Extended Prognostic Value of Urinary Albumin Excretion for Cardiovascular Events

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ABSTRACT

Because urinary albumin excretion (UAE) is a marker of cardiovascular (CV) risk, some have proposed screening the general population; however, it is unknown how the predictive power of a single screening value changes over time. In this study, data of 8496 individuals in a community-based, prospective cohort were used to evaluate this question. For each doubling of baseline UAE, the hazard ratio (HR) for a CV event was 1.36 (95% confidence interval [CI] 1.31 to 1.42). Baseline UAE similarly predicted events occurring >5 yr after baseline, suggesting that it remains a good predictor during at least the first 5 yr after measurement. Approximately 4 yr after baseline, UAE was measured again in 6800 individuals. Once again, high UAE (>75th percentile) predicted subsequent CV events, whether defined using the baseline UAE or follow-up UAE (HR 3.39 [95% CI 2.58 to 4.45] and HR 2.50 [95% CI] 1.90 to 3.29, respectively; $P = 0.3$ for difference). Finally, compared with individuals with consistently low UAE, individuals who progressed from low to high UAE during follow-up had a significantly higher risk for CV events (HR 3.68; 95% CI 2.45 to 5.53). In conclusion, UAE remains a good predictor of CV events during the first 5 yr after measurement, but repeating the measurement several years later also detects progression of UAE, which is also associated with increased CV risk. Future studies are required to determine the optimal interval of repeat testing and its cost-effectiveness.

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Elevated urinary albumin excretion (UAE) is a powerful independent predictor of cardiovascular (CV) morbidity and mortality in the general population.[1–3] As we showed previously, microalbuminuria (urinary albumin concentration >10 mg/L) has a relatively high prevalence in the general white population, being approximately 7.2%. Although it is frequently stated that such an elevated UAE is mainly the consequence of diabetes or hypertension, approximately 80% of these individuals reported not to have diabetes or hypertension, and in only approximately 30% of these latter individuals could previously undetected diabetes or hypertension be shown.[4,5] Importantly, it has been shown that treatment associated with a decrease in UAE results in a reduction of the associated CV risk.[6,7] On the basis of these observations, implementation of screening programs in the general population to detect high UAE has been proposed.[8]

As shown by the Prevention of Renal and Vascular Endstage Disease (PREVEND) study, mass screening of the general population for high UAE can be done relatively easily by the use of prescreening.[9] In this setting, individuals are initially asked to mail a portion of a first morning void urine sample to a central laboratory for measurement of albumin concentration or, alternatively, the albumin-to-creatinine ratio. Individuals who are found to have

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increased levels of albuminuria are then invited for further evaluation, which includes confirmation of increased albuminuria, by either collection of two 24-h urine collections or two first morning void urine samples.[8,10,11] The possibility of this approach gives screening for high UAE an important advantage above mass screening for other widely known CV risk factors such as high cholesterol or hypertension, because measurement of these latter risk factors will require an individual to visit a laboratory or clinic, respectively.

It is unknown at what frequency screening for UAE in the general population needs to be repeated.[8] To our knowledge, only two published studies have investigated the predictive value of a single UAE measurement over time. In the first study, Damsgaard *et al.*[12] found that in 211 individuals with and 216 individuals without diabetes surviving the first 5 yr after the UAE measurement, the initially measured UAE was no longer predictive for all-cause mortality. That study thus suggested that screening should be repeated at relatively short intervals (*e.g.*, after 1 or 2 yr). In contrast, results of the second study of Neil *et al.*,[13] using data of 236 individuals with diabetes, showed that the predictive value of UAE for all-cause mortality remains present even 5 yr after measurement. The conflicting findings of these studies may be due to the small number of individuals in both studies. Interpretation of these studies is furthermore hampered by the fact that both studies used all-cause mortality as end point, whereas UAE is mainly used to predict CV morbidity and mortality. Finally, as mainly individuals with diabetes have been studied, it remains difficult to extrapolate these findings to the general population.

In this study, we therefore investigated the course of the predictive value of a UAE measurement for CV morbidity and mortality over time using data from a large community-based cohort study. We investigated furthermore the effect of repeating the UAE measurement after approximately 4 yr after the baseline screening for CV risk stratification.

RESULTS

The baseline characteristics of the 8496 individuals are shown in Table 1. Starting at baseline screening, we observed 58,176 person-years during a median follow-up of 7.5 yr (interquartile range 6.9 to 7.8). In total, 558 CV events occurred in this period, giving a cumulative incidence of 6.6% and an incidence rate of 9.4 per 1000 person-years. The unadjusted CV event rate increased with increasing UAE, being 5.8, 14.5, 22.3 and 26.3 per 1000 person-years, for a UAE <15, 15 to 30, 30 to 150, and >150 mg/24 h, respectively ($P = <0.001$ for trend).

In Table 2, the hazard ratio (HR) for a CV event associated with baseline UAE is given after increasing follow-up. Individuals who were censored because of an event or loss to follow-up were removed stepwise from analyses using 1-yr intervals. Thus the HR is given for individuals still under observation after 1 yr, 2 yr, *etc.* of follow-up. Consequently, the number of individuals under observation decreased from 8496 at baseline to 7609 after 5 yr of follow-up. The number of observed person-years after exclusion of the first 5 yr of follow-up decreased to 18.928 and the number of events to 194. It can be seen in Table 2 that with increasing follow-up, there seemed to be a slight decrease in CV risk predicted by the baseline UAE, with the HR going from 1.36 to 1.30 for each doubling of UAE (*e.g.*, 20 *versus* 40 mg/24 h). Also, the 95% confidence interval (CI) widened slightly with increasing follow-up. Accordingly, when receiver operating characteristic (ROC) curves were computed using *baseline* UAE as predictor of CV events, there was a minimal decrease in the area under the curve when using only individuals still under observation after 5 yr of follow-up (HR 0.65; 95% CI 0.61 to 0.69) compared with the area under the curve using follow-up starting at baseline (HR 0.67; 95% CI 0.65 to 0.70). This difference, however, was not statistically significant ($P = 0.18$). Using categories of UAE—<15, 15 to 30, 30 to 150, and >150 mg/24 h—with individuals with UAE <15 mg/24 h as reference group, the HR from baseline were for the respective UAE categories 2.35 (95% CI 1.89 to 2.92), 3.82 (95% CI 3.12 to 4.68), and 4.5 (95% CI 3.24 to 6.3), respectively. After exclusion of the first 5 yr of follow-up, the HR were 1.72 (95% CI 1.17 to 2.53), 3.14 (95% CI 2.23 to 4.43), and 2.92 (95% CI 1.53 to 5.60). When we performed sensitivity analyses by repeating the analyses after excluding individuals with diabetes, the results were similar (Table 2). In addition, exclusion of individuals with a history of myocardial infarction at baseline or known hypertension also did not essentially change the results. Furthermore, to detect a possible effect of collection errors of the 24-h urine samples on our results, we repeated our measurements after excluding individuals with a >20% difference in 24-h creatinine excretion

Table 1. Characteristics of the 8496 individuals at baseline[a]

Characteristic	Value
Age (yr)	49.2 (12.7)
Male (*n* [%])	4247 (50.0)
White (*n* [%])	8333 (98.1)
BMI (kg/m^2; mean [SD])	26.1 (4.2)
Smoking (*n* [%])	3215 (37.8)
SBP (mmHg; mean [SD])	129 (20)
DBP (mmHg; mean [SD])	74 (10)
Use of antihypertensive medication (*n* [%])	1315 (15.5)
Cholesterol (mmol/L; mean [SD])	5.6 (1.1)
Use of lipid-lowering medication (*n* [%])	533 (6.3)
Diabetes (*n* [%])	318 (3.7)
Use of antidiabetic medication (*n* [%])	152 (1.8)
History of myocardial infarction (*n* [%])	513 (6.0)
eGFR (ml/min per 1.73 m^2; mean [SD])	81 (15)
UAE (mg/24 h; median [IQR])	9.4 (6.3 to 17.6)
UAE categories (mg/24 h; *n* [%])	
0 to 15	5983 (70.4)
15 to 30	1270 (14.9)
30 to 300	1123 (13.2)
>300	120 (1.4)

[a]BMI, body mass index; DBP, diastolic BP; eGFR, estimated GFR; IQR, interquartile range; SBP, systolic BP.

Table 2. Course of CV risk associated with baseline UAE during follow-up[a]

Year	Total Population					Individuals without Diabetes				
	n	Observed Person-Years	No. of Events	HR	95% CI	*n*	Observed Person-Years	No. of Events	HR	95% CI
0	8496	58,176	558	1.36	1.31 to 1.42	8178	57,500	504	1.37	1.31 to 1.43
1	8388	51,111	491	1.35	1.29 to 1.41	8085	49,367	449	1.37	1.31 to 1.43
2	8258	42,789	410	1.34	1.28 to 1.41	7962	41,344	373	1.36	1.29 to 1.43
3	8060	34,628	333	1.33	1.26 to 1.41	7781	33,472	307	1.35	1.28 to 1.43
4	7850	26,589	264	1.35	1.27 to 1.43	7582	25,786	244	1.36	1.28 to 1.45
5	7609	18,928	194	1.30	1.21 to 1.40	7357	18,309	181	1.31	1.22 to 1.42

[a]Risk is presented as the HR for a cardiovascular event for each doubling of UAE. Individuals with an event or who were lost to follow-up during the first, second year, etc. were successively removed from analyses.

between the first and second day of urine collection or, alternatively, as a >10% difference. This was done on the basis of the assumption that the day-to-day 24-h creatinine excretion in an individual reflects his or her muscle mass and is expected to be near constant. Also, analyses were repeated after adjustment for start of antihypertensive, lipid-lowering, or antidiabetic medication after the baseline screening. Finally, we repeated our analyses using all-cause mortality as outcome (440 events). These sensitivity analyses did not essentially change our findings.

In 6800 individuals of our cohort, the UAE was measured at baseline and repeated after approximately 4 yr of follow-up. After this follow-up screening, we observed 22,059 person-years during a median follow-up of 3.3 yr (interquartile range 2.8 to 3.8). In total, 208 events occurred in this period, giving a cumulative incidence of 3.1% and an incidence rate of 9.4 per 1000 person-years. In Figure 1A, the CV event–free survival curves after follow-up screening are shown according to the presence or absence of a high UAE (above or below the 75th percentile respectively; see the Concise Methods section). The survival curves for the 6800 individuals were drawn using first the *baseline* UAE measurement to define high and low UAE and then repeated by using the *follow-up* UAE measurement to define high and low UAE. Note that to allow for an easy comparison, we projected the survival curves using either the *baseline* or the *follow-up* measurement in the same graph. The curves in Figure 1A suggest that use of the repeat UAE measurement at follow-up results in a better stratification for CV risk than use of the *baseline* UAE measured 4 yr before; however, the differences between the curves of the two measurements in Figure 1A were not statistically significant ($P = 0.3$ for difference between curves for high UAE). The HR to get a CV event after follow-up screening for individuals with a high UAE was 2.50 (95% CI 1.90 to 3.29) using the UAE measurement from *baseline* screening and 3.39 (95% CI 2.58 to 4.45) using the UAE measurement from *follow-up* screening. When analyses were repeated after defining high UAE as a UAE above the median baseline value, the results were comparable (Figure 1B; $P = 0.4$ for difference between curves for high UAE), with the HR being 2.10 (95% CI 1.57 to 2.80) using the UAE measurement from *baseline* screening and 2.71 (95% CI 2.01 to 3.65) using the UAE measurement from the *follow-up* screening. Also, when we repeated the analyses after excluding individuals with diabetes and additionally individuals with known hypertension or using all-cause mortality as outcome (134 events after follow-up screening), results were essentially similar.

Finally, we looked at the effect of change in UAE during follow-up for assessment of CV risk. In Table 3, the risk for a CV event after follow-up screening is shown according to change in UAE from baseline to follow-up screening. Individuals who had an increase in UAE ($n = 494$) had a significantly higher CV risk (HR 3.68; 20.6 events per 1000 person-years) compared with individuals whose UAE remained low during follow-up (HR 1.00; 5.6 events per 1000 person-years). Conversely, the CV risk for individuals who showed a decrease in UAE during follow-up ($n = 480$) was significantly lower (1.84; 10.2 events per 1000 person-years) than the CV risk for individuals whose UAE remained high (HR 3.62; 20.9 events per 1000 person-years). This effect was independent from additional adjustment for age, gender, and start of new medication after screening. When we repeated these analyses after excluding individuals with diabetes, results did not change. Also, additionally excluding individuals with known hypertension or a history of myocardial infarction did not essentially change the results. Furthermore, after repeating these analyses defining a high UAE alternatively as a UAE above the median baseline value, the results were essentially similar. Finally, repeating the analyses after exclusion of individuals with a >20% or, alternatively, a >10% difference in 24-h creatinine excretion between the first and second day of urine collection at baseline and/or follow-up screening or after using all-cause mortality as outcome did not change our findings.

DISCUSSION

In this study, we investigated the time course of the predictive value of a UAE measurement for CV morbidity and mortality. By stepwise removing censored individuals using 1-yr intervals, there seemed to be a small decrease in the CV risk associated with UAE during follow-up. Furthermore, our results indicate that repeating the UAE measurement after

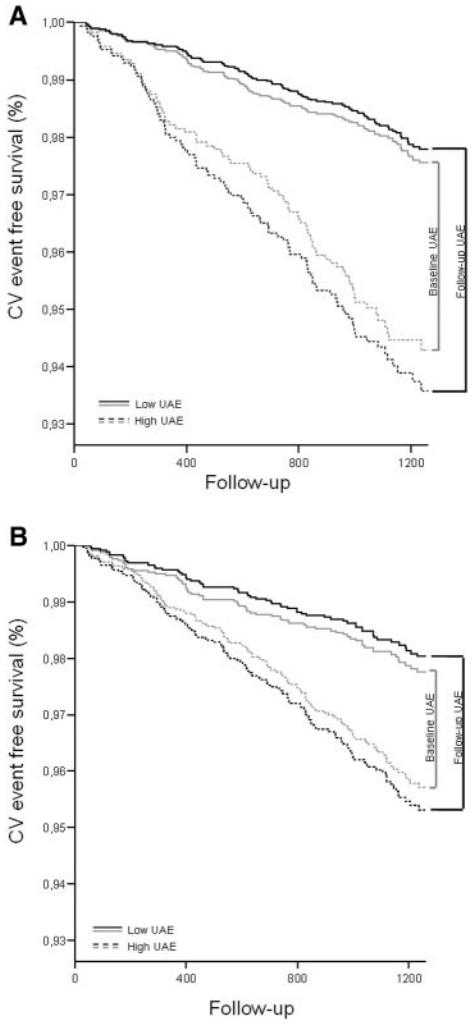


Figure 1. Event-free survival for CV morbidity and mortality after *follow-up* screening. Individuals are stratified according to the presence of a high or low UAE. High and low UAE are defined either using the UAE measurement from the baseline screening (gray lines) of approximately 4.2 yr before follow-up screening or the repeated UAE measurement at time of the follow-up screening (black lines). To allow comparison, the survival curves for the 6800 individuals using either the baseline or follow-up measurement of UAE are plotted in the same graph. (A) A high UAE (dashed lines) is defined as a UAE ≥16.2 mg/24 h, being the 75th percentile of UAE using the UAE measurement of the baseline screening. (B) A high UAE (dashed lines) is defined as a UAE ≥9.1 mg/24 h, being the median UAE using the UAE measurement of the baseline screening. These cutoff points were defined using the 6800 individuals participating at both baseline and follow-up screening.

approximately 4 yr may help to improve risk stratification for CV events, especially in individuals who, at repeat measurement, are found to have an increase in UAE during follow-up. Such increase in UAE is associated with an increased risk for CV events.

UAE is a dynamic process with individuals relatively frequently showing regression or progression of UAE over time.[14] It has been shown in populations with diabetes and hypertension that these changes, whether spontaneous or medication induced, are associated with a parallel change in risk for CV disease.[6,7,15–17] In analogy, when we looked at our community-based study population, changes in UAE were associated with parallel changes in CV risk. With these parallel changes in UAE and CV risk, it is expected that the predictive value of UAE diminishes over time. It is therefore surprising to notice that, in contrast to the findings of Damsgaard *et al.*, there was only a small decrease in the predictive value of the UAE with increasing follow-up time. This difference with the study of Damsgaard *et al.* may be explained by the relatively small sample size of that study ($n = 451$), which may have resulted in a type I error (false rejection of the null hypothesis). Another explanation may be differences between study populations, with individuals in the study of Damsgaard *et al.* being older (all >60 yr) and more frequently having diabetes (approximately 50%) in comparison with our study. Furthermore, in that study, only all-cause mortality was used as an end point instead of CV morbidity and mortality. Thus, although our findings indicate that with increasing follow-up there is a decrease in the predictive value of UAE for the development of a CV event, in our community-based sample, this effect was limited.

One might reason that the observation that the predictive value of UAE remains relatively stable over time argues against a repeated measurement within the first 5 yr after screening; however, our results do indicate that a repeat measurement may have added value, because combining the results from the baseline and follow-up measurement allows one to identify individuals with changes in UAE. As mentioned, such changes were found to be associated with a significant parallel change in CV risk in our study. Because it is estimated that in the general population after approximately 4 yr of follow-up the incidence of progression is approximately 10%,[14] this suggested that by repeating the UAE measurement, a substantial number of individuals with an increased CV risk can be detected.

To our knowledge, this is the first study to investigate the time course of the predictive value of UAE for CV events during follow-up in large community-based study population. This issue is important for the design of screening programs that are based on measurement of UAE, because the costs in-

Table 3. Relative risk for a CV event according to UAE at baseline and follow-up[a]

Baseline Screening	Follow-up Screening	
	Low UAE	High UAE
Low UAE	1.00 ($n = 4606$)	3.68 (2.45 to 5.53)[b] ($n = 494$)
High UAE	1.84 (1.06 to 3.18)[c,d] ($n = 480$)	3.62 (2.65 to 4.94)[b] ($n = 1220$)

[a]A high UAE was defined as a UAE >16.2 mg/24 h as described in the Concise Methods section (Statistical Analysis). Individuals with low UAE at both baseline and follow-up are used as reference group. The number in each group is given.
[b]$P < 0.001$ *versus* individuals with low UAE at baseline and follow-up.
[c]$P = 0.030$ *versus* individuals with low UAE at baseline and follow-up.
[d]$P = 0.017$ *versus* individuals with high UAE at baseline and at follow-up.

volved with screening form a factor that influences the cost-effectiveness of such a program. Cost-effectiveness is an important requirement for implementation of screening programs according to the Wilson-Jungner criteria[18]; therefore, it is important to keep the frequency of screening as low as possible. Because it is already recommended in international guidelines to screen annually for UAE in individuals with diabetes, we repeated our analyses after exclusion of individuals with diabetes.[19] This did not change the essence of our results. Furthermore, as for a screening program aimed to detect CV disease risk, it is most important to detect individuals with an unknown increased CV risk, therefore we also repeated our analyses after individuals with a history of myocardial infarction or treated hypertension were excluded. This again did not change our findings. Thus, on the basis of our observation that the predictive value of UAE for CV events shows only limited decrease during the first 5 yr after measurement, we believe that for population screening, an interval of at least several years between screening rounds for UAE can be applied; however, the exact interval with which the measurement of UAE has to be repeated in the population without diabetes should be based on the time point at which the benefits of detecting and treating individuals with a newly elevated UAE is sufficient to allow for the extra costs involved in repeat screening.

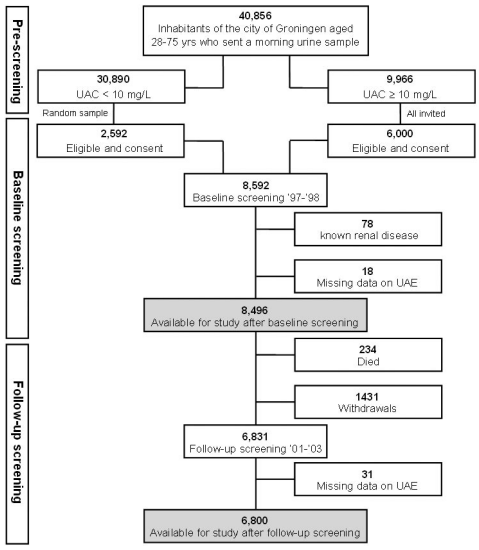
Strengths of our study are the use of a large community-based cohort, use of a CV end point to estimate the time course of the predictive value of UAE, and the availability of a repeat measurement of UAE during follow-up. It is also important to note that because the aim of our study was to evaluate the use of measurement of UAE as a primary screening tool, we did not adjust for potential confounders that may explain the association of UAE with the development of CV disease. Other studies, however, have already shown extensively that this association is indeed independent of other potential CV risk factors.[1–3] Three limitations should be mentioned. First, the PREVEND cohort is selected from a predominantly white population; therefore, our findings cannot be simply generalized to other populations and will need to be confirmed in other studies using nonwhite individuals. Second, in this study we used UAE measured in 24-h urine samples. As we stated at the beginning of this article, a screening program for UAE will probably use a method of prescreening by estimating the UAE in a first morning urine sample; however, because it has been shown that a urinary albumin concentration or albumin-to-creatinine ratio measured in a first morning void are good predictors of 24-h UAE, this is only of little significance for interpretation of our results.[11] Third, it cannot be excluded that the change in UAE in our population is partly due to misclassification at baseline or follow-up. It should be noted, however, that we tried to minimize the effect of misclassification by asking participants to collect *two* consecutive 24-h urine samples. Also repeating our analyses after excluding individuals with a possible collection error at baseline and/or follow-up (as assessed by a >20 or >10% difference in creatinine excretion in the two consecutive 24-h urine collections) did not change the results; therefore, it is unlikely that misclassification can explain the association between changes in UAE and the parallel changes in CV risk.

We conclude from this prospective, community-based cohort study that UAE remains a good predictor of CV morbidity and mortality during at least the first 5 yr of follow-up. Although this may suggest that repeating the UAE within the first 5 yr of follow-up does not have added value for CV risk stratification, repeating the UAE measurement within this follow-up period does have added value, because it detects individuals who show an increase in UAE during follow-up. Such an increase in UAE is associated with an increased CV risk. Future studies will have to determine at what time interval the benefit of detecting and treating individuals with an increase in UAE is sufficient to allow for the extra costs involved in repeat population screening for UAE.

CONCISE METHODS

Study Design and Population

This study is part of the ongoing PREVEND Study, a large, prospective, cohort study that is investigating the predictive value of UAE for CV and renal disease progression. Details of this study have been published elsewhere.[20,21] The participants of the PREVEND cohort were selected in 1997 from 40,856 individuals from the general population who were aged 28 to 75 yr and sent a vial containing a portion of a first morning void urine sample to a central laboratory. Selection was based on their albumin concentration in this urine sample to enrich the cohort for the presence of elevated UAE. In total, 8592 individuals completed the baseline survey (1997 to 1998). After exclusion of individuals with missing data on baseline UAE ($n = 18$) or known renal disease defined as (past) renal disease requiring dialysis or treated proteinuria ($n = 78$), 8496 individuals were available for our analyses (Figure 2).



Fiure 2. Flowchart of the PREVEND Study.

To study the effect of repeating the UAE measurement after several years of follow-up, we used data of our baseline survey and of the first follow-up screening (2001 to 2003). For this follow-up screening, individuals participating in the baseline survey were invited after a median follow-up of 4.2 yr (interquartile range 4.0 to 4.5). By then, 234 individuals had died and 1431 declined participation. After exclusion of individuals with missing data on UAE at follow-up ($n = 31$), 6800 individuals were available for analyses with follow-up data (Figure 2).

The PREVEND Study is approved by the medical ethics committee of our institution and conducted in accordance with the guidelines of the declaration of Helsinki. All participants gave written informed consent.

Measurements and Definitions

At baseline as well as at follow-up screening, participants completed two visits at our outpatient unit. Before the first visit, all participants filled out a questionnaire on demographics; CV and renal disease history; smoking habits; and use of medication for hypertension, hyperlipidemia, or diabetes. During the first visit, height and weight were measured. Before the second visit, two 24-h urine samples were collected on two consecutive days after thorough oral and written instructions on urine collection, and at this visit, a fasting blood sample was drawn. During the first and second visits, BP was measured, in supine position, every minute for 10 and 8 min, respectively, with an automatic device (Dinamap XL Model 9300; Johnson-Johnson Medical, Tampa, FL). BP values are given as the mean of the last two recordings of both visits. Furthermore, information on medication use was collected from community pharmacies. Individuals were considered to use antihypertensive, lipid-lowering, or antidiabetic medication when according to the questionnaire or community pharmacist they took such medications. Urinary albumin concentration was determined by nephelometry with a threshold of 2.3 mg/L and intra-assay and interassay coefficients of variation of 2.2 and 2.6%, respectively (BN II; Dade Behring Diagnostic, Marburg, Germany). The UAE is given as the mean of the two 24-h urinary albumin excretions. Plasma creatinine, plasma cholesterol, and plasma glucose were determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY), an automated enzymatic method. Diabetes was defined according to the guidelines of the American Diabetes Association.[19] Individuals were defined as having known hypertension when they were using antihypertensive medication. The GFR was estimated with the simplified Modification of Diet in Renal Disease formula, taking into account gender, age, race, and serum creatinine concentration.[22]

To define individuals as having a high UAE at *baseline* or at *follow-up*, we used as cutoff value the 75th percentile (UAE = 16.2 mg/24 h) of the baseline UAE measurement. This cutoff point was chosen to ensure the presence of sufficient numbers of individuals and CV events in the group with a high UAE. Of note, this cutoff point was calculated using the baseline data of the 6800 individuals participating at both the baseline and the follow-up screenings. A change in UAE was defined as going from a high to a low UAE (regression), or *vice versa* (progression). For sensitivity analyses, we defined high UAE as the median (UAE = 9.1 mg/24 h) of the baseline UAE measurement.

Follow-up and Outcome

As CV outcome, we used the combined incidence of CV mortality and hospitalization for CV morbidity. Data on mortality were received through the municipal register. Cause of death was obtained by linking the number of the death certificate to the primary cause of death as coded by the Dutch Central Bureau of Statistics. Information on hospitalization for CV morbidity was obtained from PRISMANT, the Dutch national registry of hospital discharge diagnoses. The validity of this database has been shown to be good with 84% of the primary diagnoses and 87% of the secondary diagnoses matching the diagnoses found in the patient chart.[23,24] All data were coded according to the *International Classification of Diseases, Ninth Revision* and the classification of interventions. For this study, CV events were defined as acute myocardial infarction (code 410), acute and subacute ischemic heart disease (411), coronary artery bypass grafting or percutaneous transluminal coronary angioplasty or subarachnoid hemorrhage (430), intracerebral hemorrhage (431), other intracranial hemorrhage (432), occlusion or stenosis of the precerebral (433) or cerebral arteries (434), and other vascular interventions such as percutaneous transluminal angioplasty or bypass grafting of aorta and peripheral vessels. Survival time for the participants was defined as the period from the date of urine collection of the participant to the date of CV event or December 31, 2005, until which date information about CV morbidity and mortality was available. When a person had moved to an unknown destination ($n = 396$), the date on which the person was dropped from the municipal registry was used as census date.

Statistical Analysis

Analyses were performed using the statistical package SPSS 14.0 (SPSS, Chicago, IL). The level of significance was determined as $P < 0.05$. Continuous data are reported as mean with SD or as median and interquartile range in case of skewed distribution. Prevalence and incidence are presented as percentages. Incidence rates are given as number of events per 1000 person-years.

Differences in survival rate for different exposure categories were compared using the log-rank test. Survival curves were plotted using the Kaplan-Meier technique. HR for CV outcome were calculated using Cox proportional hazards analyses. For fulfillment of the assumptions of the Cox regression model, UAE was log-transformed before entering the model. HR and 95% CI are given. Multivariate models were tested for possible interactions between independent variable terms. An interaction was considered statistically significant at $P < 0.01$. ROC curves were calculated to compare the discriminative power of UAE at different years of follow-up. The area under the curve and 95% CI are given.

For studying the predictive value of baseline UAE with increasing follow-up time, the HR and ROC curves for baseline UAE in the prediction of CV outcome were calculated repeatedly after stepwise removal of individuals who were censored after increasing follow-up using 1-yr intervals, until a maximum of 5 yr. The HR associated with an increase in UAE were unadjusted for other confounders to mimic the situation of a screening program in which measurement of UAE is the initial evaluation. To study the effect of repeating the measurement of UAE for CV risk stratification of the individuals in our study, we compared the survival curves for CV events occurring after fol-

low-up screening using the *baseline* measurement of UAE (1997 to 1998) or the *repeated* measurement of UAE from the follow-up screening (2001 to 2003) to stratify individuals.

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DISCLOSURES

None.

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