Towards improved risk prediction of incident atrial fibrillation and progression of atrial fibrillation

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DOI:
10.33612/diss.136550017

Part 1

Risk markers for incident atrial fibrillation

Chapter 2

Relation of renal dysfunction with incident atrial fibrillation and cardiovascular morbidity and mortality: The PREVEND study.

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ABSTRACT AND KEYWORDS

Aims. Renal dysfunction is a risk factor for cardiovascular disease, including atrial fibrillation (AF) and mortality. However, the exact pathobiology linking different renal dysfunction measures, such as albumin excretion or glomerular filtration rate (GFR), to cardiovascular- and AF risk are unclear. In this study we investigated the association of several renal function measures and incident AF, and whether the relation between renal measures and outcomes is modified by AF.

Methods. We examined 8,265 individuals (age 49±13 years, 50% women) included in the PREVEND study. We used albumin excretion (morning void and 24-hours urine samples), serum creatinine, cystatin C, and Cystatin C-based, creatinine-based, and creatinine-cystatin C-based GFR as renal function measures.

Results. During a follow-up of 9.8±2.3 years, 267 participants (3.2%) developed AF. In the multivariate-adjusted model, GFR, estimated by creatinine, cystatin C, or the combination was not associated with incident AF. However, increased albumin excretion was strongly associated with incident AF; urine albumin concentration and excretion ($HR_{\text{morning void}}$ 1.10, P=0.005, and $HR_{\text{24-hr collection}}$ 1.05, P=0.033) and albumin creatinine ratio ($HR_{\text{morning void}}$ 1.05, P=0.010, and $HR_{\text{24-hr collection}}$ 1.06, P<0.001). Interaction-terms of incident AF and renal measures were not significant for incident cerebrovascular events, peripheral vascular events, ischemic heart disease, heart failure and mortality.

Conclusion. In this community-based cohort, increased albumin excretion, and not GFR, was associated with incident AF, independent of established cardiovascular risk factors. Incidence of AF did not largely alter the association of renal dysfunction and cardiovascular outcomes.

Keywords. Atrial fibrillation; Renal function; Epidemiology; Risk factor

CONDENSED ABSTRACT

In 8,265 individuals from the community-based PREVEND study, albuminuria was associated with incident AF, independent of established cardiovascular risk factors. The association between albumin excretion and incident AF was not found for GFR. Incidence of AF did not significantly alter the association of renal dysfunction and cardiovascular outcomes.

What's New

- Albuminuria, a measure of renal dysfunction, but not GFR, is related to incidence of AF, independent from other cardiovascular risk factors in the general population.
- Albuminuria can be measured in first morning void or 24-hour urine collection, the association with incident AF was comparable for both methods.
- Albumin excretion can be used in those with and without incident AF to predict cardiovascular events, since the association of renal measures and incident cerebrovascular events, peripheral vascular events, ischemic heart disease, heart failure, and all-cause mortality, was largely similar in those with and without incident AF.

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia and is a major public health problem with an incidence of 1 in 4 for persons over the age of 55 years in the Netherlands.[1] Individuals with AF are at increased risk for cardiovascular complications such as stroke, dementia, heart failure, and death.[2,3] Known risk factors and conditions associated with AF are advancing age, male sex, diabetes mellitus, hypertension, valve disease, myocardial infarction, heart failure, and obesity.[2] More recently, renal dysfunction has also been related to incident AF.[4,5] Renal dysfunction is casually related to hypertension, left ventricular hypertrophy, inflammation, hypercoagulability, and may activate the renin-angiotensin-aldosterone system.[6] All these mechanisms also increase the susceptibility of the development of AF. Thus far, no studies have studied different measures of renal function such as serum creatinine or cystatin C, estimated glomerular filtration rates, and albumin excretion, in relation to development of AF.

There is abundant data that reduced renal function is associated with increased cardiovascular events, in both populations with and without prevalent AF.[7,8] Also in prevalent AF populations, renal dysfunction has been associated with increased stroke risk.[9] Whether the relation of renal function and outcomes is modified by AF has not been investigated. It has been postulated that in the setting of AF, the associated potential decreased cardiac output, potential electrolyte disturbances, changed pharmacokinetics of medication used in AF, or associated comorbidities,[10] may influence renal measures in AF, and potentially its relation with cardiovascular outcome.

Although the exact pathobiology linking renal dysfunction to cardiovascular and AF risk are unknown; both albumin excretion and glomerular filtration rates were demonstrated independent markers of cardiovascular risk.[11] Albumin excretion is mainly a consequence of glomerulus damage, and is considered a marker of systemic vascular damage or microvascular disease. The above led to the idea that there may be differences between renal measures and the association with AF, and that the magnitude of effect of renal measures and cardiovascular outcome may be influenced by AF.

METHODS

Population. The PREVEND was founded in 1997, and includes a cohort of 8,592 individuals, enriched with individuals with a urinary albumin excretion >10ml/L in their morning void, since the purpose study was to investigate the natural course of increased levels of albuminuria and its relation to cardiovascular and kidney disease.[12] In total, 7,786

individuals with an urinary albumin excretion >10mg/L and 3,395 individuals with an urinary albumin excretion <10mg/L were invited to the PREVEND outpatient clinic. The final cohort consisted of 8,592 individuals. At the baseline visit, in addition to detailed information about demographics, health behaviours, anthropometric measurements, cardiovascular and metabolic risk factors, also blood samples and two 24-hour urine samples on 2 consecutive days were collected. For present analysis, we excluded participants without any ECG (n=248), and those with prevalent AF (n=79), leaving 8,265 individuals for analysis. Characteristics and outcomes of the excluded individuals were comparable to the included population. The PREVEND study was approved by the institutional medical Ethics Committee and conducted in accordance with the Declaration of Helsinki. All individuals provided written informed consent.

Follow up. The follow-up duration was calculated as the time between the baseline visit to the last contact date, death, or December 31, 2008, whichever came first.

Covariate definitions. Systolic and diastolic blood pressures were measured by using an automatic Dinamap XL Model 9300 series device, and were calculated as the mean of the last two measurements of the two visits. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or self-reported use of antihypertensive medication. The ratio of weight to height squared (kg/m2) was used for calculation of body mass index (BMI). Obesity was defined as a BMI >30 kg/m^2. Diabetes mellitus was defined as a fasting plasma glucose >7.0 mmol/L (126 mg/dL), a nonfasting plasma glucose >11.1 mmol/L, or use of anti-diabetic medication. Hypercholesterolemia was defined as total serum cholesterol above 6.5 mmol/l (251 mg/dl), or serum cholesterol above 5.0 mmol/l (193 mg/dl) in those with previous myocardial infarction or when lipid-lowering medication was used. Smoking was defined as using nicotine within the previous year. Alcohol consumption was defined as 2 or more alcoholic drinks per week. Previous myocardial infarction or stroke was defined as hospitalization for myocardial infarction or stroke for at least 3 days. A committee of heart failure experts adjudicated all individuals with heart failure at baseline according to previously published criteria.[12] Peripheral artery disease was defined as an ankle-brachial index <0.9.

Renal measures. Serum cystatin C were determined by nephelometry (BNII, Dade Behring Diagnostics, Marburg, Germany). Intra- and interassay coefficients of variation were <4.1% and 3.3% for cystatin C. Serum and urine creatinine were determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, New York, USA) using an automated enzymatic method. The intra- and interassay coefficients of variation of serum creatinine were 0.9% and 1.1%.[13] The intra- and interassay coefficients of variation of urine creatinine were 0.9% and 2.9%.[14] We defined several GFR measures. The

GFR based on serum concentration of creatinine (eGFR-creatinine) was estimated using the Simplified Modification of Diet in Renal Disease formula (MDRD). The GFR based on serum concentration of cystatin C (eGFR-cystatin C) was estimated with the Chronic Kidney Disease (CKD) Epidemiology Collaboration equation for cystatin C. The GFR based on serum concentrations of both creatinine and cystatin C (eGFR-creatinine-cystatin C) was estimated using the Epidemiology Collaboration equation for creatinine-cystatin C. Urinary albumin was determined by a commercial immunoturbidimetry assay with a sensitivity of 2.3 mg/L and interassay and intra-assay coefficients of variation of 4.4% and 4.3%, respectively (BNII, Dade Behring Diagnostics, Marburg, Germany). Urine albumin concentration was measured in the first morning void. Urine albumin excretion was measured in two consecutive 24-hour urine collections, and the average value was calculated. Urine albumin-creatinine ratio was calculated based on both the first morning void and 24-hour urine collections.

Atrial Fibrillation and cardiovascular events during follow up. Incident AF ascertainment has been described in detail previously.[2] Briefly, incident AF was diagnosed if either atrial flutter or AF was present on a 12-lead ECG obtained at 1 of the 3 PREVEND follow-up visits or at an outpatient visit or hospital admission in the 2 hospitals in the city of Groningen. For the date of incident AF, the date of the first ECG with a definite diagnosis of AF or atrial flutter was used. Information on cardiovascular events was obtained from PRISMANT, the Dutch national registry of hospital discharge diagnoses. Ischemic heart disease consisted of acute myocardial infarction [ICD code 410], acute and subacute ischemic heart disease [ICD 411], coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, cerebrovascular events consisted of occlusion or stenosis of the precerebral (ICD 433) or cerebral arteries (ICD 434), subarachnoid haemorrhage (ICD 430), and peripheral vascular events consisted of other vascular interventions such as percutaneous transluminal angioplasty or bypass grafting of aorta and peripheral vessels. A committee of heart failure experts adjudicated all heart failure events according to previously published criteria. Data on mortality were obtained through the municipal registration.

Statistical analysis. A statistical weighting method was used in the prespecified Cox proportional-hazards regression analyses, to adjust the overselection of individuals with microalbuminuria at baseline, and allow generalization of results to the general population. In the weighted Cox regressions, people with urinary albumin excretion <10 mg/l had a weighing factor of 11.92 and people with urinary albumin excretion >10 mg/l had a weighing factor of 1.66. The numbers 11.92 and 1.66 were selected based on the unequal inclusion probabilities.

Individual characteristics were presented as mean ± standard deviation or median (range) for continuous variables and counts with percentages for categorical variables. We performed 3 prespecified Cox proportional-hazards regression models to relate the renal measures to incident AF. Model 1 were univariate analyses, in Model 2, we adjusted for established AF risk factors (age, sex, BMI, antihypertensive treatment, previous stroke, heart failure, previous myocardial infarction, diabetes, peripheral artery disease, smoking, PR-interval duration, NT-proBNP).[15] In Model 3 we adjusted for all covariates included in Model 2, plus interim myocardial infarction and heart failure, occurring after baseline before incident AF. The proportionality assumption was checked by calculating the Schoenfeld residuals, and where needed time-varying covariates were included to avoid proportionality violations. We used Cox time-dependent regression analyses, to study whether the association of renal measures and cardiovascular outcome, is modified by AF, by including interaction terms of renal measures and AF as time-varying covariate. We adjusted for age, sex, heart failure, antihypertensive drug use, diabetes, previous stroke, previous myocardial infarction, peripheral artery disease, N-terminal prohormone of brain natriuretic peptide (NT-proBNP). All analyses were performed using R package (version 3.03)**,** and a p-value <0.05 was considered statistically significant.

RESULTS

Individual characteristics. The study sample consisted of 8,265 individuals with mean age of 49±13 years, half of them were women. Individual characteristics are shown in **Table 1**. In total, 466 individuals (5.7%) had an estimated creatinine-based GFR<60 ml/min/1.73m^2, and 1762 (21.3%) had albuminuria (urinary albumin concentration ≥20 mg/L).

Renal measures and incident atrial fibrillation. Total follow-up duration was 81,018 person-years. During a mean follow-up of 9.8 years, 267 (3.2%) individuals developed incident AF. None of the GFR measures was associated with incident AF, with no differences between the GFR based on creatinine, cystatin C or combined method. Albumin excretion was strongly associated with incident AF (**Table 2**). Higher urine albumin concentration and albumin creatinine ratio, measured in first morning void samples, were associated with an increased risk of incident AF (multivariable-adjusted hazard ratio was 1.12 [95% confidence interval (CI) 1.04-1.20] and 1.05 [95% CI 1.00-1.11], respectively). The association remained unchanged after adjustment for interim heart failure or myocardial infarction occurring after baseline but before incident AF. A Kaplan Meier curve for three groups based on urine albumin concentration (<20, 20-200, and >200 mg/L) determined in first morning void samples is shown in **Figure 1**. Also, higher urine

Table 1. Individual characteristics.

Clinical characteristics	Total population (n=8265)
Age (years)	49±13
Male sex	4120 (49.8%)
Caucasian	7844 (94.9%)
Smoked	3670 (44.7%)
Alcohol consumption	4873 (59.3%)
Diastolic blood pressure (mmHg)	74±10
Systolic blood pressure (mmHg)	129±20
Peripheral artery disease	291 (3.7%)
BMI (kg/m^2)	26±4
Antihypertensive therapy	1098 (16.1%)
NT-proBNP (ng/L)	37 (17-73)
High sensitive CRP (mg/L)	1.3 (0.6-2.9)
Previous stroke	57 (0.7%)
PR-interval duration (ms)	158 (143-172)
Diabetes	310 (3.8%)
Heart rate (bpm)	69±10
Hypercholesterolemia	361 (4.6%)
Hypertension	2237 (27.8%)
Previous myocardial infarction	251 (3.1%)
Heart failure	18 (0.2%)
Renal measures	
Serum creatinine (umol/L)	82 (74-92)
Serum cystatin C (mg/dL)	0.77 (0.69-0.87)
eGFR creatinine-based(ml/min/1.73m^2)	80 (71-90)
eGFR cystatin- C (ml/min/1.73m^2)	100 (85-118)
eGFR creatinine-cystatin-C(ml/min/1.73m^2)	91 (80-104)
Urinary albumin concentration(mg/L)	6.9 (4.16-13.03)
Urinary albumin excretion(mg/24hrs)	9.4 (6.3-17.63)
Albumin creatinine ratio(mg/g)	7.0 (4.8-13.0)

Abbreviations: BMI=body mass index; CRP=C-reactive protein; eGFR=estimated glomerular filtration rate; NT-proBNP=N-terminal prohormone of brain natriuretic peptide

albumin excretion and albumin creatinine ratio, determined from 24-hour urine collections, were associated with an increased risk of incident AF, also after adjustment for interim heart failure or myocardial infarction (multivariable-adjusted hazard ratio was 1.07 [95% CI 1.02-1.11] for urine albumin concentration, and 1.07 [95% CI 1.04-1.10] for albumin creatinine ratio). The association remained also unchanged after adjustment for interim heart failure or myocardial infarction.

Table 2. Association of renal function measure and incident AF.

Variable	Model 1		Model 2		Model 3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Creatinine (per 10umol/L)	1.07(1.05-1.09)	<0.001	0.88(0.76-1.02)	0.092	0.90(0.78-1.04)	0.155
Cystatin C (per 0.3mg/dL)	1.49(1.38-1.61)	<0.001	0.99(0.80-1.23)	0.945	0.98(0.76-1.26)	0.852
eGFR creatinine (per 15ml/min/1.73m^2)	0.73(0.62-0.86)	<0.001	1.21(1.00-1.48)	0.052	1.19(0.97-1.45)	0.096
eGFR cystatin C (per 15ml/min/1.73m^2)	0.70(0.64-0.77)	<0.001	0.95(0.87-1.03)	0.216	0.96(0.88-1.05)	0.350
eGFR creatinine-cystatin C (per 15ml/min/1.73m^2)	0.60(0.53-0.68)	<0.001	1.01(0.93-1.09)	0.886	1.01(0.92-1.10)	0.897
Urine albumin concentration (per 100mg/l) in first-morning void sample	1.19(1.15-1.23)	<0.001	1.12(1.04-1.20)	0.002	1.10(1.03-1.17)	0.005
Albumin creatinine ratio (per 100mg/g) in first-morning void sample	1.10(1.07-1.12)	<0.001	1.05(1.00-1.11)	0.038	1.05(1.00-1.10)	0.033
Urine albumin excretion (per 100mg/24 hrs) in 24-hrs urine collection	1.10(1.08-1.12)	<0.001	1.07(1.02-1.11)	0.003	1.05(1.01-1.09)	0.010
Albumin creatinine ratio (per 100mg/g) in 24-hrs urine collection	1.09(1.07-1.10)	<0.001	1.07(1.04-1.10)	<0.001	1.06(1.02-1.09)	<0.001

Model 1: Unadjusted.
Model 2: Adjusted for age, sex, BMI, antihypertensive treatment, previous stroke, heart failure, previous myocardial infarction, diabetes, peripheral artery disease, smoking, PR-interval duration, NT-proBNP.
Model 3: Adjusted for age, sex, BMI, antihypertensive treatment, heart failure, previous myocardial infarction, diabetes, peripheral artery disease, smoking, PR-interval duration, NT-proBNP, interim myocardial infarction, interim heart failure.
Abbreviations: BMI=body mass index; CI=confidence interval; eGFR=estimated glomerular filtration rate; HR=hazard ratio; NT-proBNP=N-terminal prohormone of brain natriuretic peptide.

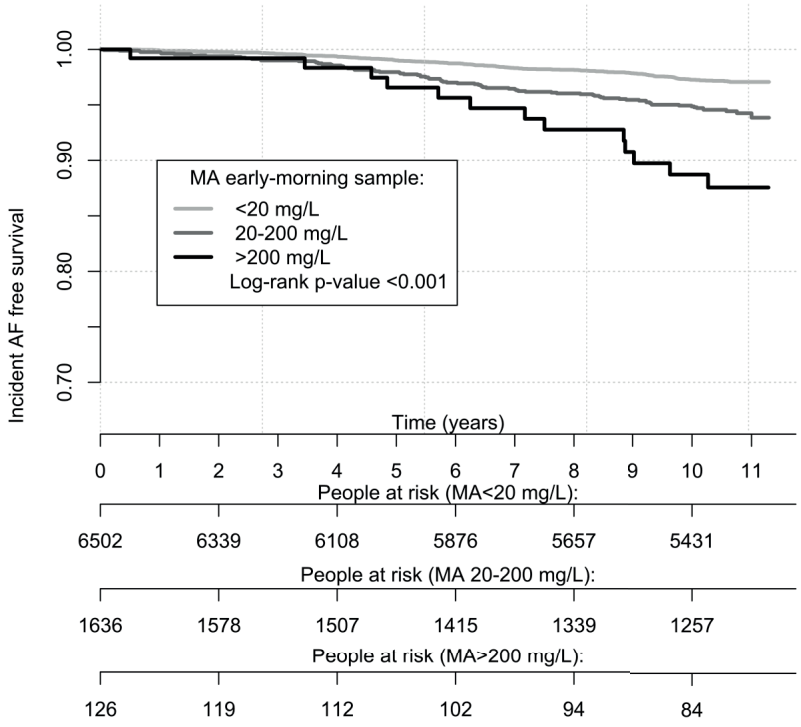

Figure 1. Kaplan-Meier estimates of the cumulative incidence of AF, according to three groups of urine albumin concentration (<20, 20-200, and >200 mg/L).

Relation between renal measures and cardiovascular outcome in atrial fibrillation. We studied whether the association of renal function and cardiovascular outcome is different in individuals with incident AF versus those without incident AF. We included interaction terms of each renal measure and incident AF as time-varying covariate, into the regression model. Except for cystatin C, there were no significant interaction terms between renal function measures and outcome, implying no different relation between renal measure and cardiovascular outcome (**Table 3**). There was one significant interaction between cystatin C and incident AF for the association with the combination of cerebrovascular events, peripheral vascular events, ischemic heart disease (hazard ratio 0.72 [95% CI 0.57-0.91], p=0.007). The hazard ratio of cystatin C to predict the combination of cerebrovascular events, peripheral vascular events, ischemic heart disease is lower in individuals with incident AF compared to those without AF.

Table 3. Association of renal function measure and incident cardiovascular events, heart failure and death, modified by time-varying AF.[1]

Interaction term of renal measure and time-varying AF	Combination of cerebrovascular events, peripheral vascular events, ischemic heart disease		Heart failure[3]		Death	
	Multivariate HR[2] (95% CI)	P-value	Multivariate HR[2] (95% CI)	P-value	Multivariate HR[2] (95% CI)	P-value
Creatinine (per 0.05units)*AF	0.77(0.52-1.13)	0.186	1.42(0.87-2.32)	0.162	1.08(0.83-1.40)	0.578
Cystatin C (per 0.1units)*AF	0.72(0.57-0.91)	0.007	0.74(0.37-1.46)	0.386	0.78(0.56-1.08)	0.128
eGFR creatinine (per 0.1units)*AF	1.41(0.62-3.23)	0.415	0.57(0.29-1.11)	0.097	0.80(0.50-1.28)	0.342
eGFR cystatin C (per 0.1units)*AF	1.15(0.73-1.80)	0.548	1.01(0.62-1.65)	0.967	1.27(0.90-1.78)	0.178
eGFR creatinine-cystatin C (per 0.1units)*AF	1.40(0.65-3.00)	0.389	0.66(0.33-1.33)	0.246	1.06(0.61-1.84)	0.826
Urine albumin concentration in first-morning void sample (per 1.0 units)*AF	1.24(0.63-2.43)	0.531	0.80(0.27-2.42)	0.695	0.69(0.31-1.53)	0.361
Albumin creatinine ratio in first-morning void sample (per 1.0 units)*AF	1.28(0.64-2.57)	0.486	1.58(0.62-4.07)	0.340	0.97(0.39-2.41)	0.953
Urine albumin excretion in 24-hrs urine collection (per 0.5 units)* AF	1.20(0.89-1.63)	0.240	0.86(0.51-1.44)	0.569	0.91(0.65-1.28)	0.585
Albumin creatinine ratio in 24-hrs urine collection (per 1.0 units)*AF	1.56(0.87-2.81)	0.139	0.69(0.22-2.15)	0.518	0.77(0.39-1.54)	0.466

No significant interaction means no difference in the association between renal function measure and cardiovascular outcome for the AF versus no AF group. A significant interaction means that the association between renal function and cardiovascular outcome is different for those with AF versus no AF. When the hazard ratio of the interaction-term is greater than 1, the association between the renal function measure and cardiovascular event stronger for the AF group than it is for the no AF group.

[1]All renal function measures were logarithmically transformed and centered around their means.

[2]Adjusted for sex, age, AF, NT-proBNP, antihypertensive drug use, diabetes, peripheral artery disease, previous myocardial infarction, prevalent heart failure, previous stroke and the renal function measure variable (as included in the interaction-term) itself.

[3]In the analysis with outcome heart failure, individuals with prevalent HF were excluded.

Abbreviations: AF=atrial fibrillation; CI=confidence interval; eGFR=estimated glomerular filtration rate; HR=hazard ratio; NT-proBNP=N-terminal prohormone of brain natriuretic peptide

DISCUSSION

In present community-based cohort we found that albumin excretion was associated with incident AF, and not plasma markers of renal function or GFR. These associations were independent of established cardiovascular risk factors, and not mediated via the development of heart failure or myocardial infarction during follow up. Furthermore, the association of renal measures and incident cerebrovascular events, peripheral vascular events, ischemic heart disease, heart failure and all-cause mortality, was largely similar in those with and without incident AF.

Renal dysfunction and incident AF. We used both first morning void samples and 24-hour urine collections, and albumin excretion was predictive for AF, independent of the sampling method. The relation between renal dysfunction and risk of AF has been established in several cohorts, albeit that not all studies found an association. This may be the result of different populations studied, and different measures of renal function used. Especially in high-risk populations such as coronary heart disease, or hypertension; loss of GFR, measured mainly using creatinine, but also cystatin C has been used, was associated with prevalent AF.[16] In longitudinal, community-based cohorts the relation between GFR and incident AF was less prominent. In elderly included in the Cardiovascular Health Study no relation was found.[17] In the Atherosclerosis Risk in Communities (ARIC) study and Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, however, a relation between GFR and incident AF was found.[4, 5] Those studies, and others also found a positive relation between albumin excretion measured in the first morning void sample and incident AF.[4, 5] From prior studies it is known that GFR is especially predictive in populations with chronic kidney disease,[18] and less predictive in the general population with predominantly healthy individuals with normal renal function. In the general population, however, albumin excretion is more predictive than GFR of future cardiovascular events.[19] So, both albumin excretion and GFR are markers of renal dysfunction, and as recently demonstrated in a large meta-analysis, both have additional value when predicting future cardiovascular events.[11] More mechanistically, albumin excretion is considered a marker of systemic vascular damage or microvascular disease, where GFR is more a marker of kidney disease.[11] This may explain our divergent findings on albumin excretion and GFR in our community-based cohort. The mechanisms underlying the association between renal dysfunction and incident AF, may relate to the association of renal dysfunction, and especially albumin excretion, and endothelial dysfunction and hypertension, and is considered a marker of generalized vascular disease.[6] Both clinical and subclinical vascular disease are associated with incident AF. Also, renal dysfunction is associated with inflammation and hypercoagulability, and both are a known pathophysiological mechanisms involved in development and progression of

AF.[20] Furthermore, renal dysfunction may activate the renin-angiotensin-aldosterone system and lead to salt and water retention, causing left ventricular hypertrophy, and subsequent diastolic dysfunction with volume overload of the atria, which in turn may lead to AF by atrial dilatation. More studies are needed to determine whether there is a direct causal link between renal dysfunction and incident AF.

Renal dysfunction and cardiovascular outcomes. Several studies have shown that renal disease measured by a decrease in GFR or increase in albumin excretion are associated with increased risk of death and cardiovascular events in patients with coronary artery disease and in general population.[8] There are also studies performed solely in patients with AF. In those studies renal dysfunction is associated with an increased risk of stroke.[9] However, it is unknown whether effect modification by incident AF is present. We found no significant interaction between each renal measures and AF when studying the combination of cerebrovascular events, peripheral vascular events, ischemic heart disease, heart failure and mortality, with one exception. So, we found no robust evidence that the relation between renal measures and cardiovascular outcome is different when AF occurs. Therefore, we cannot confirm the postulation by Boriani et al. that in AF, the decreased cardiac output, electrolyte disturbances, changed pharmacokinetics, or associated comorbidities,[10] may influence the relation between renal measures and cardiovascular outcome in AF. This may imply that specific risk prediction models including renal measures for populations with and without AF are not necessary.

Strengths and limitations. Strengths of our study are the large and contemporary community-based cohort, with a detailed clinical and renal assessment and a strong validation of incident AF and cardiovascular events. We had in PREVEND a wide range of renal measures available; albumin excretion (morning void and 24-hours urine samples), serum creatinine, cystatin C, and Cystatin C-based, creatinine-based, and creatinine-cystatin C-based GFR.

Most limitations are the result of the observational design of the community-based cohort study. Despite the statistical weighting method to adjust for overselection of individuals with microalbuminuria at inclusion, our sample may not be completely similar to a randomly selected population cohort, and comparisons with other cohorts should be made carefully. We may have not captured all asymptomatic paroxysmal AF episodes because we did not have continuous ECG recordings. Further, treating physicians were informed about the presence of AF or other undiagnosed cardiovascular diseases, treatment was left to the discretion of the physician. We did not have detailed information about the AF-related therapies. Data on obstructive sleep apnea, and valvular disease were widely captured in our cohort. Since the majority of patients were of

European ancestry, and had no or only mildly reduced renal dysfunction, results cannot be extrapolated to individuals with more impaired renal function, nor to other races and ethnicities. Furthermore, the number of individuals with incident AF was modest, which reduced our statistical power to detect significant interactions in the secondary analyses.

Conclusion. In this community-based cohort, increased albumin excretion, and not GFR, was associated with incident AF, independent of established cardiovascular risk factors. Presence of AF did not largely alter the association of renal dysfunction and cardiovascular outcomes.

Funding. The PREVEND study was supported by the Dutch Kidney Foundation (grant E0.13) and the Netherlands Heart Foundation (grant NHS2010B280). Dr. Rienstra is supported by a grant from the Netherlands Organization for Scientific Research (Veni grant 016.136.055).

CONFLICTS OF INTEREST. NONE DECLARED.

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