Atherosclerosis 270 (2018) 173–179

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Uric acid is associated with long-term adverse cardiovascular outcomes in patients with acute coronary syndrome undergoing percutaneous coronary intervention

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ARTICLE INFO

Article history:
Received 4 August 2017
Received in revised form
21 December 2017
Accepted 2 February 2018

Keywords:
Uric acid
Hyperuricemia
Acute coronary syndrome
Percutaneous coronary intervention
Long-term adverse outcomes

ABSTRACT

Background and aims: Evidence links uric acid (UA) with the promotion of cardiovascular disease. We assessed the prognostic value of UA on long-term major adverse outcomes (MACE) in patients with acute coronary syndrome (ACS), undergoing percutaneous coronary intervention (PCI).
Methods: As primary endpoint, we assessed the association of UA (continuous and dichotomized) with MACE, including cardiovascular death, myocardial infarction (MI) and stroke, using Cox regression and propensity matching. As secondary endpoints, the influence of hyperuricemia (defined as UA levels > 6.0 mg/dl in women, and >7.0 mg/dl in men) was analysed separately for cardiovascular death, MI, and stroke. The incremental prognostic value of UA was tested using the net reclassification improvement (NRI), and the integrated discrimination improvement (IDI).
Results: We included 1215 patients. Hyperuricemia was present in 356 (29.3%) patients. Mean follow-up was 5.5 years.
UA (HR 1.091 [1.035–1.150]; $p = 0.001$) and hyperuricemia (HR 1.750 [1.388–2.207]; $p < 0.001$) were significantly associated with MACE. Results were consistent between Cox regression and propensity matched analysis. Patients with hyperuricemia had a 1.6-fold increased relative risk for cardiovascular death ($p = 0.005$) and a 1.5-fold increased risk for MI ($p = 0.032$). For stroke, hyperuricemia only constituted a confounder (HR 1.104; $p = 0.970$). The prognostic accuracy of an established risk prediction model was significantly increased by adding UA (continuous NRI $p = 0.004$; categorical NRI $p = 0.029$; IDI $p = 0.002$).
Conclusions: Our data suggest an independent association of elevated UA with long-term MACE in ACS patients undergoing PCI. Whether lowering UA might be beneficial remains to be elucidated in large clinical trials.

1. Introduction

Cardiovascular disease is the most common cause of death in the world, with coronary artery disease (CAD) making up its greatest proportion [1]. Considerable time and effort have been invested in the identification of cardiovascular risk and prognostic factors contributing to both progression and risk stratification.

In this regard, uric acid (UA), the final product of purine metabolism, metabolized by xanthine oxidase, and its association with cardiovascular disease has recently shifted back into focus of scientific interest, although the independent role of UA is still matter of debate. UA has been shown to be related to arterial hypertension,

Abbreviations: ACE-I, angiotensin-converting-enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin-receptor blocker; ASS, acetylsalicylic acid; CAD, coronary artery disease; CK, creatine kinase; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IDI, integrated discrimination improvement; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; NRI, net reclassification improvement; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack; UA, uric acid.

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https://doi.org/10.1016/j.atherosclerosis.2018.02.003
0021-9150/

diabetes mellitus, metabolic syndrome and chronic kidney disease and may be also linked to general cardiovascular risk [2–4]. Growing evidence links elevated levels of UA to enhanced oxidative stress at an intracellular level, vascular inflammation and endothelial dysfunction and, as consequence, to atherosclerosis and cardiovascular disease progression [5–10]. Elevated levels of UA have been reported to be associated with lipid-rich plaques, reduced coronary flow reserve and impaired coronary microvascular function, factors known to be associated with future adverse outcome [11–14]. In the context of acute coronary syndromes (ACS), especially contemporarily managed, data on UA and long-term cardiovascular mortality and morbidity is limited [15,16].

We have therefore investigated the association and prognostic value of elevated UA levels with regard to long-term major adverse cardiovascular events (MACE) in patients with myocardial infarction, undergoing percutaneous coronary intervention (PCI).

2. Materials and methods

2.1. Study population

This is a *post-hoc* analysis of a prospective registry including all consecutive patients presenting with ACS, undergoing PCI between January 2007 and July 2012. Data on cardiovascular risk factors, comorbidities, laboratory measures, coronary morphology, and discharge medication were collected for all patients.

ACS patients presented either with persistent ST-segment elevation myocardial infarction (STEMI) or non ST-elevation acute coronary syndromes (NSTE-ACS). Criteria for STEMI were biomarker evidence of MI with ST-segment elevation of 1 mm or more in two or more contiguous leads, while NSTE-ACS patients required elevated troponin I, troponin T or creatine-kinase MB (CK-MB) levels and/or ST-segment depression of $\geq$1 mm for diagnosis. PCI was performed according to the applying standard guidelines and the concomitant treatment and management of the patient was at the discretion of the attending cardiologist. Hyperuricemia was defined as serum UA values $\geq$ 6.0 mg/dl in women and $\geq$7.0 mg/dl in men.

Patients without successful coronary intervention, and patients not residing in the Vienna metropolitan area, were excluded from the present investigation.

The study was performed according to the ethical guidelines of the Declaration of Helsinki and was approved by the local ethics committee (EK-16-269-VK). All subjects have given written informed consent.

2.2. Laboratory parameters

Venous blood samples for the measurement of kidney function, serum glucose and haematocrit were taken at hospital admission, and for the measurement of uric acid, high- and low-density lipoprotein cholesterol (HDL-C and LDL-C) and triglycerides, on the first morning after admission in fasting condition. Troponin I, CK, CK-MB, and high-sensitive C-reactive protein (hs-CRP) were monitored every 6 h until peak values were reached.

2.3. Clinical outcomes

As primary endpoint of interest, the influence of uric acid and hyperuricemia on long-term major adverse cardiovascular events, a composite of (1) cardiovascular death, (2) non-fatal myocardial infarction, and (3) non-fatal ischemic stroke, was investigated. Mortality data for all patients were obtained from the Statistics Austria Institute. The Statistics Austria Institute is an independent and non-profitmaking federal institution under public law and supports scientific services. Data on recurrent myocardial infarction or stroke was obtained, using the common Vienna regional hospital database system.

As secondary endpoints, the influence of hyperuricemia was tested separately for cardiovascular death, non-fatal myocardial infarction, and non-fatal ischemic stroke.

2.4. Statistical analysis

All continuous variables are expressed as mean (standard deviation [SD]) for variables following normal distribution and for variables not following normal distribution as median (interquartile range [IQR]). Variables were tested for normal distribution by Kolmogorov-Smirnov-Liliefors test. Categorical variables are expressed as number and percentage. Continuous variables were compared by either Student's *t*-test or Mann-Whitney-*U*-test, as appropriate. χ2-tests were performed for categorical variables. All statistical analyses were 2-tailed, and a p-value < 0.05 was required for statistical significance. All statistical analyses were performed with SPSS 21.0 (SPSS Inc., Chicago, IL, USA), and R 3.4.0 (http://www.r-project.org/). Used R packages were “PredictABEL”, and “ABE”.

2.5. Outcome analysis

A Cox proportional hazard model was applied for the primary and secondary endpoints according to the augmented backward elimination algorithm proposed by Dunkler et al., an adaption of the purposeful selection algorithm [17]. As first step, all potential prognostic variables were included into a step-wise backward elimination model using a likelihood-ratio test with a significance level of $\alpha > 0.2$ for exclusion. In a second step, all primarily excluded variables were re-entered separately and kept in the model in case of a change-in-estimate of >5% to identify relevant confounders.

The following variables were included into the primary model:

Uric acid (continuous and dichotomized), age, gender, body-mass index, cardiogenic shock, TIMI minor or major bleeding, traditional cardiovascular risk factors, prior MI, prior coronary revascularisation (either PCI or coronary artery bypass graft [CABG]), prior stroke or transient ischemic attack (TIA), peripheral artery disease, atrial fibrillation, heart failure, malignancy, estimated glomerular filtration rate (eGFR), peak troponin I, peak hs-CRP, serum blood glucose at admission, haematocrit at admission, vascular access site, number of affected coronary vessels, type of used stents, number of used stents, total stent length, and drug therapy (beta-blocker, ACE-I or ARB, PPI, diuretics, high-intensity statins, allopurinol and antithrombotic-therapy).

Additionally, we performed a 1:2 matched propensity score analysis including all the abovementioned variables.

2.6. Risk reclassification

The incremental prognostic value of UA to an established risk prediction model was tested using the net reclassification improvement (NRI), and the integrated discrimination improvement (IDI) [18,19]. To this purpose, variables of the GRACE 2.0 risk score (Global Registry of Acute Coronary Events) including age, heart rate, systolic blood pressure, serum creatinine, elevated cardiac markers, Killip class, and ST-segment deviation were used to build a risk prediction model [20]. Following the GRACE risk score, the 3-year estimated incident risk for MACE was calculated for each participant using regression analysis. The risk estimates were categorized as 0–10%, 10–30%, and $\geq$30%, corresponding to low, intermediate and high risk respectively, as with the GRACE risk score.