

## Identification of the Uric Acid Thresholds Predicting an Increased Total and Cardiovascular Mortality Over 20 Years

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**Abstract**—Serum uric acid (SUA) levels discriminating across the different strata of cardiovascular risk is still unknown. By utilizing a large population-based database, we assessed the threshold of SUA that increases the risk of total mortality and cardiovascular mortality (CVM). The URRAH study (Uric Acid Right for Heart Health) is a multicentre retrospective, observational study, which collected data from several large population-based longitudinal studies in Italy and subjects recruited in the hypertension clinics of the Italian Society of Hypertension. Total mortality was defined as mortality for any cause, CVM as death due to fatal myocardial infarction, stroke, sudden cardiac death, or heart failure. A total of 22 714 subjects were included in the analysis. Multivariate Cox regression analyses identified an independent association between SUA and total mortality (hazard ratio, 1.53 [95% CI, 1.21–1.93]) or CVM (hazard ratio, 2.08 [95% CI, 1.146–2.97];  $P<0.001$ ). Cutoff values of SUA able to discriminate total mortality (4.7 mg/dL [95% CI, 4.3–5.1 mg/dL]) and CVM status (5.6 mg/dL [95% CI, 4.99–6.21 mg/dL]) were identified. The information on SUA levels provided a significant net reclassification improvement of 0.26 and of 0.27 over the Heart Score risk chart for total mortality and CVM, respectively ( $P<0.001$ ). Sex-specific cutoff values for total mortality and CVM were also identified and validated. In conclusion, SUA levels increasing the risk of total mortality and CVM are significantly lower than those used for the definition of hyperuricemia in clinical practice. Our data provide evidence of a cardiovascular SUA threshold that might contribute in clinical practice to improve identification of patients at higher risk of CVM. (*Hypertension*. 2020;**75**:302–308. DOI: 10.1161/HYPERTENSIONAHA.119.13643.) • [Online Data Supplement](#)

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Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide.<sup>1</sup> Despite the development of risk prediction scores that enable identification of subjects at greater risk of future events, CVD risk assessment based on common cardiovascular risk factors still lacks precision.<sup>2</sup> To improve CVD risk prediction, and thereby enhance patient care, novel risk factors and more accurate CVD risk profiling may be necessary.

Several observational studies have documented robust and strong associations between elevated levels of serum uric acid (SUA) and greater risk of CVD, including its clinical and subclinical manifestations.<sup>3,4</sup> These associations are independent of the presence of gout and remain highly significant even after adjustment for other common CVD risk factors, including renal function. Based on this large body of evidence, the novel European guidelines on the management of arterial hypertension have introduced SUA among the routine workup for evaluation of the CVD risk of hypertensive patients.<sup>5</sup> As epidemiological data suggest a progressive worldwide increase of circulating levels of SUA,<sup>6</sup> definition of SUA and of the risk associated with its circulating levels might become one of the most important routine clinical investigations to be performed in the assessment of the individual CVD risk.

Despite these important considerations, defining the CVD risk associated with SUA levels remains complicated. While several observational studies have suggested a continuous relationship between SUA levels and risk of all-cause and cardiovascular mortality (CVM),<sup>3,4</sup> the identification of an SUA threshold that is more clearly associated with the risk of both outcomes might support clinician in routine medical decisions and facilitate inclusion of SUA in the risk algorithm scores commonly used in clinical practice. Furthermore, some preliminary data suggest that the so-called cardiovascular threshold limit may substantially differ from that identified as a cutoff able to trigger the acute gout attack.<sup>7-9</sup> With this scope, the Working Group on SUA and cardiovascular risk of the Italian Society of Hypertension has designed the URRAH project (Uric Acid Right for Heart Health).<sup>10</sup> The primary objective of this project was to define the level of uricemia above which the independent risk of CVD may increase in a significant manner in a general population. In this article, we report the analyses aimed to identify the threshold of SUA associated to a significant increase in all-cause mortality and CVM.

## Methods

The URRAH project was performed according to the Declaration of Helsinki for Human Research. The processing of the patients' personal data collected complies with the European Directive on the privacy of data. All data to be collected, stored, and processed are anonymized and available from the corresponding author on request.

## Population

The URRAH project is a multicentre retrospective, observational cohort study, which involves data from several cohorts recruited within the Italian centers of hypertension and distributed in almost all the Italian regions. White patients attending hypertension clinics, as well as subjects recruited in prospective observational cohort studies with a follow-up period of at least 20 years up to July 31, 2017, were included in the study. More details are available in the [online-only Data Supplement](#). Full details of the URRAH project have been published previously.<sup>10</sup>

## Data Collection

SUA levels were collected from all participants, together with information on cardiovascular risk factors, where available. Anthropometric measures and anamnestic information were also collected. Systolic and diastolic blood pressure was measured twice, in a quiet room, after 5 minutes resting and with the participant in sitting position. The second measure was used for all analyses. Renal function was evaluated through estimation of the glomerular filtration rate, according to the Chronic Kidney Disease Epidemiology Collaboration equation.<sup>11</sup>

Chronic kidney disease was defined for estimated glomerular filtration rate values <60 mL/min. More details are available in the [online-only Data Supplement](#).

## Outcomes

The following hard end points were evaluated at the end of the follow-up: total mortality, fatal events due to acute myocardial infarction, heart failure, or stroke. Information about death was obtained from hospital records or death certificates. Mortality from major CVDs (*International Classification of Diseases, Tenth Revision*) included deaths from diseases of heart, essential hypertension, hypertensive renal disease, and cerebrovascular diseases (Table S1 in the [online-only Data Supplement](#)).

## Statistical Analyses

An extended version of the statistical methods is provided in the [online-only Data Supplement](#).

Normally distributed continuous variables were presented as mean±SD and variables not following normal distribution as median (interquartile range). Differences in baseline characteristics between individuals with and without major adverse events at the follow-up were evaluated by independent samples *t* test or Mann-Whitney *U* test for continuous variables and  $\chi^2$  test for nominal variables. Cox proportional-hazards models were used to examine the association between baseline SUA and the 2 end points. Data were censored at the time of the last visit or, for patients lost during follow-up, at the last date they were known to be alive. Associations are presented as hazard ratio (HR) with 95% CIs. Subsequently, data were analyzed by multivariable Cox regression models for both main end points that included all available clinical variables with biological plausibility. To investigate the potential nonlinear association between SUA and survival outcomes, restricted cubic splines with 3 knots fixed at the 10th, 50th, and 90th percentile of SUA were used and produced a smooth curve versus  $\log_{\text{HR}}$  in the y axis (dose-response curves).<sup>12</sup> The prognostic value of SUA was analyzed by a clinically relevant cutoff. To this purpose, the survival receiver operating characteristic curve was implemented using Kaplan-Meier estimates and identified a cutoff point that optimized the combination of sensitivity (true-positive) and 1-specificity (false-positive). Subsequently, the prognostic performance of SUA, based on the novel identified cutoff point, was assessed by calculating its capacity to provide additional information on all-cause and cardiovascular death compared with the well-validated and calibrated estimate of total cardiovascular risk Heart Score by means of (1) multivariable Cox proportional-hazards models that also included the Heart Score, (2) the Harrel C statistics, and (3) the reclassification capacity of the new thresholds of SUA against the Heart Score, as estimated from the continuous Net Reclassification Index and the integrated discrimination improvement. Given the known difference in SUA levels in women and men, sex-specific cutoff points were identified, and their prognostic value for all-cause mortality and CVM was tested following the same approaches described for the entire population. Statistical calculations were performed by STATA package, version 11.1 (StataCorp, College Station, TX). We deemed statistical significance at  $\alpha=0.05$ .

## Results

The baseline characteristics of the studied population restricted to the sample with available follow-up data are reported in Table 1. On average, the population was overweight, with >50% of subject with a diagnosis of arterial

**Table 1. Baseline Characteristics of the Population With Available Follow-Up Data (n=22 714)**

Characteristics	Mean (SD) or Median (IQR) or n (%)
<b>Clinical variables</b>	
Age, y	57 (15)
Sex, male (%)	11 136 (49.03)
Smokers, n (%)	5542 (25.24)
BMI, kg/m <sup>2</sup>	27 (4.3)
Waist circumference, cm*	90 (82–99)
Systolic blood pressure, mmHg	143 (24)
Diastolic blood pressure, mmHg	85 (13)
Uric acid, mg/dL*	4.9 (4–5.9)
Total cholesterol, mg/dL	212 (40)
HDL cholesterol, mg/dL	55 (19)
Triglycerides, mg/dL*	108 (78–154)
Gout, n (%)	137 (1.08)
Diabetes mellitus, n (%)	2382 (10.52)
Chronic kidney disease, n (%)	3627 (16.70)
eGFR (mL/min per 1.73 m <sup>2</sup> )	83.3 (66.4–102.4)
Arterial hypertension, n (%)	14 392 (63.51)
Hemoglobin, g/dL*	14 (14–15)
Hematocrit, %*	43 (40–45)
<b>Medications</b>	
Allopurinol, n (%)	192 (1.40)
ACE inhibitors, n (%)	2558 (14.88)
Angiotensin receptor blockers, n (%)	1571 (11.03)
Calcium channel blockers, n (%)	1945 (9.46)
β-Blockers, n (%)	1927 (9.44)
Diuretics, n (%)	3442 (16.79)
Hydrochlorothiazide	541 (7.93)
Indapamide	77 (1.13)
Chlortalidone	196 (1.95)
Loop diuretics	492 (4.10)
Statins, n (%)	1123 (5.21)

ACE indicates angiotensin-converting enzyme; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; and IQR, interquartile range.

\*Non-normally distributed variables.

hypertension, 10% of patients with diagnosis of diabetes mellitus, and 17% of patients with chronic kidney disease. The level of SUA (4.9 mg/dL) probably accounts for the relatively low number of subjects with a diagnosis of gout ( $\approx$ 1% of the entire population). The most commonly prescribed medications were diuretics, followed by ACE (angiotensin-converting enzyme) inhibitors/angiotensin receptor blockers and statins. Table S2 in the [online-only Data Supplement](#) presents the same clinical characteristics with the population stratified by sex.

During a median follow-up time of 134 months (interquartile range, 74–164), a total of 3279 deaths were recorded, of which 1571 were due to cardiovascular causes.

By dose-response curve analysis, a linear association of SUA levels with all-cause mortality and CVM was evinced using smoothed restricted cubic spline plots ( $P=0.954$  and  $P=0.813$ , respectively; Figure S1A and S1B, respectively).

At the univariate Cox model, SUA was associated with an increased risk of all-cause mortality (HR, 1.24 per 1 mg/dL increase of SUA [95% CI, 1.21–1.27];  $P<0.001$ ) and CVM (HR, 1.28 per 1 mg/dL increase of SUA [95% CI, 1.24–1.33];  $P<0.001$ ). These associations remained highly significant even in models adjusted for age, sex, smoking, diabetes mellitus, hypertension, total cholesterol, alcohol use, creatinine and chronic kidney disease, hematocrit, and use of diuretics (for all-cause mortality: HR, 1.53 per 1 mg/dL increase of SUA [95% CI, 1.21–1.93];  $P<0.001$ ; for CVM: HR, 2.08 per 1 mg/dL increase of SUA [95% CI, 1.46–2.97];  $P<0.001$ ). Three statistically significant interaction terms were included in these models: SUA $\times$ age (all-cause mortality: HR, 0.996 [95% CI, 0.993–0.999];  $P=0.007$ ; CVM: HR, 0.992 [95% CI, 0.987–0.997];  $P=0.001$ ), SUA $\times$ diabetes mellitus (all-cause mortality: HR, 0.943 [95% CI, 0.883–1.01];  $P=0.079$ ; CVM: interaction term nonsignificant), and SUA $\times$ chronic kidney disease (all-cause mortality: HR, 1.07 [95% CI, 1.01–1.14];  $P=0.026$ ; CVM: interaction term nonsignificant).

### SUA Threshold for All-Cause Mortality

Survival receiver operating characteristic curve analysis demonstrated that the optimal cut point for SUA to discriminate all-cause mortality status was 4.7 mg/dL (95% CI, 4.30–5.10; Table 2). When the population was stratified for sex, the cutoff for SUA for all-cause mortality was 5.4 mg/dL (95% CI, 4.80–6.57) in men and 4.7 mg/dL (95% CI, 4.40–5.10) in women (Table S3 in the [online-only Data Supplement](#)).

SUA levels  $\geq$ 4.7 mg/dL were associated with an increased risk of all-cause mortality in the entire population (Figure 1A). Similar associations were observed in analyses stratified by sex (Figure S2). The predictive capacity of the new cutoffs on all-cause mortality remained significant after adjustment for the Heart Score in the entire population (HR, 1.51 [95% CI, 1.40–1.63];  $P<0.001$ ), as well as in women and men when considered separately (Table S4 in the [online-only Data Supplement](#)). Further adjustments for variables not included in the Heart Score, such as use of diuretics, alcohol consumption, and hematocrit, did not affect these results. Similarly, addition of the body mass index and estimated glomerular filtration rate to the Heart Score did not reduce the strength of the associations between SUA levels and risk of CVM in the whole population (HR, 1.4 [95% CI, 1.29–1.52];  $P<0.001$ ), as well as in women and men when considered separately (Table S5 in the [online-only Data Supplement](#)).

SUA levels  $\geq$ 4.7 or  $<$ 4.7 mg/dL incrementally predicted all-cause mortality over Heart Score (Harrell C, 0.747 versus 0.725;  $P<0.001$ ). The same information significantly improved the area under the curve (AUC) for all-cause mortality of the Heart Score alone (0.754 versus 0.735;  $P<0.001$ ; Figure 2A). The integrated discrimination improvement analysis showed that, overall, SUA provided additive discrimination value for

**Table 2. Results Obtained From Survival Receiver Operating Characteristic Curve Identifying the Best Threshold of Serum Uric Acid for All-Cause and CVD Mortality**

Outcomes	Cutoff Points, mg/dL	95% CI*	AUC	Sensitivity	Specificity
All-cause mortality	4.7	4.30–5.10	0.598	0.68	0.47
CVD mortality	5.6	4.99–6.21	0.605	0.47	0.69

AUC indicates area under the curve; and CVD, cardiovascular disease.  
 \*From 1000 replicates for bootstrap.

all-cause death on top of Heart Score ( $P<0.001$ ). Significant increments in the Harrell C and AUC, as well as additive discrimination compared with the Heart Score alone, were observed also using the sex-specific SUA thresholds with regard to all-cause mortality ( $P<0.01$  for all tests).

When the main analyses were repeated after excluding subjects with gout diagnosis or taking SUA-lowering drugs, results did not change.

Finally, the information on SUA levels  $\geq 4.7$  or  $< 4.7$  mg/dL correctly reclassified 33.5% of subjects with events over the Heart Score at a cost of false allocation of 7.74% nonevent patients to higher risk, providing a significant net reclassification improvement of 0.26 over the Heart Score ( $P<0.001$ ).

**SUA Threshold for CVM**

The optimal cut point for SUA to discriminate CVM status according to survival receiver operating characteristic curve analysis was 5.6 mg/dL (95% CI, 4.99–6.21) in the entire population (Table 2). In women, the cut point providing the better discrimination for CVM was 5.1 mg/dL (95% CI, 4.34–5.70), whereas in men, it was 5.6 mg/dL (95% CI, 5.30–5.78; Table S3 in the online-only Data Supplement).

As reported in Figure 1B, an increased risk of CVM was observed in subjects with SUA levels  $\geq 5.6$  mg/dL in the entire population, and highly significant associations were also observed when the female and male thresholds were used in the analyses stratified by sex (Figure S3). After adjustment for the Heart Score, the association between the new SUA cutoffs and CVM remained highly significant in the entire population (HR, 1.59 [95% CI, 1.43–1.76];  $P<0.001$ ), as well as in analyses stratified by sex (Table S4 in the online-only

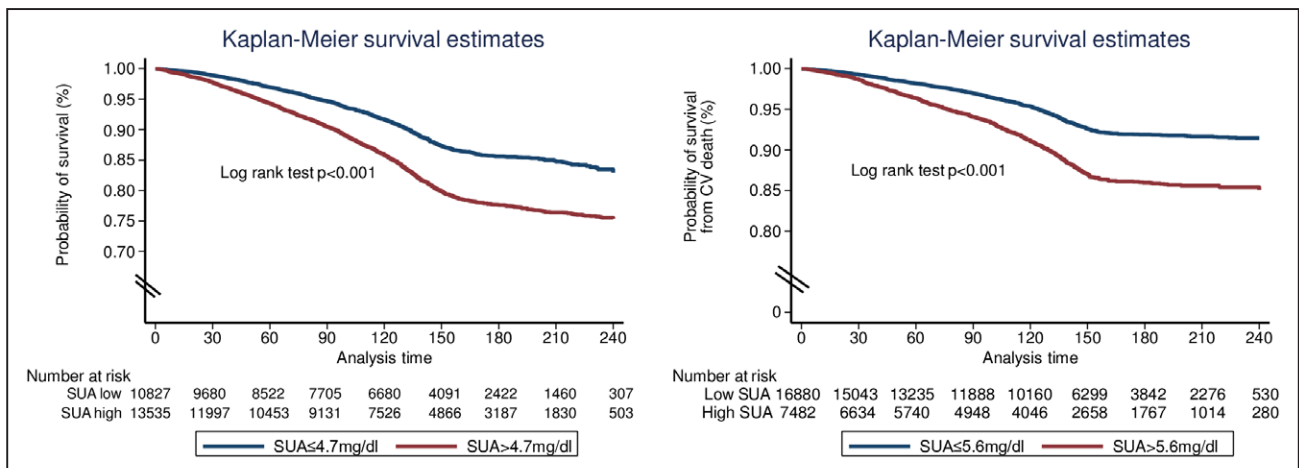
Data Supplement). Further adjustment for the use of diuretics, alcohol consumption, and hematocrit did not affect these results, while addition of the body mass index and estimated glomerular filtration rate to the Heart Score slightly attenuated the strength of the association in women only (Table S5 in the online-only Data Supplement). The information on levels of SUA  $\geq 5.6$  or  $< 5.6$  mg/dL incrementally predicted CVM over Heart Score (Harrell C, 0.780 versus 0.754;  $P<0.001$ ), leading also to a significant improvement of the AUC for CVM compared with the Heart Score alone (AUC, 0.773 versus 0.753;  $P<0.001$ ; Figure 2B). Overall, the information on SUA levels  $\geq 5.6$  or  $< 5.6$  mg/dL provided additive discrimination value for all-cause death on top of Heart Score ( $P<0.001$ ). Similarly, the use of the sex-specific thresholds for SUA thresholds led to significant improvements in the Harrell C, AUC, and integrated discrimination improvement compared with the Heart Score alone with regard to the risk of CVM ( $P<0.01$  for all tests).

Exclusion from the main analyses of subjects treated with history of gout or treated with SUA-lowering drugs did not change the results.

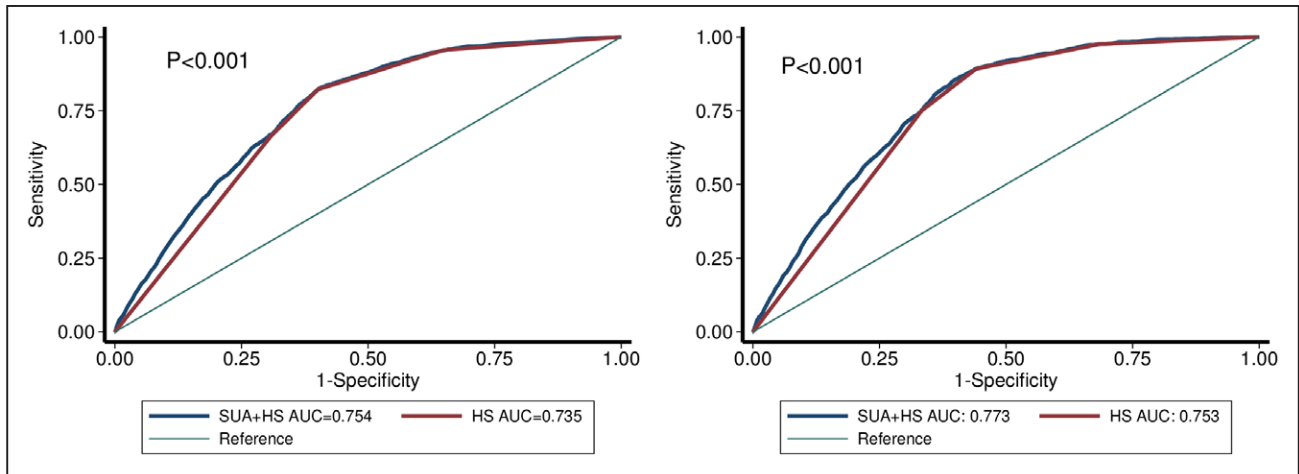
The information on SUA levels  $> 5.6$  or  $< 5.6$  mg/dL correctly reclassified 40.06% of subjects without events over the Heart Score at the cost of a false-negative association of 12.3%, providing a significant net reclassification improvement of 0.27 over the Heart Score ( $P<0.001$ ).

**Discussion**

Recent European guidelines have introduced the assessment of SUA levels among factors that might improve risk stratification in patients with arterial hypertension.<sup>5</sup> This important recognition denotes the interest around the role of SUA as an important predictor of cardiovascular death and reflects the large number of studies that reported cross-sectional or prospective associations between levels of SUA and mortality risk. However, it remains unclear how to interpret the information on SUA levels in the context of the subject’s overall all-cause and CVD risk. The present study confirmed that the information on SUA levels refines cardiovascular and all-cause mortality risk prediction models, also identifying novel cutoffs that might help discrimination of subjects at high or low mortality risk independently



**Figure 1.** Kaplan-Meier survival estimates according to the identified thresholds for a risk of all-cause mortality and cardiovascular mortality ( $P<0.001$  for all, log-rank test). **A**, all-cause mortality. **B**, cardiovascular mortality. Analysis time is expressed in months. SUA indicates serum uric acid.



**Figure 2.** Improvement of the AUC after the addition of serum uric acid (SUA) to the Heart Score. **A**, The addition of the information on the level of SUA  $\geq 4.7$  or  $< 4.7$  mg/dL significantly improved AUC for all-cause mortality compared with the AUC of the Heart Score alone ( $P < 0.001$ ). **B**, The addition of the information on the level of SUA  $\geq 5.6$  or  $< 5.6$  mg/dL significantly improved AUC for cardiovascular mortality compared with the AUC of the Heart Score alone ( $P < 0.001$ ). AUC indicates area under the curve; and HS, heart score.

from the individual burden of common CVD risk factors. Intriguingly, the levels of SUA associated with both all-cause mortality and CVM in our study are lower than those that have been commonly associated with an increased risk of gout,<sup>13</sup> suggesting that more aggressive application of urate-lowering strategies might be necessary to achieve more effective prevention of the mortality risk associated with SUA.

The role of SUA as an important predictor of all-cause mortality and CVM has been investigated in several prospective studies and meta-analyses. Some of these yielded conflicting results, likely because they analyzed data obtained from different populations or used the different (and probably not entirely justified) statistical adjustments to produce the final results.<sup>4</sup> Li et al provided the largest review of the evidence on this topic, summarizing evidence from observational studies, randomized controlled trials, and Mendelian randomization studies. The authors concluded that despite convincing evidence of a clear role of SUA level only exists for gout and nephrolithiasis, the association of coronary heart disease mortality with high SUA levels is highly suggestive.<sup>14</sup> Our findings provide an important contribution to the debate as we document that SUA levels are associated with all-cause mortality and CVM, independently from other CVD risk factors or validated score risk algorithm.

The association of SUA with all-cause mortality and CVM was continuous. Therefore, summarizing the information related to SUA levels by identification of specific thresholds might represent an excessive simplification of its impact on the mortality risk. This might explain why the improvement of the AUC related to the Heart Score after the addition of the information on SUA levels above or below the new thresholds was somewhat limited. However, as observed for cholesterol<sup>15</sup> and blood pressure,<sup>16</sup> daily clinical practice often requires reference values to enable clearer and immediate interpretation of the results obtained from the assessment of cardiovascular risk factors and to better simplify the calculation of the overall CVD risk of each subject.

The results of all our analyses confirmed that the stratification of SUA levels based on the new cutoffs adds significant

information to the assessment of the cardiovascular and all-cause mortality risk, ultimately leading also to a significant improvement in the classification of that risk over the well-validated and guideline-recommended Heart Score. The ability of SUA levels to increase all indexes of prognostic accuracy for CVM has been investigated previously, reporting some conflicting results. Using a population of 1522 naive hypertensives with preserved renal function, Peticone et al<sup>17</sup> showed that the information on SUA levels increased the Harrell C index, net reclassification index, and integrated discrimination improvement for CVM when compared with the use of the Framingham Risk Score. Dutta et al<sup>18</sup> obtained similar results in an old group of patients derived from the Established Populations for Epidemiological Studies of the Elderly and the Third National Health and Nutritional Examination Survey. Tscharre et al<sup>19</sup> showed that in patients with acute coronary syndrome undergoing percutaneous coronary intervention, the prognostic accuracy of an established risk prediction model was significantly increased by adding the information on SUA levels. Finally, Reboldi et al<sup>20</sup> recently demonstrated that, in a multiethnic setting of patients referred to specialized hypertension centers, SUA was an independent predictor of cardiovascular events and significantly improved risk discrimination and reclassification over the baseline multivariable model. By contrast, SUA was not an independent predictor of CVM and did not add to risk assessment beyond traditional cardiovascular risk factors in a larger sample of the Third National Health and Nutritional Examination Survey population that, however, involved a small population of patients not entirely representative of the US population.<sup>21</sup> Conversely, our study included a larger sample size than previous reports and was the first to document the predictive ability of a specific threshold of SUA on cardiovascular and all-cause mortality.

Beyond the large sample size, the population included in our analyses has a number of strengths for the investigation of the additive value of SUA in predicting all-cause mortality and CVM. The long follow-up enabled the accumulation of a sufficient number of events for a robust and reliable analysis including hard end points. Participants were recruited in

longitudinal cohort studies or from outpatient clinics. Thus, they are likely to present clinical characteristics similar to those of the general population. This makes our results on the thresholds of SUA more immediately applicable to routine clinical practice. Also, data on a wide range of established and novel cardiovascular disease risk factors and potential confounders were measured, allowing the independent role of many parameters to be assessed.

Our report also has some limitations. The study design is retrospective, and, as such, the SUA threshold provided for all-cause mortality and CVM should be interpreted cautiously because the risk of selection bias is high and there might be unmeasured variables that could potentially influence the relationship between SUA levels and outcomes. This limitation is common, however, to many other reports analyzing the relationship between SUA and total mortality and CVM. The appreciation of the importance of the impact of SUA on the risk of cardiovascular disease and all-cause mortality is recent, as confirmed by the evidence that only the most recent European Society of Cardiology/European Society of Cardiology guidelines on the management of arterial hypertension have suggested the assessment of SUA levels to refine the cardiovascular risk stratification of the patients. This makes the availability of measures of SUA in prospective studies limited, precluding the opportunity to perform long-term prospective analyses on large datasets.

Also, dietary intake assessment was not implemented in our study, and thus, we had no information about the type of food consumed that may affect SUA level. Similarly, information on the menopausal age was not available, making it impossible to assess whether postmenopausal women have different cutoffs of uric acid associated with all-cause mortality and CVM than premenopausal women. Moreover, the levels of SUA were relatively low as it was the mortality risk according to the Heart Score. Therefore, our findings might underestimate the mortality risk in populations with higher levels of SUA or with greater Heart Score. The URRAH study was composed of a population of white ethnicity, which included a percentage of patients selected from Hypertension clinics, thus resulting in a heterogeneous population. Consequently, further studies are needed to confirm that the thresholds of SUA emerging from our analyses are valid also in general populations and in other ethnicities.

## Conclusions

Results from the present study confirm that SUA levels are linearly associated with an increased risk of all-cause mortality and CVM, independently from common cardiovascular risk factors. If confirmed by future prospective studies, our data will represent the first large evidence of a level of cardiovascular SUA that might contribute in clinical practice to improve risk discrimination and reclassification of subjects at greater risk of total and CVM.

## Perspectives

Our results identify, for the first time, SUA thresholds that might be easily interpreted by clinicians and included in risk prediction algorithms for all-cause mortality and CVM. Importantly, these thresholds are lower than those commonly

associated with an increased risk of gout, suggesting the adoption of more stringent normality ranges for SUA and of more aggressive treatment strategies to reduce the risk of all-cause mortality and CVM related to hyperuricemia.

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## Disclosures

None.

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## Novelty and Significance

### What Is New?

- In a large population cohort, the serum uric acid (SUA) prognostic cutoff values of 4.7 and of 5.6 mg/dL able to discriminate total and cardiovascular mortality status, respectively, were identified.
- Evidence of a level of cardiovascular SUA that might be used in clinical practice to identify subjects at greater risk of cardiovascular mortality.
- Novel SUA thresholds allow a significant net reclassification improvement over the Heart Score risk chart for total and cardiovascular mortality.

### What Is Relevant?

- The identified SUA thresholds might be interpreted by clinicians and included in risk prediction algorithms for all-cause and cardiovascular mortality.

- The proposed SUA thresholds, lower than those associated with an increased risk of gout, suggest the adoption of more stringent normality ranges for SUA to reduce the risk of all-cause and cardiovascular mortality.

### Summary

In a large population cohort, multivariate Cox regression analyses identified the presence of an independent association between SUA and total or cardiovascular mortality, independently of major confounders. Cutoff values of uric acid values able to discriminate total mortality (4.7 mg/dL) and cardiovascular mortality status (5.6 mg/dL) were identified. SUA level information provided a significant net reclassification improvement over the Heart Score risk chart for total mortality and cardiovascular mortality, respectively.