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# Uric acid is an independent predictor of cardiovascular events in post-menopausal women

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ABSTRACT

*Background:* Uric acid (UA) is a risk factor for cardiovascular (CV) disease. In post-menopause UA levels are increased and strongly associated with subclinical organ damage. We investigated the prognostic significance of UA levels in predicting CV morbidity and mortality in post-menopausal women.
*Methods:* We considered 645 post-menopausal outpatients not taking hormone replacement therapy or any drugs interfering with UA levels. We evaluated major adverse cardiovascular events (MACE) as primary endpoint, with coronary, stroke or total events as secondary endpoint. Survival curves for tertiles of UA were obtained by using the Kaplan–Meier and Mantel methods. Effect of prognostic factors on survival was evaluated by multivariable Cox regression model, considering $P < 0.05$ as statistically significant.
*Results:* During a mean (SD) follow-up at 72.5 (23.5) months, there were 90 new CV events (2.31%): 62 coronary and 28 cerebrovascular events. The rate of nonfatal CV events (3.15% versus 2.03% and 1.52%, $P = 0.009$) as well as that of MACE (3.23% versus 2.11% and 1.59%, $P = 0.011$) were significantly higher in the third tertile than in the other two groups. Interestingly, cerebrovascular (1.15% versus 0.62% and 0.30%, $P = 0.027$) but not coronary events were significantly different among the three groups. In the Cox regression model, UA was independently and strongly associated with the incident risk of MACE (HR = 1.248, $P = 0.001$), cerebrovascular (HR = 1.657, $P < 0.0001$) and total events (HR = 1.391, $P < 0.0001$).
*Conclusions:* In post-menopause, independently of other CV risk factors and menopause duration, UA levels are associated with increased risk of death and MACE, in particular cerebrovascular but not coronary events.


## 1. Introduction

Uric acid (UA), the end product of purine catabolism, has a key role in human cellular oxidation–reduction processes, showing both pro-oxidant and antioxidant properties in different clinical and pathological contexts (1,2). Despite an early hypothesis regarding the possible protective role of UA against oxidative stress associated with cardiovascular (CV) disease, large epidemiological studies demonstrated that UA is an independent risk factor for CV morbidity and mortality in different settings of patients (3–5) as confirmed in two recent meta-analyses (6,7).

It is well known that post-menopausal women have an increased CV risk (8); in particular, the reduction of renal function has been associated with the increased risk of death and CV events, independently of traditional CV risk factors, menopause duration, and presence of metabolic syndrome (9). In addition, serum UA levels appear to be increased in both physiologic and post-surgical menopause independently of other confounding factors (10). This may be explained by the uricosuric effect of estrogens and, coherently, the hormone replacement therapy administration's effectiveness in UA reduction (11).

Moreover, several studies demonstrated a strong association between UA and subclinical vascular damage in different settings of patients, post-menopausal women included (12–15), and new diabetes appearance (16,17). Taken together, it might be useful to investigate the possible prognostic significance of UA levels in predicting CV events in a large group of post-menopausal women.

## 2. Methods

### 2.1. Study population

From a large cohort of Caucasian post-menopausal women, enrolled between January 1996 and March 2005 at Catanzaro University Hospital for CV risk factor screening (9), we selected the study population of the present study. The inclusion criteria were the availability of both

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baseline serum UA values and normal renal function, defined as an estimated-glomerular filtration rate (e-GFR) value ≥ 60 ml/min/1.73 $m^2$. This clinical condition was considered essential to minimize the deleterious effect of renal dysfunction on both UA levels and CV events. Because in the initial data collection UA was not a mandatory examination, it was available only in a subgroup; thus, we can assume that its measurement was absolutely random.

Exclusion criteria were: a history of any cancer in the past 5 years, venous thromboembolism, liver cirrhosis, congenital heart diseases, previous CV events, type 1 or 2 diabetes or autoimmune diseases. Women should not have used hormone replacement therapy within the past 3 months. Finally, among hypertensive patients we excluded women taking diuretic therapy or any drugs interfering with UA levels. Thus, on the basis of these criteria, the final sample consisted of 645 women.

As already described (9), post-menopause was defined as a complete lack of menstrual cycle in the past 12 months or previous ovariectomy. Participants with body mass index (BMI) ≥ 30 kg/$m^2$ were defined obese. Smoking status was defined as habitual use of at least 5 cigarettes/day in the year before the first visit.

The Ethical Committee approved the protocol and informed written consent was obtained from all participants. All the investigations were performed according to the principles of the Helsinki Declaration.

### 2.2. Follow-up and cardiovascular events

Clinical follow-up for morbidity and mortality data was available for all participants. So as previously reported (9) it included periodic clinical visits and a questionnaire sent by mail to family physicians. All clinical events had to be validated by source data (hospital records, death certificates or other original documents). We considered the following clinical events: fatal and nonfatal myocardial infarction (MI) and stroke, unstable angina, coronary revascularization procedures (percutaneous interventions and bypass graft surgery), CV death or death for any cause.

MI was defined according to the criteria of the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation (18). Stroke was defined as a new neurological deficit of sudden onset that persisted for at least 24 h (19).

We considered major adverse cardiovascular events (MACE), including CV death, MI, stroke, coronary revascularization procedures, as the primary endpoint. The secondary endpoint was represented by coronary events, stroke or total events (MACE + death for any cause).

### 2.3. Statistical analysis

Data are expressed as mean ± SD or as percent frequency. Analysis of variance was utilized to test the differences between clinical and biological data when expressed as continuous variables and the $\chi^2$ test was used for categorical variables. Event rate is reported as the number of events per 100 patient-year.

The date of censorship was defined as the last contact for patients without events and as the first event for patients who experienced multiple events. Survival curves, both crude and adjusted (for Framingham risk factors and menopause duration), according to increasing tertiles of UA were estimated by using the Kaplan–Meier product-limit method and compared by using the Mantel (logistic rank) test.

The effect of prognostic factors on survival was evaluated by using a multivariable Cox regression model. Tested covariates included linear or categorical UA, menopausal duration, and traditional risk factors [age, smoking (previous or never smokers, current smokers), LDL-cholesterol, pulse pressure, fasting glucose and BMI].

The multiple Cox regression model was constructed by including all variables associated with the incident risk of adverse events at univariate Cox regression analysis. By this strategy, we constructed a Cox model of adequate statistical power (at least 10 events for each variable into the final model). Data are expressed as hazard ratio (HR) and P value.

In two-tailed tests, a value of $P < 0.05$ was considered statistically significant. All comparisons were performed using the statistical package SPSS 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

## 3. Results

### 3.1. Study population

In Table 1 we reported demographic, clinical and biochemical characteristics of the study population stratified by increasing tertiles of UA. Mean (SD) age was 53.9 (5.9) years, there were 503 (78%) hypertensive women, 150 (23.3%) were obese and 381 (59.1%) were hypercholesterolemic. In addition, women in the third UA tertile were significantly older ($P < 0.0001$) and they had lower DBP values ($P = 0.008$) in comparison with the other two groups. There were no significant differences among groups for the other anthropometric, hemodynamic and biochemical parameters with the exclusion of number of smokers ($P < 0.0001$) and menopause duration ($P = 0.036$) that were significantly higher in the third tertile, while eGFR was significantly lower ($P = 0.016$).

**Table 1**
Baseline characteristics of the study population according to increasing tertiles of uric acid.

| | All (n = 645) | 1st tertile (n = 215) | 2nd tertile (n = 215) | 3rd tertile (n = 215) | P |
|---|---|---|---|---|---|
| Age, years | 53.9 (5.9) | 52.8 (5.5) | 54.1 (6.0) | 55.1 (6.0) | <0.0001 |
| BMI, kg/$m^2$ | 27.5 (3.7) | 27.3 (4.0) | 27.5 (3.5) | 27.7 (3.7) | 0.609 |
| Systolic BP, mm Hg | 151.2 (19.3) | 153.4 (20.1) | 150.4 (19.2) | 149.9 (18.4) | 0.118 |
| Diastolic BP, mm Hg | 86.7 (10.8) | 88.5 (11.3) | 86.3 (9.9) | 85.4 (10.9) | 0.008 |
| Pulse pressure, mm Hg | 64.5 (16.0) | 64.9 (16.0) | 64.1 (15.9) | 64.5 (16.1) | 0.861 |
| Heart rate, bts/min | 70.3 (10.1) | 69.9 (10.5) | 70.7 (9.7) | 70.2 (10.1) | 0.655 |
| Fasting glucose, mg/dl | 96.2 (12.1) | 95.5 (12.0) | 97.3 (12.0) | 95.9 (12.2) | 0.283 |
| LDL-cholesterol, mg/dl | 132.6 (44.3) | 134.1 (45.3) | 132.3 (43.9) | 131.3 (43.8) | 0.794 |
| HDL-cholesterol, mg/dl | 51.0 (12.5) | 51.7 (12.2) | 50.9 (12.4) | 50.4 (12.8) | 0.551 |
| Triglyceride, mg/dl | 138.3 (63.8) | 132.1 (62.8) | 136.3 (61.1) | 146.5 (66.9) | 0.056 |
| Uric acid, mg/dl | 5.4 (1.7) | 3.6 (0.7) | 5.1 (0.4) | 7.3 (1.1) | <0.0001 |
| Current smokers, n (%) | 215 (33.3) | 52 (24.2) | 74 (34.4) | 89 (41.4) | <0.0001 |
| Hypertensives, n (%) | 503 (78.0) | 166 (77.2) | 171 (79.5) | 166 (77.2) | 0.798 |
| Obese, n (%) | 150 (23.3) | 49 (22.8) | 48 (22.3) | 53 (24.6) | 0.833 |
| Hypercholesterolemic, n (%) | 38 (59.1) | 133 (61.9) | 121 (56.3) | 127 (59.1) | 0.500 |
| e-GFR, ml/min/1.73 $m^2$ | 79.2 (15.4) | 81.5 (16.7) | 77.7 (13.1) | 78.3 (15.9) | 0.016 |
| Menopausal duration, years | 5.0 (3.4) | 4.6 (3.2) | 5.2 (3.5) | 5.4 (3.5) | 0.036 |

BMI: body mass index, BP: blood pressure, eGFR: estimated glomerular filtration rate, MACE: major adverse cardiovascular events. Tertiles of uric acid: 1st: <4.5 mg/dl, 2nd: 4.5–6 mg/dl, 3rd: >6 mg/dl.