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The association between uric acid levels and different clinical manifestations of coronary artery disease
Trine R. Larsen¹, Oke Gerke³, Axel C.P. Diederichsend, Jess Lambrechtsenb, Flemming H. Steffensen⁹, Niels P. Sand⁴, Lotte Saabyd, Steen Antonsena and Hans Mickleyd

Aims Uric acid (UA) has been associated with the presence and severity of coronary artery disease. To further assess the role of UA role in coronary artery disease, we investigated UA levels in both healthy asymptomatic middle-aged individuals and in different subgroups of hospitalized patients with suspected or definite myocardial infarction (MI).

Patients and methods The severity of coronary artery calcification (CAC) was examined in asymptomatic individuals (n = 1039) using a noncontrast computed tomography scan. Hospitalized patients with suspected acute MI (n = 772) were grouped according to troponin I (Tnl) concentrations: (i) elevated Tnl concentrations (>0.03 µg/l) with subdivision according to the type of MI and other clinical conditions associated with myocardial injury, or (ii) nonelevated Tnl concentrations (≤ 0.03 µg/l).

Results UA was not associated with the severity of CAC in asymptomatic individuals when adjusting for relevant risk factors. Patients with type 2 MI and patients with myocardial injury associated with conditions of myocardial ischemia showed significantly higher UA levels (0.390 mmol/l, \( P = 0.002 \)) and 0.400 mmol/l, \( P = 0.001 \), respectively) than patients with type 1 MI (0.329 mmol/l), after adjusting for other risk factors.

Introduction Uric acid (UA) is the end-product of the metabolic breakdown of purine nucleotides and is excreted in urine. Increased levels of UA because of decreased renal excretion are the primary cause of arthritis urica. Arthritis urica patients, including individuals with asymptomatic hyperuricemia, have an increased risk of coronary artery disease (CAD); however, the mechanisms behind this association are not yet fully elucidated.

UA levels have been found to be associated with both adverse events and mortality in patients with acute myocardial infarction (MI) [1,2] as well as with the severity and mortality of acute CAD [3,4]. Moreover, elevated levels of UA have been associated with an increased risk of subsequent clinical events [5] and mortality in patients with stable CAD [6]. In contrast to these observations, both Cheong et al. [7] and Nossent et al. [8] did not find any relationship between either all-cause or cardiovascular mortality and UA levels in the general population.

Also, the role of UA as a risk factor for coronary artery calcification (CAC) remains controversial as some studies have reported a significant association between UA and CAC [9–12], whereas others did not find any relation between UA and CAC [13].

With the purpose of further illuminating the role of UA in relation to stable and acute clinical manifestations of CAD, we aimed to investigate (a) whether UA levels correlate with the presence and severity of CAC in...
asymptomatic middle-aged individuals from the general population and (b) whether UA levels are generally elevated or differ between subgroups of chest pain patients with suspected or definite MI.

Patients and methods

DanRisk population (the Danish risk score study)
In 2009, a random sample of 1825 asymptomatic individuals from the general population, 50 or 60 years old, was invited to participate in the DanRisk screening study [14]. A total of 1257 (69%) patients accepted the invitation. Exclusion criteria were as follows: known CAD (n = 32), atrial fibrillation (n = 9), heart valve disease (n = 1), and diabetes (n = 59). Furthermore, patients in whom noncontrast computed tomography (CT) scan was not performed (n = 4) or in whom biobank material was insufficient (n = 136) were excluded. Thus, a total of 1016 asymptomatic individuals were eligible for the final analysis. To assess the presence and severity of CAC, all participants underwent a noncontrast cardiac CT scan. An Agatston score was calculated by summing up the scores from each of the coronary artery foci [15]. Experienced cardiologists measured the Agatston score, and the participants were categorized into five groups: score 0 U, score 1–9 U, score 10–99 U, score 100–399 U, and score > 400 U. On the day of the CT scan, nonfasting blood samples were collected, centrifuged, and serum was stored at −80°C for future analysis.

DEF-AMI population (consequences of the universal 2007 definition of acute myocardial infarction studied prospectively in a Danish consecutive hospital population)
From January 2010 to January 2011, a total of 3762 consecutive patients with a suspected acute MI, who had serial cardiac troponin I values (TnI) measured during admission to Odense University Hospital, were included within 24 h after the first TnI sampling; all patients were subjected to an assessment of supplementary history by dedicated personnel, with a special focus on symptoms at admission, clinical characteristics, and co-morbidity. From 2390 patients who provided informed consent, a supplementary nonfasting blood sample was collected and stored at −80°C in the hospital’s biobank. Depending on the results of serial TnI measurements, patients were categorized as having elevated TnI concentrations (>0.03 µg/l) or nonelevated TnI concentrations (≤0.03 µg/l). Subsequently, patients with elevated TnI concentrations were classified as having an acute MI or as not fulfilling the MI diagnosis according to the criteria of the universal definition [16]. Patients with acute MI were subgrouped as having a type 1 or a type 2 MI. Type 1 MI results from spontaneous myocardial ischemia caused by coronary plaque erosion and/or rupture, fissuring, or dissection, whereas type 2 MI occurs secondary to myocardial ischemia caused by increased oxygen demand and/or decreased oxygen supply [16]. Patients classified as type 1 or type 2 MI all had at least one TnI value above the 99th percentile of the upper reference limit (URL) and showed a rise and/or fall pattern as required according to the universal definition [16]. Patients with elevated cardiac TnI concentrations but not fulfilling the MI criteria [16] were categorized as having myocardial injury as described previously [17]. Case ascertainment and individual evaluation of all patients was carried out by an experienced adjudication committee. Considering patients with myocardial injury, the following classification was used: first, patients with clinical conditions known to cause myocardial ischemia (e.g. arrhythmias, heart failure, aortic valve stenosis, chronic CAD, hypertension) who did not fulfill the biomarker criteria of the MI diagnosis were grouped. Indeed, these patients did have one or more TnI values above the 99th percentile of the URL, but the values were stable and did not show any rise and/or fall pattern as required according to the universal definition [16]. In the present study, these patients are classified as having Nonischemic myocardial injury. Second, patients with myocardial injury related to nonischemic cardiac conditions (e.g. major cardiac surgery, myocarditis, radiofrequency ablation) were classified as having Nonischemic myocardial injury. Third, patients with myocardial injury associated with systemic clinical conditions (e.g. infections, chronic kidney disease, pulmonary embolism, cerebrovascular events) were classified as having systemic myocardial injury. Finally, for comparison, patients presenting with nonelevated TnI values were included (Fig. 1). A detailed description of the DEF-AMI study, including classification of patient subgroups, has been published previously [17–19].

In this substudy, we included a total of 772 patients from the biobank. The patients were all type 1 MI patients with blood samples available (n = 177), all type 2 MI patients (n = 36), and all patients with myocardial injury (n = 196) (68 with ischemic myocardial injury, 51 with nonischemic myocardial injury, and 77 with systemic myocardial injury). Finally, from the group with nonelevated TnI values, a random selection of patients (n = 363), with a distribution of men versus women of ∼2:1 as in the other subgroups, was included. To eliminate kidney disease as a cause of elevated UA values, only patients with an enzymatic creatinine value within the reference interval (≤90 µmol/l for women and ≤105 µmol/l for men) were included. As a consequence, 191 patients were excluded before the statistical analyses because of creatinine results above the URL and these patients are not included in the above-mentioned numbers.

Ethics
Both the DanRisk and the DEF-AMI studies were approved by the Regional Scientific Ethical Committee for Southern Denmark (S-20080140 and S-20090082, Denmark).
respectively) and were carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant.

Biochemistry
Before biochemical analysis, serum samples were thawed, mixed, and centrifuged for 4 min at 2400 g. Blood samples were frozen and thawed maximally three times before analysis of UA and creatinine in this substudy. The effect of three freeze/thaw cycles was investigated and on average UA and creatinine showed deviations of −0.6 to −0.9% after the three cycles, which is considered acceptable compared with the analytical coefficients of variation (data not shown).

UA and enzymatic creatinine were analyzed using a DxC 800 (Beckman Coulter Inc., Brea, California, USA) and the DxC 800 assay kits (Beckman Coulter Inc.). The analytical coefficients of variation for UA and enzymatic creatinine were 1.6–5.8 and 1.4–5.8%, respectively.

TnI values were analyzed at the time of hospitalization on an Architect c16000 (Abbott Diagnostics, Abbott Park, Illinois, USA). TnI has an analytical coefficient of variation less than 20% at 0.02 µg/l and less than 10% at 0.028 µg/l, with an upper reference limit of the 99th percentile of 0.028 µg/l. A concentration of more than 0.03 µg/l is used as the decision limit for the diagnosis of MI. C-reactive protein (CRP) was analyzed on an Architect c16000 (Abbott Diagnostics), with analytical coefficients of variation of 2.8–5.5%.

Statistical methods
The aim of this study was to investigate the possible association between UA levels and (i) varying degrees of CAC in asymptomatic individuals and (ii) different groups of patients hospitalized with chest pain.

Descriptive statistics and bivariate analyses
Descriptive statistics were assessed according to data type and appropriateness of the normality assumption (continuous data: mean and SD vs. median and range; categorical data: frequencies and respective percentages). Bivariate correlation between UA (mmol/l) and CAC as measured by the Agatston score was visualized by a scatter plot, and the distributions of UA (mmol/l) across calcification categories (Agatston score = 0 vs. 1–9 vs. 10–99 vs. 100–399 vs. >400) as well as heart disease groups (type 1 MI vs. type 2 MI vs. ischemic myocardial injury vs. nonischemic myocardial injury vs. systemic myocardial injury vs. nonelevated TnI) were shown by means of box plots. The potential effect of different calcification categories and DEF-AMI patient subgroups on UA (mmol/l) was explored by one-way analysis-of-variance (ANOVA) including Bonferroni-adjusted multiple comparison tests for the analysis of intergroup differences [20].

Interplay of uric acid levels with the presence and severity of coronary artery calcification in asymptomatic middle-aged individuals
The influence of UA (mmol/l) in addition to the usual risk factors for CAC as measured by the Agatston score was investigated in two ways: first, the five above-mentioned categories of the Agatston score were used in ordinal logistic regression using the known risk factors age, sex, hypertension (no vs. newly diagnosed vs. known), hyperlipidemia, and smoking (never vs. active vs. former) as further covariates. The results were presented as generalized odds ratios and respective 95% confidence intervals (CI). Second, the quantitative measurement of the Agatston score was used as a dependent variable, considering its basic nature of being a count process, and zero-inflated negative binomial regression
CAC as measured by the Agatston score is visualized by a scatter plot (Supplementary Figure, Supplemental digital content 2, http://links.lww.com/MCA/A177, which shows the scatter plot of UA vs. CAC) and the distribution of UA across CAC categories (Agatston score) is shown by a box plot (Fig. 2). Using one-way ANOVA, UA was shown to be associated significantly with increasing Agatston score (Supplementary Table, Supplemental digital content 3, http://links.lww.com/MCA/A177, which shows the results of one-way ANOVA). However, this effect was abolished when adjusting for other risk factors. Ordinal logistic regression showed limited additive value of UA in addition to a model with usual risk factors (age, sex, smoking, hypertension, and hypercholesterolemia), $P=0.08$ (Supplementary Table, Supplemental digital content 4, http://links.lww.com/MCA/A177, which shows the results of ordinal logistic regression), as did zero-inflated negative binomial regression, $P=0.95$ (Supplementary Table, Supplemental digital content 5, http://links.lww.com/MCA/A177, which shows the results of zero-inflated negative binomial regression).

Role of uric acid levels in subgroups of chest pain patients with suspected or definite myocardial infarction
A multinomial logistic model was fitted for group affiliation using nonelevated TnI as a reference category, in which both known risk factors and clinical history were used as explanatory variables as follows: creatinine, CRP, age, sex, smoking (never vs. current vs. former vs. unknown), family history (none vs. yes vs. unknown), diabetes mellitus, hypertension, hyperlipidemia, previous MI, previous coronary artery bypass graft surgery, previous percutaneous coronary intervention, heart failure, previous stroke, peripheral artery disease, known kidney disease, and chronic obstructive pulmonary disease (COPD). The results were shown as relative risk ratios with respective 95% CIs. Moreover, binary logistic regression was applied on the group affiliations type 1 MI and type 2 MI as well as type 1 MI and ischemic myocardial injury using the former in both cases as the reference category and the above-mentioned covariates as explanatory variables. The results were presented as odds ratios and respective 95% CIs. For both the multinomial and the binary logistic regression model, the original UA (mmol/l) concentrations were multiplied by 10 to facilitate interpretation of 0.1 U changes instead of the usual 1 U changes.

Technical specifications
The level of significance was 5%. All analyses were carried out using Stata/MP 15.0 (StataCorp. LP, College Station, Texas, USA).

Results
Asymptomatic individuals
DanRisk participants had a median age of 59.4 (49.4–61.1) years, and 54% were women. The demographics and clinical variables of the DanRisk population are presented in Supplementary Table (Supplemental digital content 1, http://links.lww.com/MCA/A177, which contains the demographics and clinical variables of the DanRisk population). The correlation between UA and CAC as measured by the Agatston score is visualized by a box plot (Fig. 2). Using one-way ANOVA, UA was shown to be associated significantly with increasing Agatston score (Supplementary Table, Supplemental digital content 3, http://links.lww.com/MCA/A177, which shows the results of one-way ANOVA). However, this effect was abolished when adjusting for other risk factors. Ordinal logistic regression showed limited additive value of UA in addition to a model with usual risk factors (age, sex, smoking, hypertension, and hypercholesterolemia), $P=0.08$ (Supplementary Table, Supplemental digital content 4, http://links.lww.com/MCA/A177, which shows the results of ordinal logistic regression), as did zero-inflated negative binomial regression, $P=0.95$ (Supplementary Table, Supplemental digital content 5, http://links.lww.com/MCA/A177, which shows the results of zero-inflated negative binomial regression).

Patients with suspected or definite myocardial infarction
The demographics and clinical variables of the DEF-AMI population according to the different subgroups are presented in Table 1. Further, in Fig. 3, the distribution of UA levels in the different patient subgroups is illustrated using a box plot. One-way ANOVA showed multiple significant differences in UA levels between the different DEF-AMI subgroups (Supplementary Table, Supplemental digital content 6, http://links.lww.com/MCA/A177, which shows the results of the one-way ANOVA). Altogether, patients with type 2 MI and patients with ischemic myocardial injury showed significantly elevated
UA levels, compared with type 1 MI, nonischemic myocardial injury, systemic myocardial injury, and nonelevated TnI patient subgroups. Using multinomial logistic regression, patients with nonelevated TnI were shown to have significantly lower UA levels compared with type 2 MI patients ($P=0.02$) and those with ischemic myocardial injury ($P=0.01$) (Table 2). Binary logistic regression showed significant differences between type 1 MI and type 2 MI, $P=0.002$, as well as between type 1 MI and ischemic myocardial injury, $P=0.001$ (Table 3), with the type 2 MI and the ischemic myocardial injury subgroups having higher levels of UA than the type 1 MI subgroup.

**Discussion**

Earlier studies have suggested an association between UA and CAC severity in asymptomatic individuals [9,10,26,27], as well as between UA and both acute and stable CAD [1–6]. In the present study, both asymptomatic individuals without known CAD and patients with suspected or definite MI were included. Using this design, the levels of UA could be measured in a broad spectrum of individuals ranging from the clinically stable to the clinically unstable situation, including patients with different subtypes of MI, and patients in whom the MI diagnosis could not be confirmed, despite elevated TnI values.
<table>
<thead>
<tr>
<th>Type 1 MI</th>
<th>Relative risk ratio (95% CI)</th>
<th>P value</th>
<th>Relative risk ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid (mmol/l)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.25</td>
<td>1.4 (1.0-1.6)</td>
<td>0.11</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.25</td>
<td>1.4 (1.0-1.6)</td>
<td>0.11</td>
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<table>
<thead>
<tr>
<th>Type 2 MI</th>
<th>Relative risk ratio (95% CI)</th>
<th>P value</th>
<th>Relative risk ratio (95% CI)</th>
<th>P value</th>
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<tr>
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<td>1.4 (1.0-1.6)</td>
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<thead>
<tr>
<th>Ischemic myocardial injury</th>
<th>Relative risk ratio (95% CI)</th>
<th>P value</th>
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<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Uric acid (mmol/l)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.25</td>
<td>1.4 (1.0-1.6)</td>
<td>0.11</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.25</td>
<td>1.4 (1.0-1.6)</td>
<td>0.11</td>
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<thead>
<tr>
<th>Nonischemic myocardial injury</th>
<th>Relative risk ratio (95% CI)</th>
<th>P value</th>
<th>Relative risk ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid (mmol/l)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.25</td>
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<td>0.11</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>0.9 (0.7-1.1)</td>
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<tr>
<th>Systemic myocardial injury</th>
<th>Relative risk ratio (95% CI)</th>
<th>P value</th>
<th>Relative risk ratio (95% CI)</th>
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<tr>
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Table 2. Results from multinomial logistic regression on group affiliation (dependent variable) with nonelevated TnI as the reference category (N=772).
We did not find any association between the levels of UA and the presence or severity of CAC in asymptomatic middle-aged individuals. In hospitalized patients with chest pains, we found significant differences in UA levels between type 1 and type 2 MI patients. Thus, patients with type 2 MI had higher UA levels than those with type 1 MI. Furthermore, we showed that also in patients with TnI elevations, who did not fulfill the diagnostic MI criteria, the UA levels varied significantly depending on the associated clinical conditions.

**Uric acid in asymptomatic individuals**

CAC is an established predictor of cardiac events [28] and several studies have suggested an association between UA and CAC severity in asymptomatic individuals [9,10,26,27]. However, these findings might have been caused by insufficient statistics. Thus, in some of these earlier studies, Agatston scores were merely divided into the presence or absence of CAC [9,10,27], as opposed to clinically relevant groups, or the highest tertile or quartile of UA was only compared with the lowest in terms of the Agatston score [10,26,27], which is purely data driven and not clinically relevant. In contrast, Neogi et al. found no association between UA and CAC when testing for a trend over quartiles of UA [13]. In the present study, we also found no association between UA and CAC severity after adjusting for common risk factors, and in addition, there was only limited value when adding UA from our asymptomatic middle-aged individuals to a risk model predicting atherosclerosis. This observation is consistent with the findings obtained by Kavousi et al. [29], who also did not find any improved risk prediction for CAD in a middle-aged population, when adding UA to the Framingham Cardiovascular Risk Score, which has otherwise been proposed to improve the prediction of CAD in the elderly [30]. As the predictive value of the Framingham Cardiovascular Risk Score may decrease markedly with older age [31,32], this may explain why UA appears to improve the prediction in the older but not in the middle-aged individuals, consistent with our observation that adding UA to an atherosclerotic risk model only results in very limited value.

**Uric acid in acute myocardial infarction**

The results of the present study indicate that the levels of UA were significantly higher in patients with type 2 MI compared with type 1 MI patients. This observation may, according to the available literature, be surprising as a type 1 MI per definition results from acute coronary plaque rupture, plaque erosion, or fissuring, and thus to some extent must be associated with CAD [16]. A patient with type 2 MI, however, may or may not have CAD, and a type 2 MI per definition arises from an imbalance in myocardial oxygen supply/demand – without the involvement of an acute coronary plaque rupture, erosion, or fissuring [16]. Thus, from a theoretical point of view, if a
positive association between UA levels and the burden of CAD including plaque rupture exists, one would expect patients with type 1 MI to have higher UA concentrations than patients with a type 2 MI. However, the lack of stratification of patients with CAD in earlier studies into specific subgroups on the basis of the type of MI or associated clinical conditions [1–6] might have masked the fact that UA is elevated in some subgroups, but not in others, such as type 1 MI.

Indeed, the observation that UA is not elevated in type 1 MI is supported by our results in asymptomatic individuals where we did not find any association between UA and the presence or severity of CAC. These individuals may be defined as having clinically stable CAD and thus our combined results indicate that UA is not a specific marker for either stable or acute clinical CAD.

A causal role for UA in CAD has been proposed in several studies using Mendelian randomization [33–35]. Causality was suggested in a follow-up of patients hospitalized for coronary angiography [33] and for patients at high cardiovascular risk [34]. However, it cannot be ruled out that the causal association is affected by pleiotropy [35]. Furthermore, both data by Testa and colleagues and White and colleagues were comprised of a number of studies and therefore have utilized a very ‘broad’ definition of CAD, making it impossible to determine whether the association between UA and CAD is actually a general finding or is restricted to specific subgroups of CAD patients such as the ones that we examine in the present study.

Uric acid in patients with myocardial injury

On the basis of the results of this study, it may be hypothesized that UA is involved in the process leading to myocardial ischemia because of an imbalance between myocardial oxygen demand and myocardial oxygen supply. Indeed, not only in type 2 MI patients but also in patients with ischemic myocardial injury, we observed significantly higher UA concentrations compared with the concentrations in patients with type 1 MI. The relevant clinical conditions in these patients were atrial fibrillation, chronic heart failure, aortic valvular stenosis, hypertension, and chronic CAD [17]. Previously, an association has been reported between UA and atrial fibrillation in the general population [36,37] as well as in patients with ventricular tachycardia [38]. It is noteworthy that it has been shown that treatment of chronic heart failure patients with allopurinol improved prognosis [39]. Earlier data suggest that UA may be a marker of ischemia as UA has been shown to reduce the release of nitric oxide, a vasodilator, from human umbilical vein endothelial cells [40]. Reduced vasodilation might be part of the mechanism behind ischemia in CAD with elevated UA, which fits with the beneficial effect of allopurinol treatment [39]. In addition, in patients with chronic heart failure, UA has been found to be associated inversely with maximum oxygen uptake, suggesting that increased UA may reflect an impairment in oxidative metabolism in these patients [41]. In concordance with this observation, we found that patients in the ischemic myocardial injury group had a higher incidence of heart failure compared with both nonelevated TnI and type 1 MI. Furthermore, 25% of the type 2 MI patients in this study had been diagnosed with COPD, a condition with chronic hypoxia and with which elevated levels of UA have been associated [42]. COPD in the binary logistic regression did not reach the level of statistical significance (Table 3; P=0.11); however, this may be because of the relatively low number of patients in the type 2 MI subgroup.

Increased levels of UA can be associated with kidney disease [43] and inflammation [44]. Although we tried to avoid the established influence of kidney disease as a cause of elevated UA by excluding all patients with a creatinine above the URL from the study, creatinine levels were still higher in the type 2 MI and ischemic myocardial injury subgroups compared with the nonelevated TnI or type 1 MI subgroups. However, these differences did not reach statistical significance, possibly because of the relatively low number of patients in the type 2 MI subgroup. Thus, one of the main reasons for the differences in UA levels among our patient groups might be subclinical kidney dysfunction. In terms of inflammation, CRP levels were not significantly elevated in the type 2 MI and ischemic myocardial injury subgroups compared with the nonelevated TnI or type 1 MI subgroups, and in our opinion, the CPR levels do not seem to be a plausible cause for the elevated UA levels. In addition, CRP was the highest in the nonischemic myocardial injury and systemic myocardial injury subgroups, in which no elevation of UA levels was found.

Strengths and limitations

A limitation in our study is the small number of patients in a number of the subgroups. However, the stratification into specific MI subgroups according to the universal definition may help us to determine and understand the potential involvement of UA in the pathogenic processes underlying different subtypes of MI and myocardial injury. Furthermore, we use two different populations, one healthy and one diseased, the results from which supplement one another.

Conclusion

We did not find any correlation between UA levels and CAC severity in asymptomatic middle-aged individuals from the general population. Furthermore, we found that patients with type 2 MI and patients with ischemic myocardial injury had significantly higher UA levels than patients with type 1 MI. This observation might support the hypothesis that UA is involved in the pathophysiological mechanisms leading to an imbalance in the
oxygen supply/demand ratio in type 2 MI and ischemic myocardial injury.

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Conflicts of interest
There are no conflicts of interest.

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