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Serum uric acid levels are associated with cardiovascular risk score: a *post hoc* analysis of the EURIKA study

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COronary Risk Evaluation (SCORE); Systematic COronary Risk Evaluation

algorithm including high-density lipoprotein cholesterol (SCORE-HDL)

Abstract

Background: Reports are conflicting on whether serum uric acid (sUA) levels are independently associated with increased cardiovascular (CV) death risk.

Methods: This *post hoc* analysis assessed the relationship between sUA levels and CV death risk score in 7531 patients from the cross-sectional, multinational EURIKA study (NCT00882336). Patients had at least one CV risk factor but no clinical CV disease. Ten-year risk of CV death was estimated using SCORE-HDL and SCORE algorithms, categorized as low ($< 1\%$), intermediate (1% to $< 5\%$), high ($\geq 5\%$ to $< 10\%$) or very high ($\geq 10\%$).

Results: Mean serum sUA levels increased significantly with increasing CV death risk category in the overall population and in subgroups stratified by diuretics use or renal function (all $P < 0.0001$). Multivariate ordinal logistic regression analyses, adjusted for factors significantly associated with CV death risk in univariate analyses (study country, body mass index, number of CV risk factors and comorbidities, use of lipid lowering therapies, antihypertensives and antidiabetics), showed a significant association between sUA levels and SCORE-HDL category in the overall population (OR: 1.39 [95% CI: 1.34–1.44]) and all subgroups (using diuretics: 1.32 [1.24–1.40]; not using diuretics: 1.46 [1.39–1.53]; estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m^2: 1.30 [1.22–1.38]; eGFR ≥ 60 ml/min/1.73 m^2: 1.44 [1.38–1.51]; all $P < 0.0001$). Similar results were obtained when using SCORE.

Conclusions: Higher sUA levels are associated with progressively higher 10-year CV death risk score in patients with at least one CV risk factor but no CV disease.

Word count: 250 words

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate;

EURIKA, European Study on Cardiovascular Risk Prevention and Management in

Usual Daily Practice; HDL, high-density lipoprotein; SCORE, Systematic COronary

Risk Evaluation; SD, standard deviation; sUA, serum uric acid.

1. Introduction

Uric acid, the waste product of purine metabolism, has protective antioxidant properties, but has also been described as a mediator of pathological processes, including inflammation and endothelial dysfunction [1, 2]. Increasing levels of serum uric acid (sUA) have been implicated in the pathophysiology of cardiovascular (CV) and cardiorenal conditions, such as hypertension [3-5], diabetes [6, 7], metabolic syndrome [5, 8, 9], coronary artery disease [10] and kidney disease [5, 11, 12].

There is much debate around whether an independent association exists between sUA levels and increased risk of CV death. Several studies have reported an independent association [13-15], but others have been unable to confirm such a relationship [16-19]. Data from the first National Health and Nutrition Examination Survey (NHANES) Epidemiologic Follow-up Study suggested that sUA levels were independently associated with CV death regardless of diuretics use and sex [13]. Diuretics use and estimated glomerular filtration rate (eGFR) were reported as key confounders in the Framingham Heart Study and a study based on data from the NHANES, respectively [16, 18]. However, since both factors might raise sUA levels without contemporarily affecting CV risk, they must be considered as factors that can prevent the identification of a true increased CV risk and not as confounders that support the lack of a relationship. In the Framingham Heart Study, levels of sUA were associated with an increased risk of CV death in women but not in men, and the association disappeared after adjustment for well-known CV risk factors. Adjustment for potential confounders needs to be performed with care, however, because it may adjust inappropriately for factors such as blood pressure that have a direct, causal relationship with sUA rather than being markers of confounding [16].

The European Study on CV Risk Prevention and Management in Usual Daily Practice (EURIKA; ClinicalTrials.gov Identifier: NCT00882336) was conducted to assess clinical practice in the primary prevention of CV disease across Europe [20]. EURIKA included individuals from 12 European countries with at least one CV risk factor but no clinical CV disease and was performed mostly in the primary prevention, primary care setting, where hyperuricaemia is commonly managed by clinicians. This is in contrast with previously conducted studies, which were mostly population-based surveys [13, 14, 18] or conducted in the clinical trial setting [17], recruited North American individuals [13, 14, 16, 18] or were centred on predicting the effect of genetic scores [15]. The aim of the current, *post hoc* analysis was to assess the association between sUA levels and the estimated 10-year risk of CV death in patients in EURIKA, evaluated using a CV death risk score algorithm. The potential specific associations of sUA levels with hypertension and diabetes were also explored.

2. Methods

2.1. *Study design and participants*

EURIKA was conducted in 12 European countries (Austria, Belgium, France, Germany, Greece, Norway, Russia, Spain, Sweden, Switzerland, Turkey, and the UK) [21]. Data were collected between May 2009 and January 2010, with a 3-month data collection period for each country. The methods for the study have been reported in detail elsewhere [20]. In brief, the study sample was selected in a two-step process that involved recruitment of physicians and their patients [20, 22]. In the first stage, a sample of approximately 60 physicians involved in CV disease prevention (primary care physicians and specialists) was randomly selected from each country using the

Cegedim OneKey database (www.cegedim.com). A total of 809 physicians agreed to participate in EURIKA, 64% of whom were primary care physicians [22].

In the second stage, participating physicians invited patients who were aged 50 years or older, were free from CV disease and had at least one of the following five major CV disease risk factors: 1) dyslipidaemia, defined as high levels of low-density lipoprotein cholesterol (LDL-C; $\geq$ 4.1 mmol/L [$\geq$ 160 mg/dl]) or low levels of high-density lipoprotein cholesterol (HDL-C; < 1.036 mmol/L [< 40 mg/dl] for men, < 1.300 mmol/L [< 50 mg/dl] for women) or high triglyceride levels ($\geq$ 1.7 mmol/L [$\geq$ 150 mg/dl]) or receiving lipid-lowering medication; 2) hypertension, defined as a systolic blood pressure of at least 140 mmHg or a diastolic blood pressure of at least 90 mmHg or receiving antihypertensive medication; 3) smoking, defined as being a current or former smoker with more than 100 cigarettes smoked in their lifetime; 4) diabetes mellitus, defined as a fasting plasma glucose level of at least 7.0 mmol/L (126 mg/dl), or receiving insulin or oral antidiabetic medication; 5) obesity, defined as a body mass index (BMI) of at least 30 kg/m^2, or a waist circumference of at least 102 cm in men and at least 88 cm in women.

Approximately 600 patients were included per country, with a total population size of 7641 in EURIKA [21]. The current analysis includes only patients for whom information on sUA levels was available (N = 7531).

The study protocol was approved by the appropriate clinical research ethics committees in each participating country, and all patients provided signed informed consent before enrolment.

2.2.   Baseline characteristics and clinical measurements

The demographic details and medical history of participating patients were gathered from medical records and patient interviews. For each patient, a physical examination was conducted, blood pressure was measured and a 12-h fasting blood sample was collected within 1 day of the initial outpatient consultation. Blood pressure measurements were obtained under standardized conditions, using calibrated mercury sphygmomanometers or validated automated devices, and appropriate-size cuffs. The mean of three consecutive measurements in the sitting position and spaced 1–2 min apart was used for the analyses [23]. The blood sample analysis was performed by a central laboratory (Bio Analytical Research Corporation, Ghent, Belgium), with the exception of patients in Russia (approximately 5% of all patients), for whom laboratory analysis was conducted locally. All participating physicians were asked in the clinical report form to provide enrolled patients' eGFR in ml/min/1.73 m^2.

2.3.   Systematic coronary risk evaluation

Patients' 10-year risk of CV death was estimated using the Systematic COronary Risk Evaluation (SCORE) [24] and SCORE-HDL [25] algorithms. SCORE-HDL is an updated version of the SCORE algorithm that takes into account total cholesterol and HDL-C levels as independent variables. Algorithms developed for low-risk regions were used for patients in Belgium, France, Greece, Spain and Switzerland, and algorithms for high-risk regions were utilized for patients in Austria, Germany, Norway, Russia, Sweden, Turkey and the UK [24, 25].

2.4. Statistical analyses

Statistical analyses were carried out using SAS (V9.2, SAS Institute Inc., Cary, NC, USA). SCORE-HDL and SCORE were analyzed as categorical variables using four score categories: low ($< 1\%$); intermediate ($\geq 1\%$ to $< 5\%$); high ($\geq 5\%$ to $< 10\%$); and very high ($\geq 10\%$). Univariate analyses were conducted to compare explanatory variables across the four SCORE-HDL or SCORE categories, using **analysis of variance (ANOVA)** for continuous explanatory variables and chi-square test for categorical explanatory variables. Explanatory variables assessed were: blood uric acid concentration; BMI; study country; number of CV risk factors (1 to 5); number of comorbidities (0 to ≥ 4); use of lipid-lowering drug (at least one type versus no); use of antihypertensive drug (at least one type versus no); and use of antidiabetic drug (at least one type versus no). Multivariate analyses were conducted using an ordinal logistic regression model, to explore the potential association of higher 10-year risk of CV death category with increasing sUA levels and explanatory variables. Each variable was adjusted for all other variables in the explanatory model shown to be significantly related ($P < 0.1$) to risk score of CV death in the univariate analysis, and for study country and BMI as potential confounders. To validate the use of the ordinal logistic regression model, three binary logistic models were first fitted (risk score $< 1\%$ versus $\geq 1\%$, $< 5\%$ versus $\geq 5\%$, and $< 10\%$ versus $\geq 10\%$) to confirm that odds ratios (ORs) between adjacent risk categories were of the same magnitude.

Analyses were conducted in the overall population, and in subgroups stratified by the absence or presence of renal dysfunction according to eGFR (eGFR ≥ 60 ml/min/1.73 m^2 versus eGFR < 60 ml/min/1.73 m^2, respectively), or by diuretics use (yes versus no). In addition, multivariate analyses were utilized to model the

likelihood of having hypertension or diabetes by sUA levels in the overall population, with ORs calculated for an increase of 1 mg/dl of sUA. The sUA cut-off value at which the likelihood of having hypertension or diabetes was increased was chosen to maximize the Youden index.

3. Results

3.1. Patient demographics and baseline characteristics

Demographic and clinical characteristics of the 7531 included patients are listed in Table 1, overall and by diuretics use and eGFR. The mean age of participants was 63.2 years (standard deviation [SD]: 9.0) and 51.7% were women. The mean concentration of sUA was 5.2 mg/dl (SD: 1.4), with 26.6% of patients having sUA concentrations above 6 mg/dl. In terms of CV disease risk factor distribution, the proportion of patients with one, two, three, four or five major risk factors was 21.5%, 31.9%, 27.3%, 15.0% and 4.3%, respectively. Overall, 23.6% of patients were classified as being at high or very high 10-year risk of CV death using the SCORE-HDL algorithm; the proportion was 41.0% when using the SCORE algorithm.

A total of 2214 individuals (29.4%) had an eGFR below 60 ml/min/1.73 m^2 and 2356 participants (31.3%) were receiving diuretics treatment. The proportion of individuals at high or very high 10-year risk of CV death was greater in patients using diuretics than in patients not using diuretics (Table 1).

The countries with the highest proportions of study patients with high or very high risk of CV death were Austria, Germany, Norway, Sweden and the UK, both when using SCORE-HDL (33.4%, 40.9%, 39.0%, 41.9% and 36.1%, respectively) and when using SCORE (44.2%, 59.5%, 52.8%, 58.7% and 54.2%, respectively). The countries with the lowest proportions of study patients with high or very high risk of

CV death when using SCORE-HDL were Belgium, France and Spain (4.1%, 6.1%, 6.2%, respectively), and when using SCORE were Greece, Russia and Spain (27.1%, 29.3% and 29.7%, respectively).

3.2. Relationship between sUA levels and risk of cardiovascular death

Mean serum sUA levels increased with increasing SCORE-HDL risk category in the overall study population, as well as in the four subgroups stratified by diuretics use or by renal function according to eGFR (all $P < 0.0001$) (Fig. 1). Similar results were obtained when using SCORE (Fig. 2).

The following factors were significantly related to SCORE-HDL and SCORE in the univariate analysis and were adjusted for in the multivariate ordinal logistic regression analyses for SCORE-HDL and SCORE: study country; BMI; number of CV risk factors; number of comorbidities (except for SCORE-HDL in the subgroup using diuretics, for which no significant relationship was observed in the univariate analysis); use of lipid lowering drugs; use of antihypertensive drugs (except for the subgroup of patients using diuretics, who were all using antihypertensive drugs); and use of antidiabetic drugs.

Multivariate analyses using ordinal logistic regression (SCORE-HDL or SCORE category: low; intermediate; high; or very high) showed significant associations between increasing mean sUA levels and increasing SCORE-HDL or SCORE risk category: using SCORE-HDL, the odds ratio (OR) (95% CI) was 1.39 (1.34–1.44) in the overall population, 1.32 (1.24–1.40) in patients using diuretics, 1.46 (1.39–1.53) in those not using diuretics, 1.30 (1.22–1.38) in patients with an eGFR below 60 ml/min/1.73 m^2, and 1.44 (1.38–1.51) in those with an eGFR of 60 ml/min/1.73 m^2 and above (all $P < 0.0001$) (Table 2). Using SCORE, the

corresponding values were 1.29 (1.25–1.33), 1.22 (1.15–1.28), 1.33 (1.28–1.39), 1.23 (1.16–1.30), and 1.27 (1.22–1.33) (all $P < 0.0001$) (Table S1).

Other variables identified as having a significant, positive association with CV death risk in the overall population were increasing number of CV risk factors, increasing number of comorbidities, and use of lipid-lowering and antihypertensive drugs (likely to be proxies of CV risk factors/comorbidities, i.e. confounding by indication), but not use of antidiabetic drugs (Table 2 [SCORE-HDL], Table S1 [SCORE]). Study country was a factor independently and significantly associated with CV death risk in the current model (results not shown). Tying in with the "obesity paradox" in CV disease, BMI had a significant, negative (i.e. protective) effect on CV death risk.

3.3.   Relationship between sUA levels, hypertension and diabetes

sUA levels were significantly higher in patients with hypertension (mean: 5.4; SD: 1.4) than in those without hypertension (mean: 4.8; SD: 1.2) ($P < 0.0001$), and in patients with diabetes (mean: 5.4; SD: 1.5) than without diabetes (mean: 5.2; SD: 1.4) ($P < 0.0001$). On multivariate analysis, a significant association was observed between sUA levels and risk of hypertension (OR: 1.36; 95% CI: 1.30–1.43; $P < 0.0001$), but not between sUA levels and risk of diabetes (OR: 0.98; 95% CI: 0.94–1.03; $P = 0.4025$). The sUA cut-off value that determined an increased likelihood of having hypertension was 5.3 mg/dl (sensitivity: 49%; specificity: 69%; area under the receiver operating characteristic curve: 0.6232).

4. Discussion

This *post hoc* analysis was designed to determine the association between sUA levels and estimated risk of CV death in patients with at least one CV risk factor but with no clinical CV disease. Results of the analysis demonstrate a significant, positive association between sUA levels and high scores for risk of 10-year CV death. The association remained significant when adjusting for potential confounders (study country and any factors that were identified as being significantly associated with increased risk of CV death in the univariate analysis). Our results suggest a key role for sUA in CV disease. Causality cannot be inferred from this cross-sectional study. However, if verified, then monitoring sUA levels could in future be considered as part of primary CV disease prevention in at-risk patients.

The association between sUA levels and increased risk score for CV death was found in individuals with renal dysfunction (assessed via eGFR) and in those using diuretics, but also in patients without renal dysfunction and in those not taking diuretic drugs. These observations support a primary role for sUA production rather than sUA excretion in CV disease risk and have important implications regarding the mechanism of sUA involvement in CV disease.

The 2016 European guidelines recommend using the SCORE algorithm to estimate risk of CV death in apparently healthy adults without CV disease. The algorithm estimates the 10-year risk of CV death and has been calibrated for low-risk and high-risk regions based on country-specific mortality rates [24, 25]. The pattern of risk factors, control of risk factors and SCORE risk in our study population are similar to the distributions described for similar 'real world' populations in the SCORE algorithm publications [24, 25]. The original SCORE algorithm was recently updated to include HDL-C as well as total cholesterol, systolic blood pressure, age,

sex and smoking status [26, 27]. Use of the SCORE-HDL algorithm tends to result in reclassification from higher to lower risk categories when compared with the SCORE algorithm [26]. In the current study, 41.1% of patients were classified as being at high 10-year risk of CV death based on SCORE, compared with 23.6% when using SCORE-HDL. The significant association observed between sUA and increased risk of CV death in the current analysis was found both when using SCORE and when using SCORE-HDL to calculate risk. To explore whether inclusion of sUA levels would add additional, relevant information to existing CV disease risk scores, a cohort study **(either secondary data from an existing study or a new cohort study)** is needed to model the risk of CV events, with SCORE (or SCORE-HDL) and sUA as variables in the model. **Furthermore, future risk models need not be restricted just to using existing CV disease risk scores as variables; should sUA be seen to be an independent predictor, a model updating process should come into place (for example, it cannot be ruled out that sUA replaces one of the existing factors).**

More than a quarter (26.6%) of adults in EURIKA had sUA concentrations above 6 mg/dl. This is only slightly lower than the prevalence in the USA, which was found to be 32.8% in a study based on data from the NHANES [28]. In contrast, a population-based study conducted in Italy observed a much lower prevalence for sUA concentrations above 6 mg/dl, at 8.5% and 11.9% in 2005 and 2009, respectively [29]. Reference ranges for sUA values tend to be based on levels measured in the general population, but a causal role of sUA in CV disease suggests that aiming for lower than average population values may be more appropriate [30]. In the current study, the mean concentration of sUA was 5.2 mg/dl, which is similar to the mean of 5.5 mg/dl observed in the NHANES studies [13, 28]. Mean sUA levels were significantly higher in patients with hypertension than in those without hypertension. Levels of 5.3 mg/dl

or above determined an increased likelihood of having hypertension in the current analysis, supporting the suggestion that the definition of the normal range of sUA levels may need to be revised [30].

Strengths of EURIKA include the use of standardized procedures to collect data and of a central laboratory for blood analyses. A limitation of the current analysis is that EURIKA included only a single measurement of sUA levels. Furthermore, the cross-sectional design of EURIKA means that the study does not provide insight into the longitudinal association between sUA levels and the development of CV disease. The presence of gout and use of gout-controller medications were not captured in EURIKA, and any associations of gout and treatment with CV disease risk could thus not be analyzed. Results were not analyzed by sex. A potential limitation of the current analysis is that both SCORE and SCORE-HDL are recommended for use in individuals aged 40–65 years, whereas an important proportion of the current study population will have been older than 65 years. Of note, for SCORE, the age is multiplied by a unique coefficient, whatever the age. However, for SCORE-HDL, the same coefficient as for 65-year-olds was applied to individuals older than 65 years, which will probably have resulted in an underestimation rather than an overestimation of the association between sUA levels and CV disease risk in the older patient group. Although it is unlikely that the association between sUA levels and SCORE or SCORE-HDL risk category in this population with no clinical CV disease could be explained entirely by an association of sUA levels with one of the variables included in SCORE or SCORE-HDL, this possibility cannot be ruled out entirely. Finally, the possibility that residual confounding factors may explain the association between sUA and SCORE is not excluded.

In conclusion, results of this analysis demonstrate that sUA levels are significantly, positively associated with a score for 10-year risk of CV death in patients with at least one CV risk factor but with no clinical CV disease. Prospective cohort studies are needed to establish causality and model the observed risk of CV events, with SCORE-HDL (and/or SCORE) and sUA levels as variables, to explore whether the inclusion of sUA levels would add additional, relevant information to existing CV disease risk scores.

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Table 1

Demographic and clinical characteristics of patients in EURIKA with sUA data, by diuretics use and eGFR.

	Overall (*N* = 7531)	Using diuretics (*n* = 2356)	Not using diuretics (*n* = 5175)	eGFR < 60 ml/min/1.73m² (*n* = 2214[*])
Age, years	63.2 (9.0)	65.4 (9.0)	62.1 (8.7)	66.6 (9.4)
Women, *n* (%)	3897 (51.7)	1289 (54.7)	2608 (50.4)	1329 (60.0)
BMI, kg/m²	28.9 (5.4)	30.2 (5.7)	28.4 (5.2)	29.1 (5.5)
Hypertension, *n* (%)	5466 (72.6)	2356 (100.0)	3110 (60.1)	1757 (79.4)
Dyslipidaemia, *n* (%)	4360 (57.9)	1417 (60.1)	2943 (56.9)	1359 (61.4)
Type 2 diabetes, *n* (%)	2016 (26.8)	756 (32.1)	1260 (24.3)	546 (24.7)
Obesity, *n* (%)	3273 (43.5)	1257 (53.4)	2016 (39.0)	987 (44.6)
Current or former smokers, *n* (%)	3601 (47.8)	979 (41.6)	2622 (50.7)	938 (42.4)
sUA, mg/dl	5.2 (1.4)	5.7 (1.5)	5.0 (1.3)	5.6 (1.5)

≤ 6 mg/dl, *n* (%)	5524 (73.4)	1443 (61.2)	4081 (78.9)	1461 (66.0)
> 6 mg/dl, *n* (%)	2007 (26.6)	913 (38.8)	1094 (21.1)	753 (34.0)
SCORE-HDL, %	3.6 (3.2)	4.0 (3.3)	3.5 (3.1)	3.7 (3.0)
< 1%, *n* (%)	1137 (15.3)	229 (9.8)	908 (17.8)	293 (13.4)
1 to < 5%, *n* (%)	4528 (61.0)	1469 (63.0)	3059 (60.1)	1366 (62.4)
≥ 5% to < 10%, *n* (%)	1427 (19.2)	501 (21.5)	926 (18.2)	448 (20.5)
≥ 10%, *n* (%)	328 (4.4)	131 (5.6)	197 (3.9)	81 (3.7)
Unknown, *n* (%)	111 (1.5)	26 (1.1)	85 (1.6)	26 (1.2)
SCORE, %	6.0 (6.3)	7.0 (6.8)	5.5 (6.0)	7.1 (7.0)
< 1%, *n* (%)	868 (11.7)	159 (6.8)	709 (13.9)	189 (8.6)
1% to < 5%, *n* (%)	3507 (47.3)	1023 (43.9)	2484 (48.8)	914 (41.7)
≥ 5% to < 10%, *n* (%)	1790 (24.1)	638 (27.4)	1152 (22.6)	593 (27.1)
≥ 10%, *n* (%)	1257 (16.9)	510 (21.9)	747 (14.7)	494 (22.6)
Unknown, *n* (%)	109 (1.4)	26 (1.1)	83 (1.6)	24 (1.1)

BMI: body mass index, eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, SCORE:

Evaluation, SD: standard deviation, sUA: serum uric acid.

[*]Data on eGFR missing for eight patients.

Data are mean (SD) unless otherwise stated.

Table 2

Multivariate ordinal logistic regression analysis to model the association of sUA and other patient variables w

population and stratified by diuretics use and eGFR.

Variable[*]	Overall (N = 7531)		Patients using diuretics (n = 2356)		Patients not using diuretics (n = 5175)		eGFR < 60 (n =
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)
sUA level	1.39 (1.34–1.44)	**< 0.0001**	1.32 (1.24–1.40)	**< 0.0001**	1.46 (1.39–1.53)	**< 0.0001**	1.30 (1.22–1.38
BMI, kg/m^2	0.96 (0.95–0.97)	**< 0.0001**	0.95 (0.94–0.97)	**< 0.0001**	0.96 (0.95–0.97)	**< 0.0001**	0.97 (0.95–0.99
Number of CV risk factors		**< 0.0001**		**< 0.0001**		**< 0.0001**	
1	1.00 (–)		1.00 (–)		1.00 (–)		1.00 (–)
2	1.53 (1.33–1.76)		1.73 (1.26–2.37)		1.45 (1.24–1.69)		1.42 (1.09–1.85
3	2.19		2.45		2.10		2.07

	Col1	p	Col2	p	Col3	p	Col4
	(1.86–2.59)		(1.74–3.44)		(1.74–2.54)		(1.52–2.83
4	2.47		2.79		2.44		2.15
	(2.01–3.05)		(1.88–4.15)		(1.89–3.16)		(1.44–3.22
5	3.41		4.96		2.89		3.90
	(2.50–4.65)		(2.94–8.35)		(1.92–4.34)		(2.23–6.83
Number of comorbidities		0.0074		–		0.0011	
0	1.00		na[†]		1.00		1.00
	(–)				(–)		(–)
1	1.07		na[†]		1.14		1.08
	(0.96–1.19)				(1.01–1.29)		(0.88–1.33
2	0.97		na[†]		1.04		1.02
	(0.83–1.13)				(0.86–1.26)		(0.77–1.35
3	1.29		na[†]		1.29		1.47
	(1.01–1.65)				(0.92–1.82)		(0.98–2.21
≥ 4	1.77		na[†]		2.91		1.22
	(1.22–2.55)				(1.67–5.08)		(0.69–2.15
Lipid-lowering drug[‡]	0.82	0.0002	0.85	0.0958	0.80	0.0008	0.93
	(0.73–0.91)		(0.69–1.03)		(0.71–0.91)		(0.75–1.14

Antihypertensive drug[‡]	1.27	**< 0.0001**	na[§]	–	1.24	**0.0008**	1.59
	(1.14–1.42)				(1.09–1.41)		(1.26–2.01
Antidiabetic drug[‡]	1.07	0.3255	0.96	0.7375	1.10	0.2325	1.27
	(0.94–1.22)		(0.77–1.21)		(0.94–1.29)		(0.99–1.64

BMI: body mass index, CI: confidence interval, CV: cardiovascular, eGFR: estimated glomerular filtration rate, na: not assessed, C

COronary Risk Evaluation algorithm including high-density lipoprotein cholesterol, sUA: serum uric acid.

[*]Each variable was adjusted for all other variables in the Table, and for study country as a potential confounder.

[†]Not significantly related to SCORE-HDL in the univariate analysis.

[‡]At least one, versus no.

[§]All patients were using antihypertensive drugs.

Figure legends

Fig. 1. Mean serum sUA levels according to SCORE-HDL risk category in a) the overall study population, b) patients not using diuretics, c) patients using diuretics, d) patients with eGFR $\geq$ 60 ml/min/1.73 m^2 and e) patients with eGFR < 60 ml/min/1.73 m^2. Vertical bars denote standard deviations. *P* values were calculated using **analysis of variance (ANOVA)**.

eGFR: estimated glomerular filtration rate, SCORE-HDL: Systematic COronary Risk Evaluation algorithm including high-density lipoprotein cholesterol, sUA: serum uric acid.

Fig. 2. Mean serum sUA levels according to SCORE risk category in a) the overall study population, b) patients using diuretics, c) patients not using diuretics, d) patients with eGFR < 60 ml/min/1.73 m^2 and e) patients with eGFR $\geq$ 60 ml/min/1.73 m^2. Vertical bars denote standard deviations. *P* values were calculated using **analysis of variance (ANOVA)**.

eGFR: estimated glomerular filtration rate, SCORE: Systematic COronary Risk Evaluation algorithm, sUA: serum uric acid.

Table S1. Multivariate analysis to model the association of sUA and other patient variables with SCORE in t

by diuretics use and eGFR.

Variables	Overall (N = 7531)		Patients using diuretics (n = 2356)		Patients not using diuretics (n = 5175)		eGFR < 60 (n =
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)
sUA level	1.29 (1.25–1.33)	**< 0.0001**	1.22 (1.15–1.28)	**< 0.0001**	1.33 (1.28–1.39)	**< 0.0001**	1.23 (1.16–1.30
BMI, kg/m^2	0.93 (0.92–0.94)	**< 0.0001**	0.93 (0.92–0.94)	**< 0.0001**	0.93 (0.92–0.94)	**< 0.0001**	0.94 (0.92–0.95
Number of CV risk factors		**< 0.0001**		0.3014		**0.0001**	
1	1.00 (–)		1.00 (–)		1.00 (–)		1.00 (–)
2	1.19 (1.04–1.35)		1.03 (0.78–1.37)		1.21 (1.04–1.39)		1.18 (0.93–1.50
3	1.47		1.20		1.53		1.25

	HR	p	HR	p	HR	p	HR
	(1.26–1.71)		(0.88–1.63)		(1.28–1.83)		(0.95–1.66
4	1.31		1.06		1.41		1.17
	(1.08-1.59)		(0.74–1.52)		(1.11–1.79)		(0.81–1.67
5	1.60		1.45		1.67		1.60
	(1.20–2.14)		(0.89–2.34)		(1.14–2.45)		(0.96–2.67
Number of comorbidities		**< 0.0001**		**0.0259**		**< 0.0001**	
0	1.00		1.00		1.00		1.00
	(–)		(–)		(–)		(–)
1	1.22		1.19		1.25		1.18
	(1.11–1.35)		(0.99–1.42)		(1.11–1.40)		(0.98–1.42
2	1.21		1.00		1.35		1.34
	(1.05–1.40)		(0.79–1.26)		(1.13–1.62)		(1.05–1.73
3	1.44		1.45		1.34		1.51
	(1.15–1.81)		(1.04–2.03)		(0.97–1.85)		(1.04–2.20
≥ 4	1.96		1.73		1.99		1.54
	(1.38–2.77)		(1.08–2.79)		(1.17–3.37)		(0.91–2.62
Lipid-lowering drug[†]	0.88	**0.0113**	0.94	0.4831	0.85	**0.0102**	0.93
	(0.80–0.97)		(0.78–1.13)		(0.76–0.96)		(0.77–1.12

Antihypertensive drug[†]	1.90 (1.71–2.11)	**< 0.0001**	na[‡]	–	1.70 (1.51-1.91)	**< 0.0001**	2.32 (1.87–2.87
Antidiabetic drug[†]	0.99 (0.88–1.12)	0.9024	0.84 (0.68–1.04)	0.1024	1.08 (0.93–1.25)	0.3425	1.14 (0.91–1.44

BMI: body mass index, CI: confidence interval, CV: cardiovascular, eGFR: estimated glomerular filtration rate, na: not assessed, C

COronary Risk Evaluation algorithm, sUA: serum uric acid.

[*]Each variable was adjusted for all other variables in the Table, and for study country as a potential confounder.

[†]At least one, versus no.

[‡]All patients were using antihypertensive drugs.