Low-grade albuminuria and the incidence of heart failure in a community-based cohort of elderly men

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Aims To investigate associations of urinary albumin excretion rate (UAER) and heart failure (HF) incidence in a community-based sample.

Methods and results In a prospective study of 70-year-old men free from HF at baseline (n = 1106), UAER (from timed overnight samples) was analysed with established risk factors for HF [acute MI before baseline, acute MI during follow-up (modelled as a time-dependent covariate), hypertension, diabetes, left ventricular hypertrophy, smoking, body mass index, and glomerular filtration rate] and more recently described risk factors [high-sensitive C-reactive protein and insulin sensitivity (clamp glucose disposal rate)] as predictors of HF incidence.

Ninety-eight participants developed HF during a median follow-up of 9.0 years. In Cox proportional hazards models adjusted for established and novel risk factors for HF, a 1 SD increase in log UAER increased the risk of HF in individuals without anti-hypertensive treatment (hazard ratio 1.49; 95% CI 1.13–1.98; \( P = 0.005 \)). Furthermore, UAER remained an independent predictor of HF, also in participants without diabetes at baseline or myocardial infarction at baseline or during follow-up. There were no significant associations between UAER and HF incidence in individuals with anti-hypertensive treatment.

Conclusion Our observations support the notion that low-grade albuminuria is a marker for subclinical cardiovascular damage that predisposes to future HF in the community.

KEYWORDS Heart failure; Albuminuria; Kidney failure; Epidemiology; Risk factors

Introduction

Heart failure (HF) is one of the most common,1 costly,2 disabling, and deadly diseases.3 The predominant causes of HF are hypertension and coronary heart disease. Other established risk factors for HF include left ventricular hypertrophy, valvular heart disease, diabetes mellitus, cigarette smoking, and obesity.4–8 More recently, low-grade inflammation9,10 and insulin resistance11 have been demonstrated to be independent risk factors for HF.

The presence of low but slightly elevated levels of albuminuria (microalbuminuria) has been suggested to be a marker for generalized vascular dysfunction.12 Microalbuminuria has been shown to cluster with both established risk factors for HF13 and more recently described risk factors, such as insulin resistance14 and low-grade inflammation.15 Furthermore, microalbuminuria has been demonstrated to be an independent risk factor for HF in populations with high risk for cardiovascular disease, such as patients with low ejection fraction,16 prevalent cardiovascular disease,17,18 diabetes,17,19,20 and diabetic nephropathy.21 Less is known concerning the association between low-grade albuminuria and the incidence of HF in the community.

Thus, the primary aim of the study was to analyse urinary albumin excretion rate (UAER) as a predictor of HF incidence in a community-based sample of elderly men, adjusting for both established and more recently proposed risk factors for HF. The secondary aims were to examine UAER as a predictor of HF in participants with UAER levels below the threshold for microalbuminuria, in participants without diabetes at baseline, and in participants free from myocardial infarction at baseline or during follow-up (in order to investigate the relation between UAER and the incidence of non-ischaemic HF).

Methods

Study sample

The study is based on the Uppsala Longitudinal Study of Adult Men cohort (http://www.pubcare.uu.se/ULSAM/), a health investigation focusing at identifying metabolic risk factors for cardiovascular disease. All 50-year-old men living in Uppsala during 1970–73 were invited to the investigation, and 82% (2322 men)
participated. The cohort was re-investigated 20 years later (the baseline of the present study; 1991–95), and during this interval, 422 men had died and 219 had moved out of the Uppsala region. For the present study, 1141 participants had valid measurements of UAER. Nineteen participants were excluded due to a previous diagnosis of HF, 13 due to a previous diagnosis of valvular disease at baseline, and three due to missing data on anti-hypertensive treatment at baseline, rendering 1106 men eligible for the present investigation. We also used the following subsamples for our analyses: non-diabetics (n = 992), participants without macro or microalbuminuria (UAER < 20 μg/min; n = 928) and participants without myocardial infarction at baseline or during follow-up (n = 949). All participants gave written consent and the Ethics Committee of Uppsala University approved the study.

Baseline examinations
Examinations performed when the participants were 70 years of age included a medical examination, a questionnaire, blood sampling (after an overnight fast), urinary nighttime collection, supine office blood pressure measurement, anthropometric measurements, a euglycaemic hyperinsulinaemic clamp, and lipid determinations, as previously described.

UAER was calculated from the amount of albumin in the urine collected during the night. The subjects were instructed to void immediately before going to bed and to record the time. All samples during the night and the first sample of urine after rising were collected and used for the analysis. The assay employed a commercially available radioimmunoassay kit (Albumin RIA 100, Pharmacia, Uppsala, Sweden). Macroalbuminuria was defined as UAER > 200 μg/min, and microalbuminuria as UAER between 20 and 200 μg/min.

Insulin sensitivity was determined using the euglycemic insulin clamp technique, according to DeFronzo et al., with a slight modification; insulin was infused at a constant rate of 56 instead of 40 μIU/(min m²) to achieve nearly complete suppression of hepatic glucose output. Glucose disposal rate, representing insulin sensitivity, was calculated as the amount of glucose taken up during the last 60 min of the clamp procedure and is given in milligram per kilogram body weight per minute.

High-sensitivity C-reactive protein measurement was performed by latex-enhanced reagent (Dade Behring, Deerfield, IL, USA) using a Behring BN ProSpec analyser (Dade Behring). Serum NT-pro-BNP was determined with a sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics, Basel, Switzerland). Serum cystatin C-levels were determined with a latex-enhanced reagent (N Latex Cystatin C, Dade Behring) using a Behring BN ProSpec analyser (Dade Behring). Serum creatinine was measured at the routine laboratory, Department of Clinical Chemistry, Uppsala University Hospital.

Estimations of glomerular filtration rate (GFR) were done using the established modification of diet in renal disease (MDRD) equation.

The presence of hypertension at baseline was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or use of anti-hypertensive medication. The presence of diabetes at baseline was defined as fasting plasma glucose ≥7.0 mmol/L and/or the use of oral hypoglycaemic agents or insulin. Electrographic left ventricular hypertrophy (EGLVH) was defined as high-amplitude R-waves according to the revised Minnesota code together with a left ventricular strain pattern. Coding of smoking was based on interview reports, and data of medication were based on the questionnaire. The presence of valvular disease [International Classification of Disease (ICD)-9 codes 394–397 and 424 or ICD-10 codes I05–I08 and I24–I37] and prior myocardial infarction (ICD-9 code 410 or ICD-10 code I21) were assessed from the hospital discharge register. The precision of the myocardial infarction diagnosis in the Swedish hospital discharge register is high.

Follow-up and outcome parameter
The participants had a median follow-up time of 9.0 years (range 0.1–11.4 years), contributing to 9310 person-years at risk. A total of 124 men had a hospital discharge register diagnosis of HF between the age 70 baseline and 31 December 2002. As a possible diagnosis of HF, ICD HF codes 428 (ICD-9) and 150 (ICD-10) and hypertensive heart disease with HF, I11.0 (ICD-10), were considered. The medical records from the relevant hospitalizations were reviewed by two physicians (E.I. and L.L.), who, blinded to the baseline data, classified the cases as definite, questionable, or miscoded. The classification relied on the definition proposed by the European Society of Cardiology, and the review process has been described in detail previously. After this validation, 98 definite HF cases were included in the present study. None of the participants were lost to follow-up.

Statistical methods
Logarithmic transformation was performed to achieve normal distribution for skewed variables (UAER, C-reactive protein, cystatin C, and NT-pro-BNP). Data were given as percentages for categorical variables, means ± SD for normally distributed continuous variables, or medians (interquartile range) for skewed variables. Incidence rates in quartiles of UAER were examined to exclude deviations from linearity (Figure 1). Cumulative hazard curves according to urinary albumin excretion levels were established by the Nelson-Aalen estimation method. The prognostic value of a 1 SD increase of UAER for HF incidence was investigated with Cox proportional hazards analyses. Proportional hazards assumptions were confirmed by Schoenfeld’s tests. The relations of UAER and HF were investigated in three sets of models in a hierarchical fashion:

(i) unadjusted models;
(ii) models adjusted for established risk factors for HF [acute MI before baseline, acute MI during follow-up (modelled as a time-dependent covariate), hypertension, diabetes, left ventricular hypertrophy, smoking, body mass index (BMI), and estimated GFR];
(iii) models adjusted for established risk factors for HF, C-reactive protein, and clamp glucose disposal rate.

Effect modification was examined by testing the statistical significance of the following two-way interaction terms: UAER by hypertension, UAER by anti-hypertensive treatment, UAER by diabetes, UAER by anti-diabetic treatment, and UAER by BMI. Owing to

Figure 1 Incidence rates of heart failure in quartiles of urinary albumin excretion rate in participants without anti-hypertensive treatment.
evidence of a significant interaction between UAER and anti-hypertensive treatment at baseline ($P = 0.001$), we performed all analyses in two separate strata: individuals with anti-hypertensive treatment ($n = 380$) and individuals without ($n = 726$). None of the other interaction terms reached statistical significance ($P > 0.17$ for all). In exploratory analyses, we adjusted also for cystatin C and NT-pro-BNP. The models were repeated in subsamples of participants without anti-hypertensive treatment or diabetes at baseline ($n = 672$), participants without anti-hypertensive treatment or macro- or microalbuminuria at baseline ($n = 642$), and participants without anti-hypertensive treatment, or myocardial infarction at baseline or during follow-up ($n = 659$). In accordance with our a priori analysis plan, missing data were handled such that only participants with a missing covariate needed for that particular model were excluded from the analyses in order to maximize the statistical power. Two-tailed 95% confidence intervals and $P$-values were given, with $P < 0.05$ regarded as significant. We did not correct for multiple testing in our analyses. The statistical software package STATA 8.2 (Stata Corporation, College Station, USA) was used.

### Results

Ninety-eight participants developed HF during the follow-up (58 among participants with anti-hypertensive treatment at baseline and 40 among participants without treatment). The overall incidence rate was 10.5/1000 person-years at risk. Table 1 shows the clinical characteristics at baseline. Figure 1 shows incidence rates for HF in the quartiles of UAER in participants without anti-hypertensive treatment. In crude and multivariable models adjusting for established and more recently described risk factors for HF (models A–C), 1 SD increase in log UAER was associated with 49–63% higher risk for HF in participants without anti-hypertensive treatment at baseline (Table 2). In participants with anti-hypertensive treatment at baseline, this association was attenuated. The association between UAER and HF incidence in participants without anti-hypertensive treatment remained similar, but somewhat weaker when adding cystatin C and NT-pro-BNP also to the multivariable

<table>
<thead>
<tr>
<th>Albuminuria variables</th>
<th>Total sample ($n = 1106$)</th>
<th>Participants free from diabetes ($n = 992$)</th>
<th>Participants free from macro- and microalbuminuria ($n = 928$)</th>
<th>Participants without myocardial infarction ($n = 949$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UAER ($\mu$g/min; $n = 1106$)</td>
<td>5.2 (3.4–11.2)</td>
<td>4.9 (3.3–9.9)</td>
<td>4.4 (3.2–7.2)</td>
<td>5.2 (3.4–11.2)</td>
</tr>
<tr>
<td>Microalbuminuria ($n = 1106$)</td>
<td>153 (13.8)</td>
<td>117 (11.8)</td>
<td>0</td>
<td>121 (12.8)</td>
</tr>
<tr>
<td>Macroalbuminuria ($n = 1106$)</td>
<td>25 (2.3)</td>
<td>17 (1.7)</td>
<td>0</td>
<td>23 (2.4)</td>
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<tr>
<td>Other covariates at baseline</td>
<td></td>
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<tr>
<td>Myocardial infarction at baseline or during follow-up ($n = 1106$)</td>
<td>157 (14.2)</td>
<td>138 (13.9)</td>
<td>123 (13.3)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension prevalence ($n = 1106$)</td>
<td>825 (74.6)</td>
<td>726 (73.2)</td>
<td>666 (71.8)</td>
<td>695 (73.2)</td>
</tr>
<tr>
<td>Anti-hypertensive treatment ($n = 1106$)</td>
<td>380 (34.4)</td>
<td>320 (32.3)</td>
<td>286 (30.8)</td>
<td>290 (30.6)</td>
</tr>
<tr>
<td>Diabetes prevalence ($n = 1106$)</td>
<td>114 (10.3)</td>
<td>0</td>
<td>70 (7.5)</td>
<td>95 (10.0)</td>
</tr>
<tr>
<td>ECG-LVH ($n = 1029$)</td>
<td>73 (6.6)</td>
<td>63 (6.4)</td>
<td>52 (5.6)</td>
<td>55 (5.8)</td>
</tr>
<tr>
<td>Current cigarette smoking ($n = 1081$)</td>
<td>223 (20.2)</td>
<td>199 (20.1)</td>
<td>176 (19.0)</td>
<td>191 (20.1)</td>
</tr>
<tr>
<td>Body mass index (kg/m²; $n = 1105$)</td>
<td>26.3 ± 3.4</td>
<td>26.0 ± 3.2</td>
<td>26.1 ± 3.2</td>
<td>26.2 ± 3.4</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (mL/min; $n = 1088$)</td>
<td>75.4 ± 12.3</td>
<td>75.1 ± 12.2</td>
<td>75.8 ± 11.8</td>
<td>76.0 ± 12.4</td>
</tr>
<tr>
<td>Clamp glucose disposal rate (mg/kg body weight/min; $n = 1063$)</td>
<td>5.2 ± 2.0</td>
<td>5.5 ± 1.9</td>
<td>5.3 ± 2.0</td>
<td>5.2 ± 2.1</td>
</tr>
<tr>
<td>C-reactive protein (mg/L; $n = 1078$)</td>
<td>1.9 (0.9–3.8)</td>
<td>1.8 (0.9–3.8)</td>
<td>1.8 (0.9–3.8)</td>
<td>1.8 (0.9–3.9)</td>
</tr>
<tr>
<td>Cystatin C (mg/L; $n = 1088$)</td>
<td>1.2 (1.1–1.3)</td>
<td>1.2 (1.1–1.3)</td>
<td>1.2 (1.1–1.3)</td>
<td>1.2 (1.1–1.3)</td>
</tr>
<tr>
<td>NT-pro-BNP (ng/L; $n = 1098$)</td>
<td>104.8 (57.8–205.6)</td>
<td>104.1 (57.7–205.5)</td>
<td>99.5 (56.1–185.8)</td>
<td>97.6 (56.4–185.5)</td>
</tr>
</tbody>
</table>

Values are numbers (percentages) for categorical variables, means ± SD for normal distributed continuous variables, and medians (interquartile range) for skewed variables. Macroalbuminuria is defined as UAER > 200 μg/min and microalbuminuria, UAER between 20 and 200 μg/min. Glomerular filtration rate was estimated using the established modification of diet in renal disease equation.

HF, heart failure; ECG-LVH, electrographic left ventricular hypertrophy; NT-pro-BNP, N-terminal fragment of pro-brain natriuretic peptide.
Table 2  Heart failure incidence in relation to urinary albumin excretion rate in the total sample, stratified by presence (n = 380) or non-presence (n = 386) of anti-hypertensive treatment at baseline

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted (model A)</th>
<th>Adjusted for established risk factors (model B)</th>
<th>Adjusted for established risk factors, C-reactive protein, and clamp glucose disposal rate (model C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of anti-hypertensive treatment at baseline [n = 380/343/327 (model A/B/C)]</td>
<td>HR (95% CI) P-value</td>
<td>HR (95% CI) P-value</td>
<td>HR (95% CI) P-value</td>
</tr>
<tr>
<td>Log UAER, per 1 SD (1.4 µg/min)</td>
<td>1.00 (0.77–1.29) 0.98</td>
<td>1.03 (0.77–1.39) 0.85</td>
<td>1.02 (0.76–1.38) 0.89</td>
</tr>
<tr>
<td>Non-presence of anti-hypertensive treatment at baseline [n = 726/647/621 (model A/B/C)]</td>
<td>Log UAER, per 1 SD (1.1 µg/min)</td>
<td>1.63 (1.32–2.01) &lt;0.0001</td>
<td>1.56 (1.21–2.03) 0.001</td>
</tr>
</tbody>
</table>

Data are Cox proportional HRs (95% CIs), unadjusted (model A), adjusted for established risk factors for HF [acute MI before baseline, acute MI during follow-up (modelled as a time-dependent covariate), hypertension, diabetes, left ventricular hypertrophy, smoking, body mass index, and glomerular filtration rate estimated from creatinine; model B], and adjusted for C-reactive protein, clamp glucose disposal rate and established risk factors (model C). UAER, urinary albumin excretion rate; HF, heart failure; HR, hazard ratio; CI, confidence interval.

Figure 2  Nelson–Aalen plot of cumulative incidence rate of heart failure in the sample, free from heart failure and valvular disease, and without antihypertensive treatment at baseline, by two groups of urinary albumin excretion rate (above vs. below or at the median, 4.7 µg/min).

Analyses in participants without diabetes, micro- or macroalbuminuria, or myocardial infarction before baseline or during follow-up

In the subsample without participants with anti-hypertensive treatment or diabetes at baseline (Table 3, upper part), 1 SD increase in log UAER was associated with 45–64% higher risk for HF in crude and multivariable models adjusting for established and more recently described risk factors for HF (models A–C).

Discussion

Principal findings

In this community-based sample of elderly men free from HF and valvular disease at baseline, UAER predicted HF incidence independent of both established and more recently described risk factors for HF in individuals without antihypertensive treatment at baseline, whereas the association was attenuated in individuals with treatment. Interestingly, this association was largely independent of C-reactive protein, insulin sensitivity, and GFR, and to some extent of cystatin C and NT-pro-BNP. Furthermore, UAER remained an independent predictor of HF incidence also in a subsample of non-diabetics and in a subsample without myocardial infarction (either at baseline or during follow-up), suggesting that UAER also predicts the incidence of non-ischaemic HF.

Comparisons with previous studies

Our finding that increased levels of albuminuria independently predict HF incidence is in accordance with previous studies in individuals with prevalent cardiovascular disease and/ or diabetes.16–21 We are aware of only one previous community-based study that has investigated the association of albuminuria and HF incidence.32 In this study by Kistorp et al., an increased urinary albumin/creatinine ratio did not predict HF incidence. It should be noted that in that study, HF incidence was considered a secondary endpoint, and there was only a low number of HF events during follow-up (n = 19). One reason why our findings differ from that report may be that we had a larger sample size, a greater number of HF events, and consequently, greater statistical power to detect associations. Moreover, in this study, effect modification by anti-hypertensive medication was not investigated. To our knowledge, the present study is the first to show that albuminuria is an independent risk factor for HF in the community.

Recent community-based studies have suggested a linear relation between the level of albuminuria and the risk of cardiovascular events and that even very low degrees of...
Low-grade albuminuria and the incidence of HF

Table 3  Heart failure incidence in relation to urinary albumin excretion rate in subsamples of participants without anti-hypertensive treatment and diabetes at baseline (n = 672), macro- or microalbuminuria at baseline (n = 642), or myocardial infarction at baseline or during follow-up (n = 659)

<table>
<thead>
<tr>
<th>Unadjusted (model A)</th>
<th>Adjusted for established risk factors (model B)</th>
<th>Adjusted for established risk factors, C-reactive protein, and clamp glucose disposal rate (model C)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants without anti-hypertensive treatment or diabetes [n = 672/604/579 (model A/B/C)]</strong></td>
<td><strong>Log UAER, per 1 SD (1.0 μg/min)</strong></td>
<td><strong>Log UAER, per 1 SD (0.6 μg/min)</strong></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>P-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>1.64 (1.31–2.05)</td>
<td>&lt;0.0001</td>
<td>1.45 (1.02–2.06)</td>
</tr>
<tr>
<td><strong>Participants without anti-hypertensive treatment or macro- and microalbuminuria [n = 642/574/553 (model A/B/C)]</strong></td>
<td><strong>Log UAER, per 1 SD (0.6 μg/min)</strong></td>
<td><strong>Log UAER, per 1 SD (1.1 μg/min)</strong></td>
</tr>
<tr>
<td>1.53 (1.18–1.98)</td>
<td>0.001</td>
<td>1.65 (1.31–2.09)</td>
</tr>
</tbody>
</table>

Data are Cox proportional HR (95% CI), unadjusted (model A), adjusted for established risk factors for HF [acute MI before baseline, acute MI during follow-up (modelled as a time-dependent covariate), hypertension, diabetes, left ventricular hypertrophy, smoking, body mass index, and albumin filtration rate estimated from creatinine; model B], and adjusted for C-reactive protein, clamp glucose disposal rate and established risk factors (model C). UAER, urinary albumin excretion rate; HF, heart failure; HR, hazard ratio; CI, confidence interval.

uninary albumin excretion, well below the conventional threshold for microalbuminuria (≤20 μg/g creatinine), may be of prognostic importance in the general population. In the present study, the incidence rates in the quartiles of UAER portrayed no obvious deviation from linearity, which lends support to the notion of a linear association. On the other hand, the fact that the association of albuminuria to HF incidence was no longer significant after exclusion of participants with micro- or macro-albuminuria could indicate that the association of albuminuria and HF incidence is driven by participants above the microalbuminuria cut-off. However, it should be noted that after the stratification for anti-hypertensive medication, our sample size was not sufficiently large to properly investigate this issue and thus no firm conclusions can be drawn from the present study about this issue. Further large-scale community-based studies are warranted to identify clinically relevant cut-off points for albuminuria as a predictor for HF.

Possible mechanisms

The basic mechanisms of the link between albuminuria and cardiovascular disease are incompletely understood. It is not likely that a very small concentration of albumin in the urine in itself is the direct cause of the increased risk for HF. There are, however, several other potential explanations for the association between albuminuria and increased risk of HF in the present study. First, increased levels of albuminuria are strongly associated with both established risk factors for HF as well as more recently described risk factors such as insulin resistance, inflammation, cystatin C, and NT-pro-BNP. The fact that UAER remained significantly associated with HF incidence even after adjustment for all of these risk factors suggests that confounding by these factors may not be the sole explanation for our findings. Secondly, albuminuria is also closely related to non-established cardiovascular risk factors, such as homocysteine, haemostatic factors, and endothelial function that may translate into a higher HF risk. In fact, albuminuria has been suggested to be an indicator of not only glomerular endothelial dysfunction, but also of generalized vascular dysfunction. Thirdly, the fact that UAER was also a risk factor for non-ischaemic HF in the present study suggests that albuminuria also reflects a direct myocardial pathology not mediated via coronary atherosclerosis. This is supported by the close relation between microalbuminuria and left ventricular hypertrophy and remodelling. Fourth, elevated albumin excretion could be an indicator of subclinical renal insufficiency, which has previously been shown to predict HF incidence in the elderly. However, albuminuria remained a significant predictor in all models in the present study even after adjustment for GFR and cystatin C. Finally, higher UAER could be a consequence of renal venous congestion, the latter being an early manifestation of preclinical HF. The reason for the effect modification by anti-hypertensive medication in the present study is not clear. The role of albuminuria in the development of cardiovascular disease appears multifaceted; previous studies have shown that albuminuria is an independent predictor for both hypertension and diabetes, whereas poorly controlled hypertension and diabetes are strong independent predictors for the development of microalbuminuria. Thus, it is possible that high levels of albuminuria reflect somewhat different cardiovascular pathology at different stages of the complex causal pathways leading to cardiovascular disease. Treatment with anti-hypertensive agents lowers both blood pressure and albuminuria and improves cardiac function. It is possible that these multiple effects of anti-hypertensive medication influence the prognostic ability of albuminuria. The lack of association in the participants undergoing anti-hypertensive treatment suggests that albuminuria does not portray any prognostic information in these individuals. However, albuminuria has previously been shown to be a strong independent risk factor for HF also in patients undergoing anti-hypertensive treatments in several large-scale intervention trials. As the strata with anti-hypertensive treatment were fairly small (n = 380), our results should be interpreted with caution.
Further studies are warranted to elucidate whether effect modification by anti-hypertensive medication is present in other community-based cohorts.

Clinical implications
In a recent report from de Zeeuw et al., a 50% reduction in albuminuria after 6 months of anti-hypertensive treatment was associated with 27% reduction in HF risk in patients with diabetic nephropathy. Additional randomized intervention trials are needed in order to elucidate whether albuminuria reduction lowers HF incidence also in the general population.

Strengths and limitations
The strengths of this study include the large, community-based population, the detailed characterization of potential confounders, and the long follow-up period. Furthermore, all HF cases were validated, limiting the inclusion of false-positive cases. Another strength of the study is that urinary albumin excretion was assessed in timed urine samples collected overnight rather than in a spot sample. There are some limitations to this study. As we only examined men of the same age with a similar ethnic background, this study has an unknown generalizability to women or other age and ethnic groups. Another limitation of the study is that we used the presence of an interim myocardial infarction during follow-up as a proxy for coronary heart disease. Even if this method is an established method for examining ‘non-ischaemic’ HF, it would be better to assess non-ischaemic HF in a more specific way, e.g. by examining all subjects with coronary angiography. Further, it is possible that individuals who choose to participate in a cohort study are healthier than those who do not attend (i.e. the ‘healthy cohort effect’). This might have led to some underestimation of the associations found in our study and driven the results towards the null hypothesis. Also, since the HF diagnosis was based on review of medical records without detailed information on the HF aetiology, it was not possible to examine whether albuminuria was associated differently to HF of different causal mechanisms. Finally, multiple statistical tests were performed in our investigation. However, the consistency of results across different models makes it unlikely that the observed associations arose owing to multiple testing.

Conclusions
In conclusion, low-grade albuminuria was a strong predictor of HF incidence predominantly in individuals without anti-hypertensive treatment. The association was independent of established risk factors, C-reactive protein, and insulin resistance in our large community-based sample of elderly men and in subsamples without individuals with diabetes at baseline and myocardial infarction at baseline or during follow-up. Our data are consistent with the hypothesis that glomerular endothelial dysfunction, as indicated by low-grade albuminuria, is an important marker of future HF events in individuals without anti-hypertensive treatment in the community. Further studies are warranted to evaluate the clinical implications of our findings.

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Conflict of interest: J.A. has received consultancy fees from HemoCue.

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