Low-Grade Albuminuria and Incidence of Cardiovascular Disease Events in Nonhypertensive and Nondiabetic Individuals

The Framingham Heart Study

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Background—Data are limited with regard to the relations of low-grade albuminuria (below the microalbuminuria threshold) and incidence of cardiovascular disease (CVD) events in nondiabetic, nonhypertensive individuals.

Methods and Results—We examined the association of urinary albumin excretion (spot urine albumin indexed to creatinine [UACR]) and the incidence of CVD events and all-cause mortality in 1568 nonhypertensive, nondiabetic Framingham Offspring Study participants (mean age, 55 years; 58% women) free of CVD. On follow-up (median, 6 years), 54 participants (20 women) developed a first CVD event, and 49 (19 women) died. After adjustment for established risk factors, increasing UACR was associated with greater risk of CVD (hazards ratio [HR] per SD increment in log UACR, 1.36; 95% CI, 1.00 to 1.87) and death (HR per SD increment in log UACR, 1.55; 95% CI, 1.10 to 2.20). Participants with UACR greater than or equal to the sex-specific median ($\geq$3.9 μg/mg for men, $\geq$7.5 μg/mg for women) experienced a nearly 3-fold risk of CVD (adjusted HR, 2.92; 95% CI, 1.57 to 5.44; $P<0.001$) and a borderline significantly increased risk of death (adjusted HR, 1.75; 95% CI, 0.95 to 3.22; $P=0.08$) compared with those with UACR below the median. The increased CVD risk associated with UACR at or above the median remained robust in analyses restricted to individuals without microalbuminuria (n=1470) and in subgroups with intermediate (n=1469) and low (n=1186) pretest probabilities of CVD.

Conclusions—In our community-based sample of middle-aged nonhypertensive, nondiabetic individuals, low levels of urinary albumin excretion well below the current microalbuminuria threshold predicted the development of CVD. Our observations add to the growing body of evidence that challenges the notion that UACR <30 μg/mg indicates "normal" albumin excretion. **(*Circulation*. 2005;112:969-975.)**

Key Words: endothelium ■ epidemiology ■ mortality ■ risk factors

Microalbuminuria, defined as an urine albumin to urine creatinine ratio (UACR) of 30 to <300 μg/mg,[1] is an established risk factor for cardiovascular morbidity and mortality and for end-stage renal disease in individuals with an adverse cardiovascular risk profile such as those with hypertension or diabetes mellitus.[2–7] Accordingly, national and international guidelines recommend screening for microalbuminuria in patients with diabetes or hypertension.[8–10]

It is less clear, however, whether screening for microalbuminuria should be extended to the general population or to individuals at lower risk of cardiovascular disease (CVD) such as nondiabetics or nonhypertensives. Investigators have postulated that microalbuminuria may be a marker of risk even in apparently healthy people because it reflects vascular damage in the kidneys and systemic endothelial dysfunction (the Steno hypothesis).[11,12] Indeed, microalbuminuria has been associated with increased incidence of coronary heart disease events[13,14] and elevated risk of all-cause and CVD mortality[15,16] in some community-based samples. It is noteworthy that 3 of the 4 prior community-based studies included varying proportions of hypertensive individuals[13–15]; 2 studies also included diabetics[14,15]; and 1 study included people with prior myocardial infarction or stroke.[15] Additionally, these community-based investigations reported on dif-

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ferent outcome events and yielded inconsistent results with regards to the prognostic significance of levels of albuminuria below the microalbuminuria threshold. For instance, in the European Prospective Investigation Into Cancer in Norfolk (EPIC-Norfolk) study, low-grade albuminuria was not associated with increased risk of coronary heart disease, but microalbuminuria was.[14] In the Nord-Trondelag Health (HUNT) study, low-grade albuminuria (>60th percentile [6.7 μg/mg]) was associated with increased all-cause mortality, but that study did not evaluate the incidence of CVD.[16] Moreover, the HUNT study sample included untreated hypertensives, and exclusion of these individuals attenuated the risk associated with low-grade albuminuria. In the Prevention of Renal and Vascular Endstage Disease (PREVEND) study, a more graded increase in vascular mortality was observed across the entire range of UACR.[15] Thus, 2 key questions about the prognostic significance of albuminuria remain unanswered. First, does the presence of low-grade albuminuria (below the threshold of microalbuminuria, ie, UACR <30 μg/mg) in nonhypertensive, nondiabetic individuals portend an increased risk of future CVD events or death? And if so, at what level of urine albumin excretion is the increased risk evident? The answers to these questions may provide valuable insights into what constitutes "normal" urine albumin excretion.

To answer these questions, we examined the relations of urine albumin excretion to incidence of CVD events and death in a community-based sample of nonhypertensive, nondiabetic individuals. Additionally, we evaluated the association of low-grade albuminuria with vascular risk and all-cause mortality in individuals without microalbuminuria and in those with low to intermediate pretest probability of cardiovascular events as defined by the Framingham Risk Score.[17,18]

Methods

Study Sample

The design and selection criteria of the Framingham Heart Study have been previously described.[19] We evaluated 3532 subjects who attended the sixth examination cycle (1995 through 1998) of the Framingham Offspring Study. We excluded 1964 participants for the following reasons, hierarchically: prevalent CVD (n=415), prevalent hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications; n=1188),[9] prevalent diabetes mellitus (fasting glucose ≥126 mg/dL or use of insulin or hypoglycemic medications; n=82),[8] missing blood sugar (n=21) or serum creatinine (n=14) data, serum creatinine >2.0 mg/dL (n=1), unavailable urinary albumin data (n=235), UACR ≥300 mg/g (macroalbuminuria;, n=4), missing covariates (n=3), and lack of follow-up data (n=1). After exclusion, 1568 nonhypertensive, nondiabetic participants remained eligible. All participants gave written informed consent, and the Institutional Review Board at Boston Medical Center approved the study protocol.

Clinical Evaluation

At the baseline examination, all attendees underwent a physical examination—including medical history, blood pressure examinations, and anthropometry—and laboratory assessment of vascular risk factors as previously described.[19]

Urinary Albumin Excretion

A single-void urine sample at the baseline examination was used to measure UACR (mg/g). The urinary albumin concentration was determined by immunoturbidometry (Tina-Quant Albumin Assay, Roche Diagnostics), and the urinary creatinine concentration was measured with a modified Jaffe method. Intra-assay coefficients of variation were 7.2% and 2.3%, respectively, for the urine albumin and urine creatinine assays.[20] The UACR measured in a spot urine sample is highly correlated with 24-hour urine albumin excretion.[21–23]

Outcomes

All Framingham Heart Study participants are under continuous surveillance for the occurrence of CVD events and death. A committee of 3 investigators reviewed all suspected cardiovascular events by examining hospitalization records, physician office notes, and pathology reports. Investigators adjudicating end points had no knowledge of the results of UACR measurements. A Framingham Heart Study neurologist evaluated participants with suspected cerebrovascular events, and a separate review committee that included a neurologist adjudicated these events.

Incident CVD events during follow-up were defined as recognized or unrecognized myocardial infarction, angina pectoris, coronary insufficiency, coronary heart disease death, stroke, transient ischemic attack, congestive heart failure, or intermittent claudication. For secondary analyses, we defined incident "hard" CVD as recognized myocardial infarction, coronary heart disease death, stroke, or congestive heart failure. Criteria for the diagnoses of cardiovascular events have been described elsewhere.[24]

Statistical Analyses

We examined the association between baseline levels of UACR and the following prespecified end points during follow-up: death from any cause and incident CVD. Secondary analyses restricted the definition of incident CVD to include only hard CVD events. We analyzed UACR both as a categorical variable (at or above versus below the sex-specific median to account for sex-related differences in the distribution of urine creatinine excretion[25]) and as a continuous variable with natural logarithmic transformation to normalize the skewed distribution. The median was chosen as a cut point a priori on the basis of the modest number of events observed in this low-risk sample. The relation between sex-specific tertiles of UACR and outcomes was investigated as exploratory analyses.

Incidence rates were calculated as events per 1000 person-years of follow-up. We used sex-pooled multivariable-adjusted Cox proportional-hazards regression analysis[26] to examine the association of UACR with the incidence of CVD and death. Proportionality of hazards was confirmed by examination of Kaplan-Meier curves. Multivariable models were adjusted for sex and the following covariates defined at baseline: age, smoking, systolic and diastolic blood pressures, serum total/HDL cholesterol, body mass index (BMI), and serum creatinine. In exploratory analyses, we also adjusted for fasting blood glucose and LDL and HDL cholesterol instead of total/HDL cholesterol.

Additional Analyses

Researchers[27] have raised the possibility that associations of low-grade albuminuria with increased mortality risk in some prior reports[16] may be "driven" by the small proportion of individuals with microalbuminuria. Therefore, we repeated our analyses in a subsample without microalbuminuria (n=1470). Also, investigators have reported a positive association of microalbuminuria with the Framingham Risk Score.[28] To avoid possible excessive influence of a few high-risk individuals in our sample, we repeated our analysis, restricting it to groups with <20% (n=1469) and <10% (n=1186) 10-year probabilities of coronary heart disease as defined by the Framingham Risk Score.[17] The sex-specific median for the whole sample was used for these analyses.

We incorporated first-order statistical interaction terms into the multivariable-adjusted regression models (at or above versus below

TABLE 1. Baseline Characteristics by Sex-Specific UACR Above and Below the Median

	Whole Sample	UACR Below the Median	UACR at or Above the Median
Participants, n	1568	783	785
Women, n (%)	913 (58)	456 (58)	457 (58)
Age, y	55±9	54±9	56±9
Body mass index, kg/m^2	26.9±4.7	27.3±4.8	26.4±4.5
Systolic blood pressure, mm Hg	118±12	118±12	119±12
Diastolic blood pressure, mm Hg	73±8	73±8	73±8
Optimal blood pressure,* n (%)	764 (49)	405 (52)	359 (46)
Normal blood pressure,* n (%)	436 (28)	210 (27)	226 (29)
High-normal blood pressure,* n (%)	368 (23)	168 (21)	200 (25)
Total/HDL cholesterol ratio	4.2±1.5	4.3±1.5	4.1±1.5
Serum creatinine, mg/dL	1.1±0.2	1.1±0.2	1.1±0.2
UACR, μg/mg†	10.8±20.8	2.6±1.9	19.0±27.0
Microalbuminuria,* n (%)	98 (6)	0 (0)	98 (12)
Smoking, n (%)	263 (17)	130 (17)	133 (17)
Impaired fasting glucose, n (%)	127 (8)	68 (9)	59 (8)

UACR median: men, 3.9 μg/mg; women, 7.5 μg/mg. Data are mean±SD unless indicated.

*Optimal is systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg; normal is systolic blood pressure 120 to 129 mm Hg and diastolic blood pressure 80 to 84 mm Hg; high-normal is systolic blood pressure 130 to 139 mm Hg and diastolic blood pressure 85 to 89 mm Hg; and microalbuminuria is UACR 30 to 299 μg/mg.

†To convert from μg/mg to mg/mmol, multiply by 0.112.

median UACR) to evaluate variations in the relations of UACR to outcomes according to sex and baseline age, BMI, blood pressure, and smoking.

We constructed receiver-operating characteristic (ROC) curves[29] to examine the performance characteristics of UACR over the entire range of values for predicting each outcome event. Because the distribution of log UACR in women is shifted to the right relative to men, we standardized the distributions for each sex separately to a mean of 0 and an SD of 1 to combine sexes in the ROC analyses. We identified the UACR sex-specific percentile value that maximized the sum of sensitivity and specificity (cut point that weighs true positives and false negatives equally) corresponding to the point on the ROC curve closest to the upper left corner. For each outcome, we evaluated the sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values corresponding to the sex-specific median UACR cut point and to the optimal UACR percentile identified by the ROC analyses. The area under the ROC curve (AUC) was used as an index of global test performance, with an AUC of 0.5 indicating no discrimination ability.

A 2-sided value of $P<0.05$ was considered statistically significant. All analyses were performed on SAS version 8 for Windows (SAS Inc).[30]

Results

Baseline Characteristics

Table 1 displays the baseline characteristics of our sample. Nearly half of our middle-aged to elderly sample (age range, 29 to 83 years) had optimal levels of blood pressure, and only 8% had impaired fasting glucose.

Incidence of CVD Events and Death

During a median follow-up of 6 years (range, 0.3 to 8.8 years), 49 participants (19 women) died, 54 (20 women) experienced a first CVD event, and 29 (14 women) had a first hard CVD event. Table 2 provides the incidence rates of CVD and all-cause mortality in participants below compared with those at or above the sex-specific UACR median. The incidence rates of outcomes were higher with UACR values at or above the median. Figure 1 displays the Kaplan-Meier curves for survival free of CVD in the 2 groups and confirms the higher incidence of CVD events in people with UACR above the sex-specific median (log rank $P<0.001$).

TABLE 2. Event Rates in Individuals Below Versus at or Above the Median of UACR

Outcome	UACR Below the Median (n=783)	UACR at or Above the Median (n=785)
Total CVD		
Events, n	14	40
Event rate (per 1000 person-years of follow-up)	2.9	8.8
Hard CVD		
Events, n	6	23
Event rate (per 1000 person-years of follow-up)	1.26	5.00
Total mortality		
Events, n	16	33
Event rate (per 1000 person-years of follow-up)	3.3	7.1

Multivariable Analyses

Cardiovascular Disease

After adjustment for established cardiovascular risk factors, an SD increment in log UACR was associated with an increased risk of CVD (hazard ratio [HR], 1.36; 95% CI, 1.00 to 1.87; $P=0.05$; Figure 2). Participants with UACR at or above the sex-specific median had a nearly 3-fold risk of CVD compared with participants with UACR below the median (HR, 2.92; 95% CI, 1.57 to 5.44; $P=0.0007$; Figure 2). The increased vascular risk associated with UACR at or

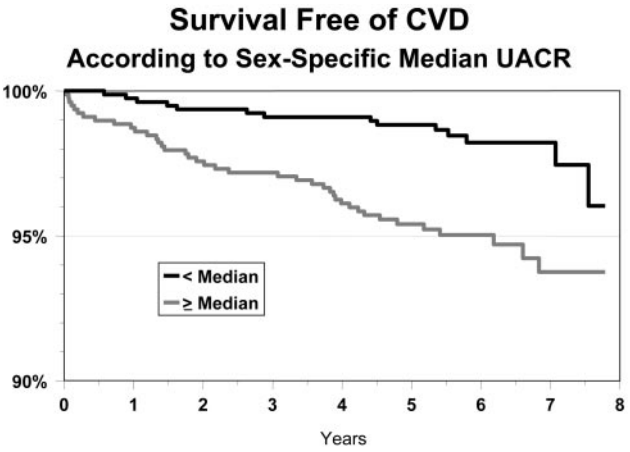

Figure 1. Kaplan-Meier curves showing survival free of CVD over follow-up period in individuals above vs those below sex-specific median of UACR.

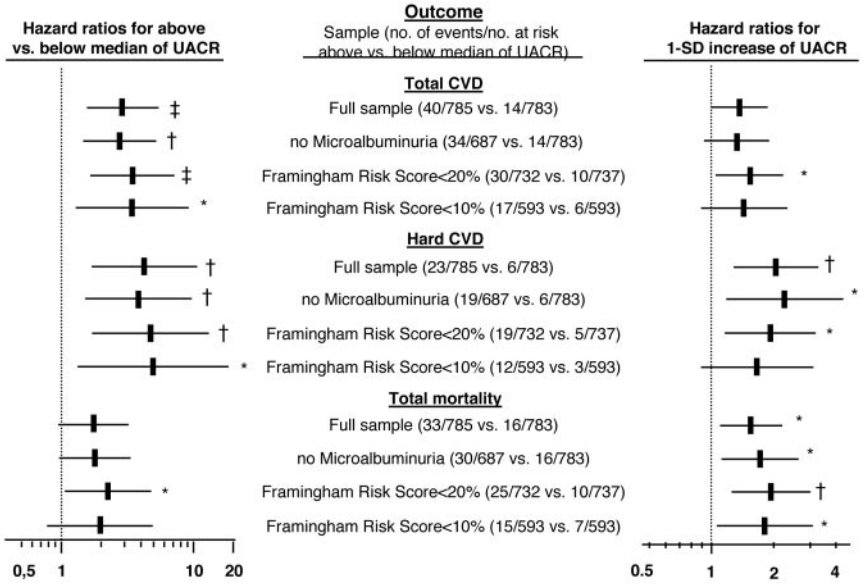

Figure 2. Multivariable HRs (shown on logarithmic scale along *x* axis) for at or above vs below sex-specific median UACR and for 1-SD increase in log-UACR for development of CVD and all-cause mortality during follow-up in entire sample, in individuals of from microalbuminuria, and subsamples with 10-year coronary disease probability (estimated with the Framingham Risk Score) <20% and <10%. All models are adjusted for age, sex, smoking, systolic blood pressure, diastolic blood pressure, total/HDL cholesterol, BMI, and serum creatinine. **P*<0.05, †*P*<0.01, and ‡*P*<0.001.

above the median was consistent in analyses restricted to people without microalbuminuria and in the subsamples with 10-year coronary heart disease probabilities of <20% and <10% (Figure 2). These results remained robust on additional adjustment for fasting glucose and on incorporating LDL cholesterol and HDL cholesterol separately in the model instead of total/HDL-cholesterol (HR for UACR at or above the sex-specific median, 2.70; 95% CI, 1.45 to 5.03; *P*<0.002). In secondary analyses, participants in the highest sex-specific tertile of UACR had a 2-fold increased risk of CVD (Figure 3). No significant effect modification according to sex or baseline age, BMI, blood pressure, or smoking was observed.

In analyses relating UACR to incidence of hard CVD events, an SD increase in log UACR was associated with a 2-fold increased risk of hard CVD events in the whole sample (HR, 2.05; 95% CI, 1.28 to 3.29; *P*<0.003) and in the subgroup without microalbuminuria (Figure 2). Participants with UACR at or above the sex-specific median experienced a 4-fold increased risk of hard CVD in the whole sample (HR, 4.26; 95% CI, 1.70 to 10.66; *P*=0.002) and in the subgroup without microalbuminuria (Figure 2). The association of UACR at or above the median with increased risk of hard CVD events was maintained in subsamples with 10-year predicted probabilities of coronary events <20% and <10% (Figure 2). Participants in the highest sex-specific tertile of UACR had a >3-fold increased risk for hard CVD events (Figure 3).

Total Mortality

An SD increase in UACR was associated with a 55% higher mortality risk in the whole sample after adjustment for established cardiovascular risk factors (HR, 1.55; 95% CI, 1.10 to 2.20; *P*=0.014). Furthermore, an SD increase in UACR was associated with a 72% to 94% higher mortality risk in the subgroup without microalbuminuria and in subsamples with Framingham Risk Scores <20% and <10% (Figure 2). UACR values at or above the median were associated with a 75% to 80% increased mortality risk that was of borderline statistical significance in both the whole sample (HR, 1.75; 95% CI, 0.95 to 3.22; *P*=0.08) and those without microalbuminuria (Figure 2). A statistically significant 2.25-fold increased risk and a nonsignificant 2-fold increased mortality risk were observed in those with 10-year coronary disease probabilities <20% and <10%, respectively (Figure 2). In secondary analyses, participants in the highest sex-specific tertile of UACR had a >2-fold increased risk for total mortality (Figure 3).

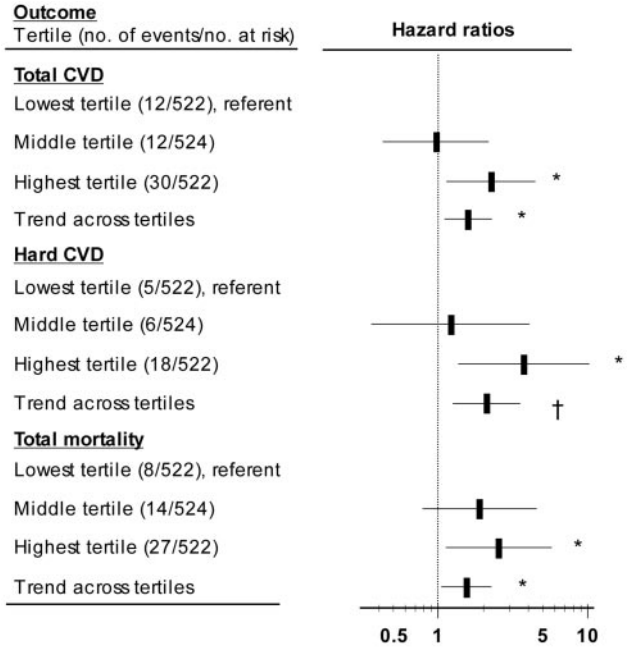

Figure 3. Multivariable HRs (shown on logarithmic scale along *x* axis) for tertiles of UACR and for trend across UACR tertiles for development of CVD and all-cause mortality during follow-up in entire sample. For men, lowest tertile was <2.4 μg/mg, middle tertile was ≥2.4 to <5.5 μg/mg, and highest tertile was ≥5.5 μg/mg. For women, lowest tertile was <4.3 μg/mg, middle tertile was ≥4.3 to <11.9 μg/mg, and highest tertile was ≥11.9 μg/mg. All models are adjusted for age, sex, smoking, systolic and diastolic blood pressures, total/HDL cholesterol, BMI, and serum creatinine. **P*<0.05, †*P*<0.01.

Performance Characteristics of UACR for Predicting Outcome Events

In ROC analyses (bivariate analyses predicting events with log UACR), the AUC ranged from 0.63 for CVD to 0.65 for death to 0.68 for hard CVD events. The sensitivity, specificity, PPV, and NPV, respectively, for the sex-specific median cut point were as follows: 0.74, 0.51, 0.05, and 0.98 for CVD; 0.79, 0.50, 0.03, and 0.99 for hard CVD; and 0.67, 0.50, 0.04, and 0.98 for death. In ROC analyses, the sex-specific 55th percentile value (4.4 μg/mg in men, 9.1 μg/mg in women) yielded the most optimal performance for CVD (sensitivity, 0.74; specificity, 0.57; PPV, 0.06; NPV, 0.98). The UACR thresholds that provided optimal performance for hard CVD and death were the sex-specific 64th percentile (5.3 μg/mg in men, 10.8 μg/mg in women; sensitivity, 0.76; specificity, 0.64; PPV, 0.04; NPV, 0.99) and 62nd percentile (5.1 μg/mg in men, 10.3 μg/mg in women; sensitivity, 0.63; specificity, 0.63; PPV, 0.05; NPV, 0.98), respectively.

Discussion

Principal Findings

Our study has 2 principal findings. First, low-grade urinary albumin excretion was associated with increased risk of CVD and mortality in nonhypertensive, nondiabetic individuals and in individuals with low to intermediate pretest probability of vascular events. Second, the increased risk was evident at levels well below the current diagnostic threshold for microalbuminuria. Although vascular and mortality risks were elevated in participants with low-grade albuminuria, the increases were modest in terms of the absolute event rates.

Comparisons With the Literature

Previous reports clearly show that the presence of microalbuminuria and macroalbuminuria is associated with a higher risk of CVD incidence and mortality in high-risk individuals[7] and in patients with hypertension[3,4] or diabetes.[5,6] Furthermore, a few prior investigators have reported that microalbuminuria predicts CVD and mortality in community-based samples.[13–16] As noted, these prior reports included hypertensives and/or diabetics.[13–16] Whereas investigators adjusted for hypertension and diabetes in multivariable analyses, it is possible that residual confounding exists because microalbuminuria may be a marker of target organ damage and chronicity of blood pressure elevation or diabetes. The present study extends prior research by demonstrating that albuminuria levels well below the levels that constitute microalbuminuria are associated with increased risk of cardiovascular events and death even in nondiabetic, nonhypertensive individuals with a low to intermediate pretest probability of CVD.

Possible Mechanisms for Observed Association

Microalbuminuria is associated with several CVD risk factors such as diabetes,[31] nondiabetic degrees of hyperglycemia,[32] hypertension,[33] dyslipidemia,[31] and smoking.[34] We excluded individuals with hypertension and diabetes from our sample, and increased UACR predicted CVD and mortality risk incrementally over other established risk factors in our study.

Several studies have shown that microalbuminuria is associated with low-grade systemic inflammation[35,36] and endothelial dysfunction.[37–40] Thus, our data are consistent with the hypothesis that glomerular endothelial dysfunction, as indicated by low-grade albuminuria, is an important marker of future CVD events even in individuals free of diabetes and hypertension.

Clinical Implications

Our data suggest that very low degrees of urinary albumin excretion, below the conventional threshold for microalbuminuria (UACR, 30 μg/mg), may be of prognostic importance. The group with UACR values at or above the sex-specific median (≥3.9 μg/mg for men and ≥7.5 μg/mg for women) was associated with a 3-fold risk for developing CVD compared with the group with UACR below the median values. Our findings support the notion that the contemporary threshold for microalbuminuria may be higher than the cut point at which increased vascular risk begins and challenge the designation of the entire range below 30 μg/mg as normoalbuminuria.[1,7]

The high relative risk for CVD associated with values above the sex-specific median UACR notwithstanding, it is important to emphasize that its utility as a screening tool in low-risk samples may be quite limited, as evidenced by the low PPV for CVD in our sample and as noted by others.[41] ROC analyses identified UACR thresholds with optimal performance characteristics for predicting outcome events (values ranging from the sex-specific 55th to 64th percentiles for different outcomes). However, these thresholds were also associated with low PPVs for outcomes uniformly. Overall, the AUCs for different outcomes were <0.70, indicating suboptimal performance of UACR overall.

It is important to point out that our observational data cannot suggest that lowering albuminuria will improve vascular prognosis. Several large trials have demonstrated that a reduction in albuminuria is associated with slowed progression of renal disease.[42–44] However, similar data with regard to CVD outcomes are limited. A few recent reports indicate that lowering albuminuria levels reduces the incidence of cardiovascular events,[42,45,46] although other studies do not.[47] Additional large intervention trials are needed before it will be possible to evaluate the potential utility for measuring low-grade albuminuria in nonhypertensive, nondiabetic individuals in the community.

Study Strengths and Limitations

The strengths of our investigation include the large community-based sample of individuals without hypertension or diabetes, the multivariable-adjusted analyses, and the continuous surveillance for CVD events blinded to albuminuria status.

There are several limitations of our study. First, urinary albumin was assessed on only a single urine specimen in our sample. Prior studies suggested that urinary albumin levels may exhibit considerable intraindividual variability.[48,49] Nonetheless, national practice guidelines recommend the use of spot specimens for UACR because the test is easily performed in the clinic and the results correlate well with

those of 24-hour collections.[50] Furthermore, any potential measurement error (in UACR) would result in an underestimation of the true risk associated with UACR. Second, the number of events occurring in our sample was small, as would be expected given its low-risk nature. Consequently, we had too few events in those with UACR values below the median to examine this group separately. Also, the modest number of events precluded a detailed assessment of the linearity of the association of UACR with outcomes. Our results indicate that continuous UACR values yielded more statistical significance for predicting total mortality, whereas the sex-specific median thresholds performed better for CVD. Further studies of larger samples are required to elucidate the relations of UACR to individual outcomes across the entire distribution of values. Third, the present investigation focused on a single biomarker of vascular risk. Additional studies are warranted that compare the prognostic significance of UACR with that of other novel risk factors reflecting inflammation, fibrinolysis, insulin resistance, and dyslipidemia. Finally, our sample was predominantly white and middle-aged to elderly, limiting the generalizability of our results to other ethnicities/races and younger individuals.

Conclusions

Our observations support the notion that low-grade albuminuria in apparently healthy individuals may be a marker for subclinical vascular damage that predisposes to future CVD and death. Further studies are warranted to evaluate the clinical implications of our findings.

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