Original Article

Relationships between diuretic-related hyperuricemia and cardiovascular events: data from the URic acid Right for heArt Health study

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Objective: Although the relationship between hyperuricemia and cardiovascular events has been extensively examined, data on the role of diuretic-related hyperuricemia are still scanty. The present study was designed to collect information on the relationship between diuretic-related hyperuricemia and cardiovascular events.

Methods: The URic acid Right for heArt Health (URRAH) study is a nationwide, multicentre, observational cohort study involving data on individuals recruited from all the Italy territory under the patronage of the Italian Society of Hypertension with an average follow-up period of 122.3 ± 66.9 months. Patients were classified into four groups according to the diuretic use (yes vs. no) and serum uric acid (SUA) levels (higher vs. lower than the median value of 4.8 mg/dl). All-cause death, cardiovascular deaths and first cardiovascular event were considered as outcomes.

Results: Seventeen thousand, seven hundred and forty-seven individuals were included in the analysis. Mean age was 57.1 ± 15.2 years, men were 45.3% and SBP and DBP amounted to 144.1 ± 24.6 and 85.2 ± 13.2 mmHg. 17.2% of individuals take diuretics of whom 58% had SUA higher than median value. Patients with hyperuricemia without diuretic use served as reference group. In multivariate adjusted analysis (sex, age, SBP, BMI, glucose, total cholesterol, and glomerular filtration rate) individuals with hyperuricemia and diuretic use exhibit a similar risk for the three outcomes as compared with the reference group.

Conclusion: Our study showed that diuretic-related hyperuricemia carry a similar risk of cardiovascular events and all-cause mortality when compared with individuals that present hyperuricemia in absence of diuretic therapy.

Keywords: cardiovascular events, cardiovascular mortality, diuretic, uric acid

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BP, blood pressure; CCB, calcium channel blockers; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ESC/ESH, European Society of Cardiology/European Society of

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Hypertension; HCTZ, thiazide; ICD-10, *International Classification of Diseases Tenth Revision*; LLT, lipid-lowering therapy; SUA, serum uric acid; URRAH, URic acid Right for heArt Health

INTRODUCTION

Serum uric acid (SUA) has been identified as an independent predictor of not only all-cause and cardiovascular mortality but also of specific cardiovascular events, such as myocardial Infarction, stroke, and heart failure [1–7]. Furthermore, SUA has also been found to be related to the in-hospital mortality during acute coronary syndrome and heart failure [8,9], incident atrial fibrillation [10], and cardiac and vascular target organ damage [11]. Indeed, the latest European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines [12] introduced SUA among the factors that should be tested in order to stratify patient's cardiovascular risk. As SUA has been also associated with metabolic derangement [13,14], its role as a cause of cardiovascular disease or mere marker of metabolic disease is still debated [14,15]. This will remain an unanswered question until the publication of the results of the ongoing randomized clinical trials aimed at evaluating the role of hypouricemic agents on cardiovascular events and mortality [16–18]. SUA levels may be increased by overproduction (because of xanthine oxidase hyperactivity), increased intake or decreased excretion. The latter mechanism may be the result of an increased urate renal reabsorption associated with diuretic treatment (especially thiazides), which is quite common in hypertensive patients. To the best of our knowledge, whether diuretic-related hyperuricemia is associated with an adverse cardiovascular outcome is still unknown.

The aim of the present study was to assess the relationship between diuretic-induced hyperuricemia and cardiovascular events in the patients included in the database of the URc acid Right for heArt Health (URRAH) project, a nationwide, multicentre, observational cohort study involving data on individuals recruited on a regional community basis from all the territory of Italy under the patronage of the Italian Society of Hypertension.

METHODS

Study participants and follow-up

In this context, the Working Group on uric acid and cardiovascular risk of the Italian Society of Hypertension has designed the URRAH project. The protocol of this study has been described extensively in a previous publication [19]. Briefly, this is a multicenter retrospective, observational cohort study, which involved collection of data on outpatients (principally hypertensive patients) and individuals from general population with a mean follow-up period of 10 years up to 31 July 2017. Data from participant centers were collected and have been included into a general database. Data of the various cohorts included were provided by the Italian Centers of Hypertension, geographically distributed in almost all the Italian regions and recognized by the Italian Society of Hypertension (listed under Acknowledgements). Inclusion criteria were the availability of at least one SUA level determination and complete information about demographics, cardiovascular risk factors (history of hypertension, diabetes mellitus, smoking habit, overweight/obesity defined through BMI and waist circumference), BMI, previous cardiovascular events, cardiovascular drug therapies, blood pressure (BP) values and biochemical data (total and fractioned cholesterol, triglycerides, and renal function estimated using a standardized serum creatinine assay and the Chronic Kidney Disease Epidemiology Collaboration – CKD-EPI equation). Individuals were followed for a mean follow-up of 126.7 ± 63.4 months, during which the following hard endpoints were collected and coded by the *International Classification of Diseases, Tenth Revision – ICD-10*: all-cause death, first fatal or nonfatal myocardial infarction or stroke (first cardiovascular event), fatal myocardial infarction or stroke (cardiovascular death).

Statistical analysis

The median value (4.8 mg/dl) was used to separate normal from high SUA. This value was very close to that found to be the best cut-off for total and cardiovascular mortality in the same database (4.7 mg/dl) [4]. Data obtained in each individual were averaged, and individual data were summed and expressed as means and standard deviations (SD) or percentage. On the base of diuretic use (yes or no) and normal (<4.8 mg/dl) or high (≥ 4.8 mg/dl) SUA, four groups of individuals were created. The characteristics of groups were compared using the ANOVA for continuous variables and chi-square test for categorical ones. Post hoc Bonferroni correction was also used. Associations between each group and risk of outcome were examined using the Cox proportional hazard model. In all Cox analyses, the group with hyperuricemia and without diuretic therapy was taken as reference. Calculations were done unadjusted and adjusted for sex, age, SBP, BMI, blood glucose, total and HDL serum cholesterol, smoking, antihypertensive therapies [including angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) and calcium channel blockers (CCB) but excluding diuretics] and lipid lowering therapy (LLT)], and estimated glomerular filtration rate. A P value less than 0.05 was taken as statistically significant. Ethical approval has been obtained from Ethical Committee of the coordinating centre (Internal Medicine, University of Bologna, Italy).

RESULTS

Database characteristics

The mean values of the descriptive variables of the 17747 individuals included in the study are shown in Table 1. The mean age was 57.1 ± 15.2 years and the prevalence of male sex was 45.3%. Mean SBP and DBP were 144.2 ± 24.6 and 85.3 ± 13.2 mmHg, respectively. The average BMI was compatible with a slight overweight (26.6 ± 4.4 kg/m^2) and the mean SUA was 4.9 ± 1.4 mg/dl. During the follow-up, 2789 (15.7% of the enrolled individuals) all-cause deaths occurred, of which 611 (3.4% of the enrolled individuals, 21.9% of the total deaths) were for cardiovascular causes. A first cardiovascular event was observed in 1275 (7.2%)

TABLE 1. Mean values of the descriptive variables of the whole population

Number	17 747
Age (years)	57.1 ± 15.2
Males (%)	45.3
SBP (mmHg)	144.2 ± 24.6
DBP (mmHg)	85.3 ± 13.2
HR (bpm)	72.4 ± 12.6
BMI (kg/m^2)	26.6 ± 4.4
Glycemia (mg/dl)	98.6 ± 25.8
Total cholesterol (mg/dl)	214.1 ± 39.1
HDL cholesterol (mg/dl)	52.9 ± 15.0
Triglycerides (mg/dl)	127.9 ± 79.2
Creatinine (mg/dl)	0.92 ± 0.22
GFR (ml/min)	82.5 ± 27.3
Antihypertensive drugs (%)	53.1
ACE-I/ARB (%)	20.4
CCB (%)	8.3
Diuretic (%)	17.2
LLT (%)	3.6
Serum uric acid (mg/dl)	4.9 ± 1.4
All cause death (*n*, %)	2789, 15.7
First CV event (*n*, %)	1275, 7.2
CV death (*n*, %)	611, 3.4

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; CV, cardiovascular; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HR, heart rate; LLT, lipid-lowering therapy.

cases. Individuals taking antihypertensive drugs were 53.1% (20.4% ACE-I or ARB; 8.3% CCB, and 17.2% diuretics) whereas those taking LLT were 3.6%.

Diuretic use and hyperuricemic participant group

Table 2 shows the mean variables of the four groups defined on the base of diuretic use (yes or no) and level of SUA (<4.8 and ≥4.8 mg/dl). Individuals with hyperuricemia and diuretic use were older, exhibited higher SBP and DBP, BMI, blood glucose, and serum triglycerides with lower serum HDL-cholesterol and estimated glomerular filtration rate as compared with the two groups not using diuretic therapy. Furthermore, they also were under ACE-I/ARB, CCB, and LLT in a percentage greater than the one detected for individuals without diuretic treatment.

Outcomes analysis: hyperuricemic without diuretic vs. hyperuricemic with diuretics

Outcome analysis has been focused on individuals with hyperuricemia (SUA higher than media value of 4.8 mg/dl) further classified accordingly to diuretic use. As shown in Table 2, individuals with hyperuricemia using diuretic drugs showed a significantly higher prevalence of death for any cause (21.9 vs. 19%, $P < 0.001$) as well as for a first cardiovascular event (11.3 vs. 8.1%, $P < 0.001$) whereas no differences were seen regarding cardiovascular deaths (5.1 vs. 4.1, $P = 0.013$). The relative Kaplan–Meier curves are showed in Fig. 1.

Figure 2 shows outcomes analysis for the two hyperuricemic group (SUA greater than median value of 4.8 mg/dl) defined on the base of diuretic use. Patients with hyperuricemia without diuretic use were considered as reference. Unadjusted analysis showed a higher hazard ratio for all-cause death, first cardiovascular event and cardiovascular death in hyperuricemic individuals using diuretics as compared with those not using diuretics (Fig. 2, panel a). When the analysis was adjusted for the main confounders (age, sex, SBP, BMI, glycemia, total and HDL cholesterol, smoking, cardiovascular therapies, and estimated glomerular filtration rate) the above-mentioned findings were not confirmed (Fig. 2, panel b) for all the three evaluated outcomes.

TABLE 2. mean values of the variables of the four groups defined on the base of diuretic therapy (yes or no) and of the level of serum uric acid (>4.8 mg/dl and ≥4.8 mg/dl)

Diuretic	No	Yes	No	Yes
SUA (4.8 mg/dl)	<	<	≥	≥
Number	7183	1179	7506	1879
Age (years)	54.8 ± 15.2^*°	57.3 ± 13.8°	58 ± 15.4°	62.3 ± 13.8
Males (%)	36.1^*°	49.6°	54.3*°	40.7
SBP (mmHg)	138.8 ± 24.6^*°	153.9 ± 22.6	145.3 ± 23.9*°	154.1 ± 23.5
DBP (mmHg)	82.7 ± 12.7^*°	90.9 ± 12.8°	85.9 ± 12.9*°	89.2 ± 13.7
HR (bpm)	72.7 ± 12.1^*	73.6 ± 11.5°	72 ± 13.4	72 ± 11.8
BMI (kg/m^2)	25.5 ± 4.2^*°	27 ± 4.4°	27.2 ± 4.2°	28.4 ± 4.4
Glycemia (mg/dl)	95.5 ± 27.1^*°	99.4 ± 26.1°	99.7 ± 23.6°	104.3 ± 28.2
Total cholesterol (mg/dl)	212.1 ± 39.1^°	213.7 ± 37.1	215.3 ± 39.4	217.2 ± 39.1
HDL cholesterol (mg/dl)	56.1 ± 15.5^*°	53.4 ± 13.9°	50.6 ± 14.3*	49.9 ± 14
Triglycerides (mg/dl)	107.6 ± 60.5^*°	124.8 ± 76.6°	141.2 ± 87*°	154.6 ± 91.7
Creatinine (mg/dl)	0.84 ± 0.15^*°	0.9 ± 0.26°	0.97 ± 0.2*°	1.07 ± 0.32
GFR (ml/min)	88.8 ± 28.3^*°	86.4 ± 25.5°	79.4 ± 26.1°	68.2 ± 20.3
Antihypertensive drugs (%)	31.5^*°	93.6	36.6*°	92.3
ACE-I/ARB (%)	10.4^*°	57.3	14.5*°	58.4
CCB (%)	5.2^*°	20.3	7.2*°	17.7
LLT (%)	2.4^*°	4.1°	3.7°	7.2
All-cause death (*n*, %)	816, 11.4^°	132, 11.2°	1429, 19*°	412, 21.9
First CV event (*n*, %)	384, 5.3^°	69, 5.9°	610, 8.1*°	212, 11.3
CV death (*n*, %)	179, 2.5^°	25, 2.1°	311, 4.1*	611, 5.1

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HR, heart rate; LLT, lipid-lowering therapy; SUA, serum uric acid. ^$P < 0.05$ vs. no diuretic and uricemia greater than 4.8 mg/dl; *$P < 0.05$ vs. yes diuretic and uricemia 4.8 mg/dl or less; °$P < 0.05$ vs. yes diuretic and uricemia greater than 4.8 mg/dl.

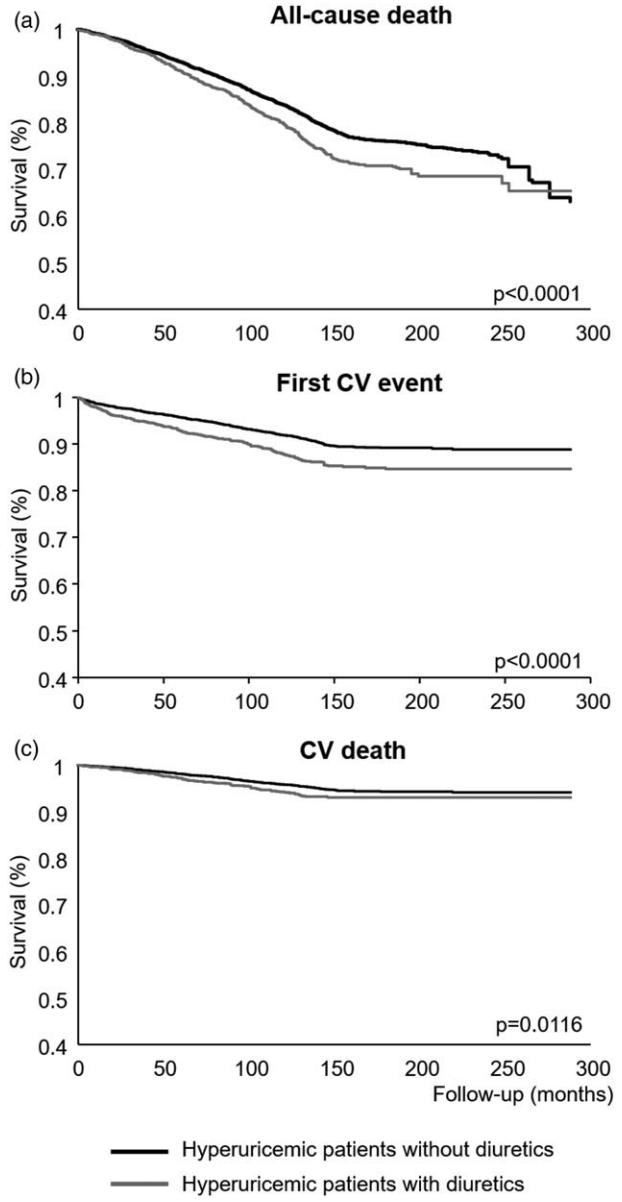

FIGURE 1 Kaplan–Meier curves for total (panel A) and cardiovascular events (panel b) and mortality (panel c); CV, cardiovascular.

Outcome analysis: uric acid tertiles

Analysis were repeated splitting the two hyperuricemic groups into tertiles of SUA. Figure 3, panel a, shows that adjusting for confounders the risk of the three outcome increases with increasing tertile of SUA. However, this becomes statistically significant only for hyperuricemic individuals in the highest tertile of SUA with or without diuretic, for cardiovascular deaths.

When we compared hypeuricemic individuals with or without diuretics into the same tertiles, no significant differences were found (Fig. 3, panel b).

DISCUSSION

The main finding of our study is the similar rate of all-cause deaths, cardiovascular deaths, and first occurrence of cardiovascular events among individuals with hyperuricemia irrespective of diuretic use. This was both observed when all hyperuricemic individuals were considered and when they were separated into tertiles of SUA, confirming the similar rate of the evaluated outcome across the whole spectrum of hyperuricemia.

The opposite result, that is, a lower risk for patients with SUA elevation associated with diuretic use, could have also been expected. Indeed, one of the main theories linking SUA to cardiovascular events is the role of xanthine oxidase as a trigger for oxidative stress [20]: superoxide anions concurring to a higher oxidative stress are generated by the two final reactions converting hypoxanthine into xanthine by the xanthine oxidase. On the basis of this hypothesis, one could expect a lower risk of cardiovascular events in individuals with a diuretic-induced reduction of SUA renal excretion.

Our data argue against this hypothesis, although two main limitations need to be discussed. First, for reasons intrinsic to its nature, our study cannot selectively discriminate the prognostic impact of SUA directly linked to the activity of the biosynthetic pathway, rather than that derived from the reduced urate excretion. Indeed, the presence of hyperuricemia during diuretic use does not exclude the coexistence of overproduction and reduced excretion of SUA. Furthermore, all the types of diuretic drugs were included in the present analysis, although the effect on SUA level is more commonly observed with HCTZ. Unfortunately, data on diuretic type were available only for a fraction of patients too small for a sub-group analysis.

A further important finding of our study is that an increased all-cause and cardiovascular mortality and a higher risk of cardiovascular events in patients with hyperuricemia taking diuretic drugs when compared with hyperuricemic patients without diuretic therapy were observed only at unadjusted analysis. These data emphasize the importance of the interaction of multiple mechanisms, potentially acting as confounders, in the relationship between SUA and cardiovascular risk. Indeed, as already mentioned, oxidative stress is strongly implicated but development of arterial hypertension [21], diabetes mellitus [22], metabolic syndrome [14], and target organ damage [11] may also play a role. Furthermore, some of these factors may also act in a bidirectional way, such as the one in which the kidney is implicated. Indeed, uric acid deposition and vascular damage at glomerular level causes a reduction in filtration rate that consequently brings to a lower SUA excretion resulting in an increase of its circulating plasma levels [23].

Furthermore, as usual in population studies, our participants were in largely healthy and with a normal kidney function. It is possible that our results could not be applied to individuals with a worse cardiovascular risk profile (such as diabetes and/or CKD).

Our study has an important element of strength and some limitations. The strength is based on the relevant number of individuals included in our analysis that reinforce the results of the present study.

The main limitation is the lack of an analysis for groups of individuals homogeneous for type of diuretic taken,

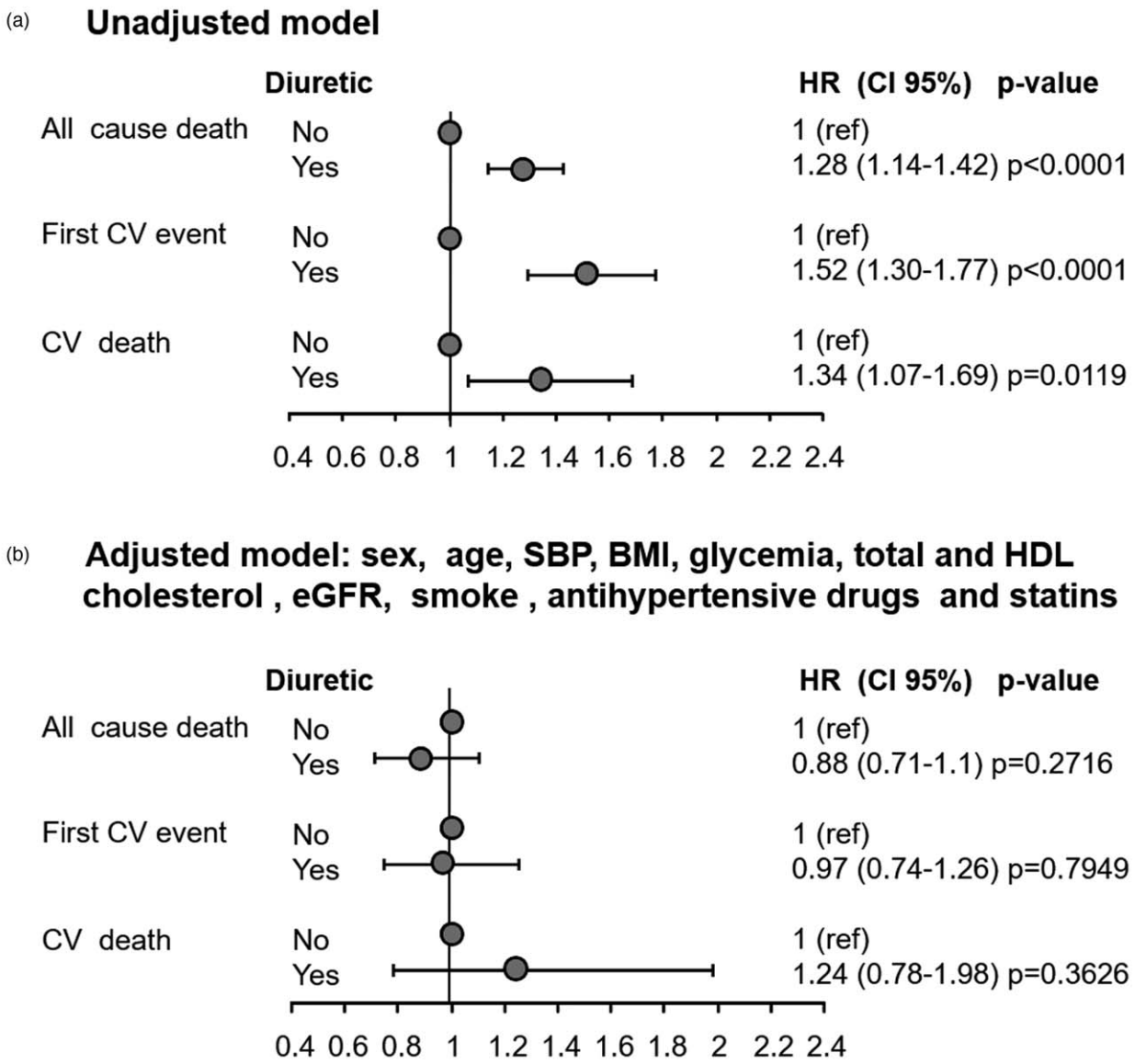

FIGURE 2 Hazard ratio for total and cardiovascular mortality and events; unadjusted model (panel a) and adjusted one (panel b). SUA, serum uric acid.

because of the fact that the number of individuals in each group would have been too low. Another limitation is the impossibility to distinguish the different conditions of reduced excretion and overproduction of SUA (because of the lack of data on urinary uric acid) and so selectively discriminate the prognostic impact of an increased SUA synthesis. Furthermore, no data were available on the trend of SUA during diuretic therapy, and this did not allow to study the impact on cardiovascular risk of the changes of SUA over time. In addition, the availability of only one value of SUA for each individual, may also have led to a misclassification bias, as this parameter is individual to changes over time.

In conclusion, our study shows that, at the epidemiological level, the increase in SUA has a similar prognostic impact, both in the case in which it is mainly attributable to overproduction (as in the case of hyperuricemic individuals who do not take diuretics), and in the case in which a presumably not negligible quota of SUA excess is linked to an increased renal tubular reabsorption (as in the case of hyperuricemic individuals taking diuretics).

Further insights on this challenging issue may be supplied by future studies, performed on longitudinal data, that may allow to collect information on the impact SUA trend in individuals under diuretic therapy. In addition, further studies may provide information on the effect on cardiovascular risk of hyperuricemia induced by different classes of diuretic drugs.

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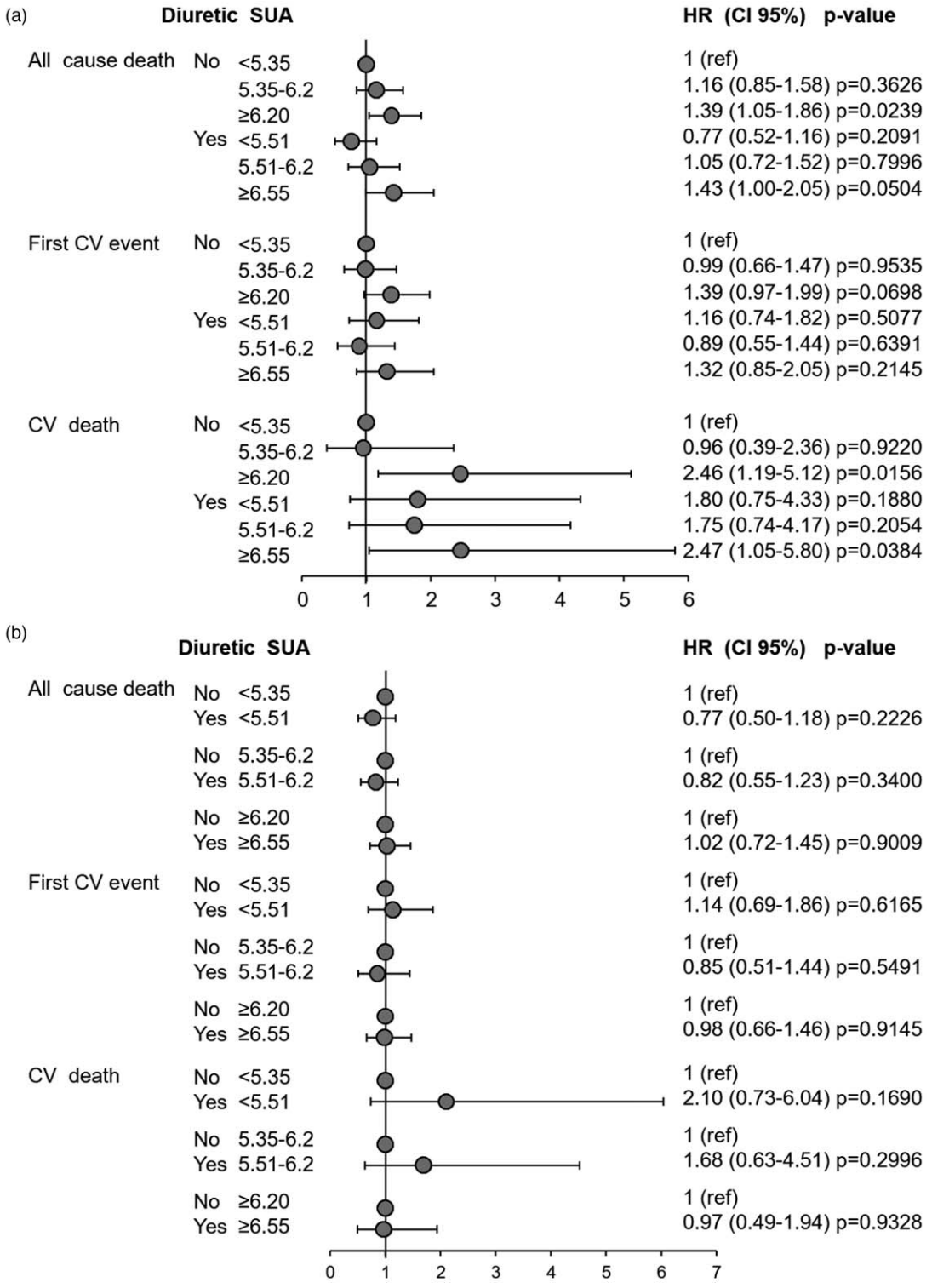

FIGURE 3 Adjusted hazard ratio for total and cardiovascular mortality and events when patients were divided into tertiles (panel a); adjusted hazard ratio when individuals with and without diuretics were compared into the same tertiles (panel b). CV, cardiovascular; SUA, serum uric acid.

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Ethical approval: all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: informed consent was obtained from all individual participants included in the study.

Conflicts of interest

There are no conflicts of interest.

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