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# Serum uric acid as a potential marker for heart failure risk in men on antihypertensive treatment: The British Regional Heart Study

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## ABSTRACT

The role of serum uric acid (SUA) as a prognostic marker for incident heart failure (HF) in hypertensive subjects is uncertain. We have prospectively examined the relationship between SUA and incident HF in 3440 men aged 60–79 years separately in those on and not on antihypertensive treatment who were followed up for a mean period of 15 years. Men on SUA lowering drugs and those with history of HF or myocardial infarction were excluded. There were 260 incident HF cases. The men were divided into three groups of SUA concentrations/levels (<350, 350–410 and >410  $\mu\text{mol/L}$ ). Raised SUA was associated with significantly increased risk of HF in men on antihypertensive treatment ( $N = 949$ ) but not in those without ( $N = 2491$ ) ( $p = 0.003$  for interaction). In men on antihypertensive treatment those with hyperuricemia (>410  $\mu\text{mol/L}$ ) had the most adverse biological risk profile for HF including the highest rates of atrial fibrillation and renal dysfunction and the highest mean level of BMI, c-reactive protein and cardiac function (cardiac troponin T). Treated hypertensive men with SUA levels > 410  $\mu\text{mol/L}$  showed an increase in risk of HF of more than twofold compared to those on treatment with levels <350  $\mu\text{mol/L}$  even after adjustment for lifestyle characteristics and biological risk factors [adjusted hazard ratio 2.26 (1.23,4.15)]. SUA improved prediction of HF beyond routine conventional risk factors ( $p = 0.02$  for improvement in c-statistics). SUA as a marker of increased xanthine oxidase activity may be a useful prognostic marker for HF risk in older men on antihypertensive treatment.

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## 1. Introduction

Serum uric acid (SUA) is the end product of purine metabolism in humans; hyperuricaemia is commonly found in patients with heart failure (HF) and hypertension [1,2]. The association of SUA and coronary heart disease has long been recognised [1] and has sparked enormous debate about the role of SUA as a risk factor for CHD and the treatment of hyperuricemia especially in hypertensive patients [1,3–5]. In more recent years several studies and meta-analysis have reported raised SUA to be associated with increased risk of incident HF in population studies [6–10]. Whether this association is causal is still a matter of debate. However a recent Mendelian randomisation study provided no evidence that the association between SUA and HF is causal, suggesting that SUA may be only a risk marker rather than a causal factor in the development of HF [11]. Hypertension is a major risk factor for HF and regardless of whether SUA is causally related to HF, SUA may be a useful biomarker of increased HF risk in hypertension [12]. Recent studies have shown a

strong association between SUA levels and AF [13], a major risk factor for HF and one study has shown SUA to predict HF in those with hypertension [14]. SUA is dependent on xanthine oxidase (XO) activity, a known cause of oxidative stress [15] which is implicated in the pathophysiology of HF [15,16] as well as hypertension [17]. SUA may be a marker of increased XO activity which is up-regulated in the failing heart [15] and may thus identify patients with increased HF risk. SUA concentration is commonly measured in hypertensive patients and although a number of studies have shown SUA to be an independent marker of CVD risk in hypertensive subjects [18,19], there is limited prospective data regarding the association between raised SUA and HF, especially in the older hypertensive adult population, who are at particularly high risk of developing HF. Whether SUA add to the prediction of HF beyond routine markers in older hypertensive patients has seldom been assessed. We have therefore examined the association between raised SUA and incident HF in older men who are on antihypertensive treatment, as well as in those who are not on antihypertensive treatment.

## 2. Subjects and methods

The British Regional Heart Study is a prospective study involving 7735 men aged 40–59 years drawn from one general practice in each of 24 British towns, who were screened between 1978 and 1980 [20]. The population studied was socio-economically representative and comprised predominantly white Europeans (>99%). In 1998–2000,

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all surviving men, then aged 60–79 years, were invited for a 20th year follow-up examination, on which the current analyses are based. Ethical approval was obtained from all relevant local research ethics committees. All men completed a mailed questionnaire providing information on their lifestyle and medical history, had a physical examination and provided a fasting blood sample. The samples were frozen and stored at  $-20^{\circ}\text{C}$  on the day of the collection and transferred in batches for storage at  $-70^{\circ}\text{C}$  until analysis, carried out after no more than one freeze-thaw cycle. 12 lead electrocardiograms were recorded using a Siemens Sicard 460 instrument and were analyzed using Minnesota Coding definitions at the University of Glasgow ECG core laboratory. Men were asked whether a doctor had ever told them that they had angina or MI, HF or stroke; details of their medications were recorded at the examination including use of blood pressure lowering drugs (BNF code 3.1) and non-steroidal anti-inflammatory drugs (NSAIDs) (BNF code 10.1.1). 4252 men (77% of available survivors) attended for examination. 4034 men had blood measurement of SUA. We excluded men with prior HF or myocardial hypertrophy (LVH) ( $N = 508$ ) in the examination and a further 86 men on treatment for gout (SUA lowering drugs) leaving 3440 men for analysis.

### 2.1. Cardiovascular risk factor measurements at 1998–2000

Anthropometric measurements including body weight and height were carried out. Details of measurement and classification methods for smoking status, physical activity, social class, alcohol intake, blood pressure and blood lipids in this cohort have been described [21,22]. SUA was measured with an enzymatic colorimetric assay using a Hitachi 747 automated analyser. C-reactive protein (CRP) (marker of inflammation) was assayed by ultra sensitive nephelometry (Dade Behring, Milton Keynes, UK). Predicted glomerular filtration rate (eGFR) (measure of renal function) was estimated from serum creatinine using the equation  $\text{eGFR} = 186 \times (\text{Creatinine} / 88.4)^{-1.154} \times (\text{Age})^{-0.203}$  [23]. N-terminal pro-brain natriuretic peptide (NT-proBNP) was determined using the Elecsys 2010 (Roche Diagnostics, Burgess Hill, UK) [22]. Troponin T was measured by a high sensitivity method on an e411 (Roche Diagnostics, Burgess Hill, UK) using the manufacturers calibrators and quality control material. The low control CV was 6.6%, and high control CV 3.0%, and the assay limit of detection was 3 pg/ml. Electrocardiographic left ventricular hypertrophy (LVH) was defined according to the relevant Minnesota codes (codes 3.1 or 3.3). Atrial fibrillation (AF) was defined according to the Minnesota codes 8.3.1 and 8.3.3.

### 2.2. Follow-up

All men have been followed up from initial examination (1978–1980) for cardiovascular morbidity [20] and follow-up has been achieved for 99% of the cohort. In the present analyses, all-cause mortality and morbidity events are based on follow-up from re-screening in 1998–2000 at mean age 60–79 years to June 2014, a mean follow-up period of 15 years (range 14–16 years). Survival times were censored at date of HF, death from any cause or end of the study follow-up period (June 2014) whichever occurred first. Evidence of non-fatal MI and HF was obtained by ad hoc reports from general practitioners supplemented by biennial reviews of the patients' practice records (including hospital and clinic correspondence) to the end of the study period. Incident non-fatal HF was based on a confirmed doctor diagnosis of HF from primary care records and confirmed by a review of available clinical information from primary and secondary care records (including symptoms, signs, investigations, treatment response) to ensure that the diagnosis was consistent with the current recommendations on HF diagnosis [24]. The incidence and determinants of HF cases identified using this process have already been reported and are consistent with the results from other studies [21,22]. Incident HF included incident non-fatal HF as well as death from HF (ICD 9th revision code 428 or ICD10th revision I28).

### 2.3. Statistical methods

The men were divided into three groups based on the tertile distribution of SUA in all men ( $<350$ ,  $350$ – $410$  and  $>410$   $\mu\text{mol/L}$ ). Hyperuricemia in men is generally defined as those with SUA  $>420$   $\mu\text{mol/L}$  [25]. Thus those in the upper tertile were effectively hyperuricemic. Kaplan–Meier methods were used to calculate the cumulative HF incidence for the three groups of SUA; the log-rank test was used to evaluate differences in the HF rates for these groups. Analyses were carried out stratified by antihypertensive treatment status. Cox proportional hazards model was used to assess the multivariate-adjusted hazards ratio (HR) in a comparison of the three SUA groups as well as in a 1 SD increase in SUA. The proportional hazard assumption was examined using time-varying covariates, calculating interactions of predictor variables and a function of survival time and including them in the models. Examination of time-varying covariates indicated no violation of the proportionality assumption. The distributions of NT-proBNP, cTnT and CRP were skewed and log transformation was used to normalise these factors. Receiver-operating characteristic (ROC) curves and areas under the curve (AUC) (*c*-statistics) were used to assess the ability of SUA to predict HF in men on antihypertensive treatment and who had no history of HF or MI beyond a score which included conventional routine risk factors as well as how SUA predicted beyond the Health ABC HF score. Conventional routine risk factors included established risk factors for HF routinely obtained in clinical practice e.g. age obesity, hypertension, history of diabetes and history of angina. The Health ABC HF score includes age, smoking, eGFR, heart rate, left ventricular hypertrophy, albumin, systolic blood pressure, history of angina, fasting blood glucose and antihypertensive treatment [26]. To assess whether the association between SUA and incident HF may be due to the development of incident CHD which in turn results in increased risk of HF, we adjusted for incident CHD by fitting CHD as a time dependent covariate.

## 3. Results

During the mean follow-up period of 15 years there were 260 incident HF events (6.31/1000 person years), in the 3440 men without MI or HF and who were not on SUA lowering drugs.

Fig. 1 show the Kaplan–Meier estimates of the cumulative incidence of HF by tertiles of SUA separately by antihypertensive treatment status. Risk of HF was increased only in those in the top tertile of the SUA distribution, and this was only seen in men on antihypertensive treatment. No association was seen between SUA and HF in those not on treatment and a test for interaction confirmed a significant difference in the relation between SUA and incident HF in those on and not on antihypertensive treatment ( $p = 0.02$ ). We therefore present the findings stratified by antihypertensive medication status.

Table 1 shows the association between SUA and biological risk factors in men on and not on antihypertensive treatment. With the exception of blood pressure, the patterns of association between SUA and biological risk factors were similar in both men on and not on treatment. Men on antihypertensive treatment with raised SUA had the highest levels of cardiovascular risk factors including renal dysfunction, AF, systolic blood pressure, cTnT and the lowest level of HDL-C and FEV<sub>1</sub>.

In men not on antihypertensive treatment, no association was seen between SUA and HF (Table 2). When this group was separated into those with measured hypertension (systolic blood pressure  $\geq 160$  or DBP  $\geq 90$ ) and those without, no association was seen in either group (data not shown). In contrast, in men on antihypertensive treatment, hyperuricemia ( $>410$   $\mu\text{mol/L}$ ) was significantly associated with increased risk of HF even after adjustment for a wide range of HF risk factors including AF, BMI, HDL-C, systolic blood pressure, renal dysfunction, CRP and cardiac function (NT-proBNP and cTnT). Further adjustment for incident CHD made little difference to the findings. The increased risk of HF associated with hyperuricaemia remained even after exclusion of men on diuretics [adjusted HR = 1.97 (1.01,3.81);model 4] or exclusion of men with renal dysfunction [adjusted HR = 2.56 (1.30,5.02);model 4] or the exclusion of 84 men on NSAIDs [adjusted HR = 2.37 (1.29,4.35); model 4].

The elevated risk associated with hyperuricaemia was seen in those with controlled blood pressure (defined as systolic blood pressure  $< 150$  and diastolic blood pressure  $< 90$ ;  $N = 321$ ) and those with uncontrolled blood pressure ( $N = 585$ ) although the association was somewhat stronger in those with controlled hypertension compared to those with uncontrolled blood pressure (adjusted HR = 4.70 (1.53,14.44) vs 2.09 (0.98,4.48);model 4]. However a test for interaction was not significant ( $p = 0.47$ ).

Table 3 shows the *c*-statistics for the conventional risk score and the Health ABC HF score and the improvement in *c*-statistics in models with and without SUA. SUA added significantly to HF prediction beyond that provided by either risk score. However, a model which included conventional risk factors and NT-proBNP showed no significant improvement on the addition of SUA [*c* statistic = 0.676 (0.624–0.728) versus 0.691 (0.640–0.742) with SUA]; evidence for improvement  $p = 0.14$ ].

## 4. Discussion

In this study of older men with no history of an MI or HF raised SUA was associated with significantly increased risk of HF which was only seen in those who were on antihypertensive treatment. No association was seen between SUA and HF risk in those who were not on antihypertensive treatment. Our finding extends those of previous studies of SUA and HF by examining the relationship by antihypertensive medication status and by examining the prognostic value of SUA and improvement in risk prediction in those with hypertension. The increased risk of HF in those on treatment was seen even after adjustment for a wide range of HF risk factors including renal dysfunction, inflammation and cardiac function (NT-proBNP and cTnT). In a recent meta-analysis which

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