affect mortality rates. **Conclusion:** Hyperuricemia detected in patients during the acute phase of an MI appears to be independently associated with an increased risk of subsequent fatal cardiovascular events. However, hyperuricemia treatment with low-dose allopurinol did not prove beneficial for these patients.

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Keywords: acute myocardial infarction • allopurinol • cardiovascular mortality • uricemia

Uric acid is the end product of the metabolism of exogenous and endogenous purines, which during the first metabolic step are transformed into hypoxanthine and xanthine, and then via xanthine oxidase into the final uric acid product. This gradual enzymatic degradation also produces a large number of reactive oxygen species having multiple pathophysiological consequences [1].

Regarding the cardiovascular system, the resulting oxidative stress leads primarily to endothelial dysfunction and affects other atherosclerotic processes [2]. However, during an acute myocardial infarction (MI), ischemia-reperfusion injury mediated by oxidative stress plays an important role [3], and since uric acid is an antioxidant, its decreased levels could be potentially associated with increased oxidative stress [4].

Hyperuricemia has been linked to cardiovascular disease for decades, and there is epidemiological evidence for its considered role as an independent risk factor. The Third National Health and Nutrition Examination Survey revealed an increased risk of total and cardiovascular mortality in 15,773 patients associated with increased uric acid levels [5]. A recent study on the incidence of MI in 12,866 men in the Multiple Risk Factor Intervention Trial showed a modest association with hyperuricemia and gout, even after adjustment for renal function, cardiovascular

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risk factors and other potential covariates [6]. A very large study from Taiwan confirmed the association between hyperuricemia and all-cause or cardiovascular mortality in 354,110 subjects, but a significant risk was also observed for low uricemia [7]. It is possible that the above-mentioned antioxidant properties of uric acid play a pivotal role in this phenomenon. The influence of hyperuricemia on long-term mortality and the occurrence of cardiovascular events has been studied in various patient populations and clinical settings (acute heart failure [8,9], hypertension [10], acute coronary syndrome [11] and atrial fibrillation [12]). The results are consistent with recent epidemiological studies and support the hypothesis of hyperuricemia being a cardiovascular risk factor. The Uric Acid Right for Heart Health study group recently determined cut-off values for uric acid levels that further increase the risk of mortality and MI in an unselected cohort of outpatients [13].

Epidemiological data collected in recent years support the association between uricemia and cardiovascular risk. This fact is reflected in the current european guidelines, which views uric acid as one of the risk factors influencing global cardiovascular risk and recommends that all hypertensives with hyperuricemia should be screened for cardiovascular comorbidities [14].

Hyperuricemia therapy often consists of allopurinol, which is a xanthine oxidase inhibitor; several other medicines can also be used to further reduce uric acid levels.

The goal of this analysis was to assess the long-term mortality risk of hyperuricemia or, conversely, low uric acid concentrations during the acute phase of an MI.

Materials & methods

The study was conducted using Good Clinical Practice principles and ethical standards formulated in the 1964 Declaration of Helsinki and later amendments. The study protocols were approved by the Ethics Committees of the University Hospital in Pilsen. The data were stored and evaluated under the provisions of the Czech Data Protection Act. All patients evaluated in the analysis signed a written informed consent during hospital admission, in other words, at the baseline visit.

Design & study population

The study represents a prospective follow-up of patients after an acute MI (i.e., an *ad hoc* build registry). Patients admitted to the Cardiology Department of University Hospital Pilsen between 1 January 2006 and 31 December 2018 for acute MI were retrospectively identified from hospital records. The main criterion was based on the final primary diagnosis, formally stated in the discharge summary.

All included patients underwent coronary angiography and were treated with coronary angioplasty, coronary bypass graft, or a conservative approach, followed by standard secondary preventive measures based on clinical judgment (e.g., dual antiplatelet treatment, statins, beta-blockers or renin-angiotensin system blockers). No formal measures concerning uricemia were taken, in other words, if patients were taking allopurinol before hospitalization, they usually continued without any change.

Data collection & management

The vital statistics of patients were registered until 31 May 2019, using the National Registry of the Institute of Health Information and Statistics of the Czech Ministry of Health. Death certificates and available documentation in hospital information systems were reviewed and used to specify the cause of death. All other data are based on information contained in the hospital information system.

The hospital is involved in a system of regular quality control of all procedures (instruments, laboratory estimations, etc.), and standard commercial kits and an analytical platform were used for all laboratory estimates. For the estimation of uric acid, a commercial kit based on an enzymatic (uricase) colorimetric test and the COBAS 8000 analytical platform (ROCHE Diagnostics, Basel, Switzerland) were used.

As outcomes, we used all-cause or cardiovascular mortality during 5 years of follow-up. A cardiovascular cause of death was based on information from hospital records (discharge letter, inspection list, etc.) or, if not available, stated as the primary cause of death (International Classification of Diseases, 10th revision [ICD-10] codes were used) on death certificates. Moreover, we also calculated the risk of death during the 1st year, between day 31 and day 1, 856 (i.e., the 5-year mortality risk for those who survived at least 30 days) and between day 366 and day 2, 191 (i.e., the 5-year mortality risk for those who survived at least 1 year after their MI).

Serum uric acid concentrations (uricemia) were ascertained at the very beginning of hospitalization since this parameter is routinely checked during admission screening in MI patients. Based on the value of this parameter, patients were divided into one of four categories: cohort A, low uricemia, <210 μmol/l in males or <140 μmol/l

in females; cohort B, normal uricemia, 210–450 μmol/l in males or 140–360 μmol/l in females; cohort C, hyperuricemia, >450 μmol/l in males or >360 μmol/l in females; cohort D, patients with long-term treatment for hyperuricemia (all with allopurinol and without other uric acid-lowering treatment). In cohort D patients, the long-term allopurinol treatment was left unchanged, and in cohort C patients, allopurinol treatment was not initiated.

Potential covariates were defined as follows: coronary revascularization (i.e., coronary angioplasty or coronary bypass graft) refers only to procedures realized in the course of qualifying coronary event. Information about ST-elevation MI was derived from the coronary angiography report. 'History of hypertension' was based on the formally stated final diagnosis in the discharge summary, while 'diabetes mellitus' was defined as: any fasting or nonfasting glucose level during hospitalization ≥7 or ≥11.1 mmol/l, respectively; treatment with antidiabetics was recommended; or the diagnosis was formally stated in the discharge summary. 'Overt heart failure' refers to: an ejection fraction known to be ≤40%; BNP during hospitalization ≥300 ng/l (Abbott Laboratories, IL, USA) or NT-proBNP ≥900 ng/l (ROCHE); chronic heart failure was formally stated in the discharge summary; or treatment with furosemide was recommended in the discharge summary. A 'peak troponin' concentration during hospitalization ≥100-times the upper limit of normal category refers to troponin I >0.4 ng/ml (AccuTnI, Beckman-Coulter, CA, USA) or hs-troponin T >140 ng/L (ROCHE).

Statistical analyses were performed using STATISTICA 8 (StatSoft Inc, OK, USA) and STATA 8 (STATA Corp LP, TX, USA). Conventional descriptive methods were applied, in other words, means and standard deviations for continuous variables and frequencies for categorical ones. The Cox proportional hazard model was performed to identify relationships between uricemia and defined outcomes (all-cause death and cardiovascular mortality). Censored data were used for the final analysis. Power calculations revealed that our population of patients was sufficiently large to estimate the expected incidence of defined outcomes with a 5% relative precision level. Statistical significance was considered present at a p-value of 0.05.

Results

Baseline cross-sectional data & outcomes

In total, 5196 patients admitted for MI (1846 with ST-elevation and 3350 without ST elevation on ECG), mean age of 64.6 (± standard deviation [SD] 11.9) years, were followed in this study. Concerning the acute MI, all patients underwent coronary angiography; percutaneous angioplasty was performed in 79.4%; and 6.7% of patients were referred for coronary artery bypass graft surgery (Table 1). Low uricemia (cohort A) was found in 2.9% of subjects (3.6 and 1.3%, in males and females, respectively), normal uricemia (cohort B) in 71.6% (74.9 and 63.4%, respectively) and hyperuricemia in 19.6% of patients (15.3 and 30.1%, respectively). Additionally, 5.9% of patients were on long-term treatment with allopurinol (6.1% of males and 5.2% of females; cohort D). In cohort D, 70.3% of patients were treated with 100 mg of allopurinol or less, 7.9% with more than 100 mg but less than 300 mg, and 21.8% with 300 mg of allopurinol or more. Moreover, none of the subjects reported gout symptoms during hospitalization, and only 34 patients reported gout in their medical history. Median uricemia (95% CI) across four predefined cohorts are shown in Figure 1.

During the median 1843 days (interquartile range: 769–2919) of follow-up, 1404 patients (27.0% of the sample) deceased and 311 (22.2%) of these fatal events were considered to be cardiovascular. Standardized 1-year incidences of all-cause and cardiovascular death were 8 and 7.4%, respectively, while 5-year incidences of both outcomes were 18.3 and 15.3%, respectively. Moreover, 5-year incidences of all-cause and cardiovascular death in a subsample of patients who survived at least 30 days (n = 5091) were 16.8 and 13.8%, respectively, while in those who survived at least 1 year (n = 4781) were 13.3 and 10.2%, respectively.

Uricemia categories & mortality risk

The survival curves based on the four defined categories of uricemia are shown in Figure 2. The lowest survival was observed in patients with hyperuricemia (cohort C), but similar, inferior survival was also observed in patients treated with allopurinol prior to their MI (cohort D). In contrast, no apparent differences in survival were found among patients with low and normal uricemia (cohort A & B). A very similar pattern was observed for all-cause and cardiovascular mortality.

We performed a series of Cox regression analyses to assess the relative risk attributable to the staging of uricemia. In the partially adjusted model (Table 2), patients with hyperuricemia (cohort C) showed more than a twofold higher relative risk of 1-year all-cause or cardiovascular mortality (compared with patients with normal uricemia,

Table 1. Baseline characteristics of the study sample (mean [standard deviation] or percent factor proportion).

n	5196
Age (years)	64.8 (11.9)
Gender (% of males)	71.1
Myocardial infarction with ST-elevation (%)	35.5
Percutaneous coronary angioplasty† (%)	79.4
Coronary artery bypass graft† (%)	6.7
History of hypertension (%)	69.1
LDL-cholesterol (mmol/l)	3.25 (1.03)
LDL ≥1.8 mmol/l (%)	93.3
Fasting glycemia (mmol/l)	8.17 (3.47)
Diabetes mellitus‡(%)	29.5
Estimated glomerular filtration§ (ml/min)	73.7 (21.7)
Estimated glomerular filtration <60 ml/min (%)	25.4
Overt heart failure¶ (%)	35.4
Peak troponin ≥100-times ULN¶ (%)	65.3
Serum uric acid (μmol/l)	355.3 (103.1)
Uricemia categories (%)	
– Low (A)	153 (2.9)
– Normal (B)	3721 (71.6)
– Hyperuricemia (C)	1017 (19.6)
– Treatment with allopurinol (D)	305 (5.9)

†During qualifying hospitalization or indicated due to current coronary event;
‡highest fasting glucose ≥7 or nonfasting ≥11.1 mmol/l;
§by CKD-EPI standard (lowest value of creatinine used);
¶See Materials & methods.
CKD-EPI: The Chronic Kidney Disease Epidemiology Collaboration; LDL: Low-density lipoprotein; ULN: Upper limit of normal.

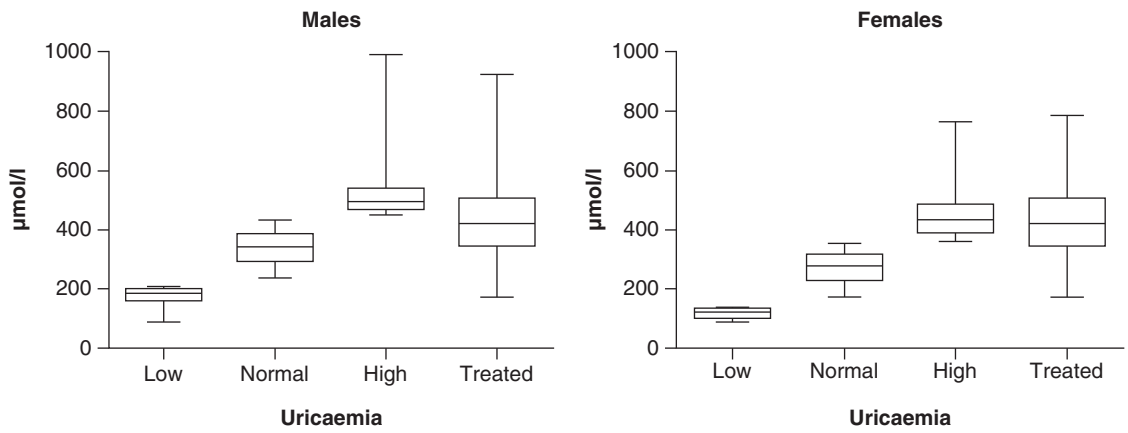

Figure 1. Box and Whisker plots of uric acid concentrations among predefined uricemia categories (see Materials & methods for definitions).

cohort B), but a nearly identical mortality risk was observed in those treated with allopurinol (cohort D). We also compared one against the other, in other words, 'hyperuricemic' cohorts, treated versus untreated (i.e., cohort D vs cohort C), and the observed differences in mortality risk were nearly nonexistent. In the next step, we excluded the most seriously ill patients, in other words, those who deceased in the first 30 days (Table 2; third row) and finally all those who deceased in the first year after the qualifying MI (Table 2; fourth row). The results were similar. In contrast, low uricemia was not associated with increased mortality risk in any of the above-mentioned regression models.

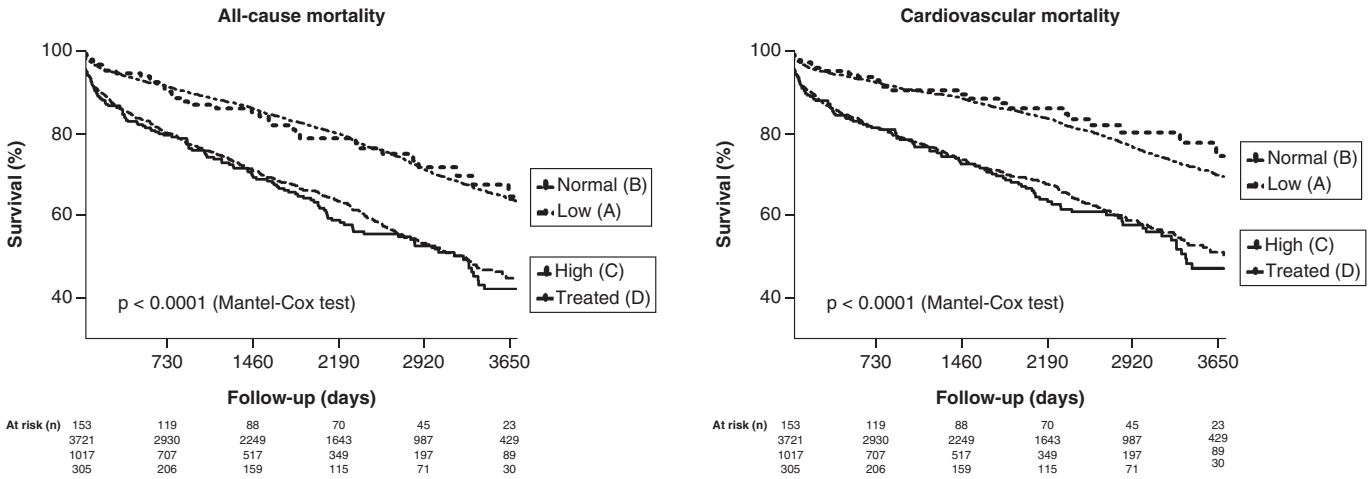

Figure 2. Kaplan–Meier survival curves for uricemia categories.

Table 2. All-cause and cardiovascular mortality risk by uricemia categories (partially adjusted model).

Uricemia categories	All-cause		Cardiovascular	
	HRR (95% CI)	p-value	HRR (95% CI)	p-value
1-year mortality risk				
– Low uricemia (A)	1.05 (0.51–2.13)	0.900	1.04 (0.49–2.23)	0.13
– Normal uricemia (B)	1	–	1	–
– Hyperuricemia (C)	2.13 (1.72–2.65)	<0.0001	2.20 (1.76–2.75)	<0.0001
– Treatment for hyperuricemia (D)	2.13 (1.54–2.95)	<0.0001	2.09 (1.48–2.95)	<0.0001
– Hyperuricemia (C)	1	–	1	–
– Treatment for hyperuricemia (D)	0.98 (0.70–1.39)	0.913	0.95 (0.66–1.36)	0.762
5-years mortality risk				
– Low uricemia (A)	1.38 (0.92–2.06)	0.128	1.13 (0.68–1.86)	0.646
– Normal uricemia (B)	1	–	1	–
– Hyperuricemia (C)	1.87 (1.62–2.17)	<0.0001	1.98 (1.69–2.31)	<0.0001
– Treatment for hyperuricemia (D)	1.80 (1.44–2.25)	<0.0001	1.89 (1.48–2.41)	<0.0001
– Hyperuricemia (C)	1	–	1	–
– Treatment for hyperuricemia (D)	0.98 (0.77–1.25)	0.857	0.97 (0.75–1.26)	0.816
5-years mortality risk, in survivals of at least 30 days†				
– Low uricemia (A)	1.49 (0.99–2.26)	0.058	1.24 (0.74–2.08)	0.419
– Normal uricemia (B)	1	–	1	–
– Hyperuricemia (C)	1.88 (1.61–2.20)	<0.0001	2.02 (1.71–2.40)	<0.0001
– Treatment for hyperuricemia (D)	1.84 (1.45–2.33)	<0.0001	1.99 (1.54–2.57)	<0.0001
– Hyperuricemia (C)	1	–	1	–
– Treatment for hyperuricemia (D)	0.99 (0.77–1.28)	0.954	0.99 (0.75–1.31)	0.956
5-years mortality risk, in survivals of at least 365 days‡				
– Low uricemia (A)	1.49 (0.92–2.39)	0.104	1.16 (0.62–2.19)	0.644
– Normal uricemia (B)	1	–	1	–
– Hyperuricemia (C)	1.61 (1.34–1.94)	<0.0001	1.67 (1.36–2.06)	<0.0001
– Treatment for hyperuricemia (D)	1.66 (1.25–2.19)	<0.0001	1.81 (1.33–2.47)	<0.0001
– Hyperuricemia (C)	1	–	1	–
– Treatment for hyperuricemia (D)	1.10 (0.81–1.50)	0.548	0.14 (0.81–1.61)	0.446

HRR Cox proportional hazard model; following covariates were included in the full model: age decade, gender, year of the event, hospitalization in the intensive care unit, percutaneous coronary angioplasty and coronary artery bypass graft; categories of uricemia referred to those on Figure 2.
Fatal event occurred between.
†Day 31 and day 1, 856.
‡Day 365 and day 2, 191 after beginning (day 0) of qualifying hospitalization for myocardial infarction.
HRR: Hazard risk ratio.

Table 3. Fully adjusted 1- year all-cause and cardiovascular mortality risk of hyperuricemia and treatment for hyperuricemia ('normal' uricemia group used as reference).

Risk factors	Model A†		Model B‡	
	HRR (95% CI)	p-value	HRR (95% CI)	p-value
All-cause mortality				
– Age decade	1.58 (1.40–1.78)	<0.0001	1.61 (1.39–1.85)	<0.0001
– Male gender	1.26 (0.99–1.60)	0.061	1.14 (0.85–1.52)	0.392
– Year of hospitalization	0.98 (0.94–1.02)	0.319	0.95 (0.91–1.00)	0.045
– Hospitalization ≥10 days	1.25 (0.95–1.67)	0.102	1.17 (0.83–1.62)	0.377
– ST-elevation myocardial infarction	1.10 (0.96–1.02)	0.500	1.13 (0.80–1.59)	0.489
– Percutaneous coronary intervention	0.49 (0.37–0.64)	<0.0001	0.55 (0.40–0.76)	<0.0001
– Coronary artery bypass graft	1.59 (1.07–2.37)	0.024	1.74 (1.05–2.87)	0.031
– History of hypertension	0.77 (0.58–1.01)	0.057	0.82 (0.59–1.14)	0.230
– Diabetes mellitus	1.53 (1.17–1.99)	0.002	1.50 (1.10–2.06)	0.012
– LDL cholesterol ≥1.8 mmol/l	0.88 (0.62–1.26)	0.489	0.94 (0.60–1.50)	0.803
– Atrial fibrillation	1.37 (1.05–1.79)	0.023	1.57 (1.15–2.15)	0.005
– Overt heart failure	2.24 (1.75–2.87)	<0.0001	2.33 (1.72–3.15)	<0.0001
– Peak troponin ≥100-times of ULN	1.42 (1.08–1.87)	0.012	1.19 (0.87–1.64)	0.284
– eGFR <60 ml/min	1.85 (1.43–2.40)	<0.0001	1.78 (1.31–2.42)	<0.0001
– Hyperuricemia (C vs B§)	1.68 (1.33–2.13)	<0.0001	–	
– Treatment for hyperuricemia (D vs B§)	–	–	1.33 (0.89–1.98)	0.160
Cardiovascular mortality				
– Age decade	1.61 (1.42–1.83)	<0.0001	1.66 (1.43–1.94)	<0.0001
– Male gender	1.18 (0.92–1.52)	0.188	1.04 (0.77–1.40)	0.807
– Year of hospitalization	0.98 (0.94–1.02)	0.274	0.95 (0.91–1.00)	0.031
– Hospitalization ≥10 days	1.24 (0.93–1.65)	0.138	1.17 (0.83–1.66)	0.363
– ST-elevation myocardial infarction	1.10 (0.82–1.45)	0.510	1.14 (0.71–1.63)	0.481
– Percutaneous coronary intervention	0.47 (0.35–0.62)	<0.0001	0.53 (0.38–0.74)	<0.0001
– Coronary artery bypass graft	1.60 (1.10–2.43)	0.024	1.70 (0.99–2.92)	0.053
– History of hypertension	0.77 (0.58–1.02)	0.071	0.80 (0.57–1.14)	0.213
– Diabetes mellitus	1.60 (1.21–2.12)	0.001	1.60 (1.15–2.25)	0.006
– LDL cholesterol ≥1.8 mmol/l	0.85 (0.59–1.21)	0.363	0.85 (0.53–1.34)	0.480
– Atrial fibrillation	1.46 (1.11–1.91)	0.007	1.65 (1.20–2.28)	0.002
– Overt heart failure	2.37 (1.82–3.08)	<0.0001	2.37 (1.72–3.27)	<0.0001
– Peak troponin ≥100-times of ULN	1.51 (1.13–2.02)	0.005	1.35 (0.96–1.91)	0.089
– eGFR <60 ml/min	1.84 (1.40–2.41)	<0.0001	1.81 (1.31–2.50)	<0.0001
– Hyperuricemia (C vs B§)	1.70 (1.33–2.17)	<0.0001	–	
– Treatment for hyperuricemia (D vs B§)	–	–	1.28 (0.85–1.95)	0.242

HRR by Cox proportional hazard model, eGFR.
† High vs normal uricemia.
‡ Treatment for hyperuricemia vs normal uricemia.
§ Refer to Figure 2.
eGFR: Estimated glomerular filtration rate; HRR: Hazard risk ratio; LDL: Low-density lipoprotein; ULN: Upper limit of normal.

Finally, we tested the additive mortality risk of hyperuricemia (cohort C), and treatment with allopurinol (cohort D) in the fully adjusted model (Table 3; normal uricemia [cohort B] was again used as a reference). Hyperuricemia was associated with a 70% higher risk in the 1-year incidence of all-cause death or fatal cardiovascular event. The predictive power of hyperuricemia was also found to be significant if: the 5-year risk was calculated (with hazard risk ratio for all-cause and cardiovascular mortality 1.45 [95% CI: 1.23–1.70] and 1.52 [95% CI: 1.28–1.80], respectively); those who deceased in the first 30 days were excluded (1.48 [95% CI: 1.25–1.77] and 1.58 [95% CI: 1.32–1.91], respectively); and after excluding all those who deceased in the first year (1.24 [95% CI: 1.01–1.53] and 1.28 [95% CI: 1.02–1.61], respectively; not in Table). In contrast, no significant relationship to incidence

risk for any of the detected end points was observed for treatment with allopurinol in the fully adjusted model (Table 3; model B).

Discussion

The present study highlights two important points: asymptomatic hyperuricemia observed during hospitalization was an independent predictor of higher mortality after MI, even in patients surviving at least 1 year; treatment with allopurinol as implemented in current clinical practice did not influence patient prognosis. Moreover, low uricemia had no apparent effect on mortality risk.

Our results are consistent with the presumed role of uric acid (as mentioned previously) and with other previously reported studies. Ranjith and colleagues [15] observed about a 70% higher risk of major adverse cardiac events in 2683 patients after MI (which was nearly identical to the results in our study). However, in our analysis, we demonstrated that the negative effects of hyperuricemia observed during hospitalization persisted in surviving patients for at least 30 or 365 days after the MI (i.e., after complete stabilization). Thus, it appears that hyperuricemia is not reflected in the immediate adverse course of an MI (i.e., leading to increased short-term mortality) but that its pathophysiological role (whether direct or not) is likely to be more long-term. This is important in light of a recent study by Lim and colleagues [16], who reported that in post-MI patients even increased uricemia variability during follow-up (i.e., a variance between outpatients visits every 3 months due to a temporary increase) was associated with a significant increase in the incidence of vascular events.

In our study, we also used different cut-off points for hyperuricemia in men and women, which is typical in clinical practice when assessing this parameter. However, it has been shown that the cardiovascular risk of hyperuricemia (in the sense of a worse prognosis after MI) is higher in women than in men [17]. Therefore, the limit for 'normal' uricemia should probably be stricter. We also performed an exploratory analysis with uniform cut-off points (either 360 or 450 μmol/l) for both genders, with confirmatory results. Additionally, our results were nearly identical when 34 patients with symptomatic gout were excluded from the analysis, and only truly asymptomatic patients were considered.

Despite all the evidence from retrospective studies (including the present study), hyperuricemia alone has not been identified as a known risk factor for vascular disease. Only an interventional trial with uricemia targeted treatment can be considered a definitive proof of causality. Without evidence of causality, it cannot be excluded that hyperuricemia is merely an 'innocent bystander' of another pathophysiology (perhaps increased apoptosis). An abundance of data have been generated in the last 5 years, but it remains doubtful whether uricemia-lowering therapy based on xanthine oxidase inhibitors provides any benefit relative to cardiovascular risk. Some clinical studies have demonstrated a significant protective effect for allopurinol in reducing the risk of acute MI [18–20], but there are also studies with nonsignificant results [21–23], and in one study, an increased cardiovascular risk was observed [24]. A recent meta-analysis of 25 studies on ≈ 14,000 patients assessed the efficacy of treatment with febuxostat or allopurinol, with no apparent benefit in terms of cardiovascular risk; however, febuxostat was associated with at least a borderline tendency to increased cardiovascular death [25].

One of the possible explanations of the ambiguous cardiovascular benefits of reducing uricemia is the question of the appropriate dose. Additionally, a relationship between the allopurinol dose and the observed effect on the cardiovascular system has yet to be demonstrated. In a study by De Abajo and colleagues on 3171 post-MI patients, the effect of allopurinol treatment was only observed at higher doses (i.e., 300 mg or more) and with prolonged treatment; allopurinol use was also shown to significantly reduce the risk of recurrence is equal to 0.16 [26].

Administration of allopurinol at a dose of 600 mg also improved exercise capacity in patients with stable angina pectoris [27], while in other studies, a dose of up to 600 mg resulted in oxidative stress reduction and less endothelial dysfunction [28]. Unfortunately, a metanalysis by Bredemeier and colleagues [29] showed the opposite. Treatment with xanthine-oxidase inhibitors reduced the incidence of adverse cardiovascular events, especially in high-risk patients, but the use of high doses of allopurinol (>300 mg/day) was associated with a loss of cardiovascular protection. It was also apparent from our analysis that treatment with allopurinol is, in general clinical practice, not dose-guided. Uric acid levels in allopurinol-treated patients were paradoxically higher than those seen in the group with 'normal' uricemia (see Figure 1). The reason is probably that the allopurinol treatment was started only in patients with very high uricemia and was not guided by any effort to normalize levels to some defined goal; it is also evident that allopurinol-treated patients were seriously underdosed (only ≈ 22% were treated with 300 mg or more). The majority of allopurinol-treated subjects (more than 90%) started treatment before admission for the qualifying MI event, and generally, no effort was made to adjust the dose of treatment during the MI hospitalization. We can also

speculate that one of the reasons for inferior survival among allopurinol-treated patients was that they may have had longer exposure to the adverse effects of hyperuricemia (i.e., having chronic higher uric acid concentrations before the allopurinol treatment was started) or were after a gout attack.

It is also necessary to stress that our study was not designed to demonstrate whether treatment with allopurinol or lowering of uricemia generally leads to any long-term cardiovascular benefit (a question that has been unresolved for decades). What we observed was that current practices for managing hyperuricemia were not accompanied by any major cardiovascular benefit.

It is evident that several drugs can increase uric acid levels, a phenomenon often observed with diuretics [30]. Therefore, we explored, using our regression models, the use of diuretics, in particular furosemide, as well as other drugs used routinely in secondary prevention after MI (antiplatelets, beta-blockers, renin-angiotensin system blockers and statins). The association between hyperuricemia and mortality risk remained independent (and more-or-less similar) regardless of secondary prevention.

Study limitations

Our analysis had several limitations. First, the definition of the hyperuricemia group was based on a single measurement of uric acid concentration, measured during the acute phase (immediately after the manifestation of the MI). We have no information about individual uric acid changes during the follow-up, in other words, were new uricemia-lowering drugs prescribed, was drug dose adjusted, etc. Therefore, our results should only be viewed in the context of the relationship between the 'acute status' of uricemia and subsequent mortality risk.

Second, we could not evaluate several factors involved in the individual risk of the patients. That is, all patients received standard recommendations for treatment and necessary lifestyle changes after their MI, but we know nothing about long-term control of major risk factors, real adherence to secondary pharmacotherapy, and other important factors (for example, smoking persistence). However, we had a chance to evaluate some of these factors in a subsample of about 680 patients, examined ≈ 1 year after the qualifying coronary event, who participated in the EUROASPIRE project. We found that the above-mentioned issues were more or less equally distributed across all four of our uricemia categories.

Conclusion

Hyperuricemia detected during hospitalization for acute MI appears to be an independent biomarker of an increased risk of a fatal recurrence of a cardiovascular event, even in subsequently fully clinically stabilized patients. Routine clinical treatment with allopurinol (i.e., mostly low-dose and not directed to achieve 'normouricemia') does not lead to any clear benefit in these patients and generally should not be considered for secondary prevention until we have evidence of its long-term benefit in the form of an interventional study.

Summary points

What is already known?

- Increased serum uric acid level is independently and significantly associated with risk of cardiovascular mortality in healthy population.
- Independent risk relationship between hyperuricemia and acute myocardial infarction (MI) is confirmed.
- Gouty arthritis is associated with an excess risk of acute MI, and this is not explained by its well-known links to renal functions, metabolic syndrome, diuretic use and traditional cardiovascular risk factors.
- All hypertonic patients with hyperuricaemia should be screened for cardiovascular diseases.

What did this study add?

- Hyperuricaemia in patients with acute MI was associated with a 70% higher risk of 1-year incidence of cardiovascular death.
- Treatment with allopurinol did not reduce the incidence of fatal cardiovascular events.
- Low uricaemia was not associated with increased mortality risk.
- Hyperuricaemia is an independent biomarker of increased risk of fatal cardiovascular event recurrence.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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