MACROALBUMINURIA IS A BETTER RISK MARKER THAN LOW ESTIMATED GFR TO IDENTIFY INDIVIDUALS AT RISK FOR ACCELERATED GFR LOSS IN POPULATION SCREENING

Nynke Halbesma
Dirk-Sjoerd Kuiken
Auke H. Brantsma
Stephan J.L. Bakker
Jack F.M. Wetzels
Dick de Zeeuw
Paul E. de Jong
Ron T. Gansevoort

Journal of the American Society of Nephrology 2006; 17:2582-2590
ABSTRACT
Macroalbuminuria, erythrocyturia, and impaired renal function are strong predictors of poor renal outcome in patients with known renal disease. However, the yield of mass screening for these variables to identify individuals who are at risk for GFR loss is yet unknown in a Western population.

With the use of data from the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, a prospective, population-based cohort study, the cardiovascular and renal prognosis was investigated in patients with classical renal risk markers: Macroalbuminuria (>300 mg albumin/24 h urine), erythrocyturia (>250 erythrocytes/L, without leukocyturia), and impaired renal function (both 24-h creatinine clearance and Modification of Diet in Renal Disease clearance below the fifth percentile of age- and gender-matched control subjects). The 8,592 patients who were included in this study were followed for a 4-yr period.

We identified 134 patients with macroalbuminuria, 128 with erythrocyturia, and 103 with impaired renal function. There was only a little overlap among the three groups. The prevalence of macroalbuminuria, erythrocyturia, and impaired renal function was calculated to be in the general population 0.6, 1.3, and 0.9%, respectively. In all three groups, fewer than 30% of patients were known to have this laboratory abnormality before screening. The incidence of cardiovascular disease was high in the macroalbuminuria group (e.g., the age- and gender-adjusted hazard ratio for mortality as a result of cardiovascular disease is 2.6 [1.1 to 6.0]) and for the impaired renal function group 3.4 [1.5 to 8.0]. After a mean follow-up of 4.2 yr, the macroalbuminuria group showed a 7.2 ml/min per 1.73 m² estimated GFR (eGFR) loss, compared with 2.3 ml/min per 1.73 m² in the control group (difference P < 0.001), whereas the rate of eGFR loss in the impaired renal function group (-0.2 ml/min per 1.73 m²; P=0.18) and the erythrocyturia group (2.6 ml/min per 1.73 m²) was not different from the control group.

Macroalbuminuria and impaired renal function both predict a worse prognosis with respect to cardiovascular morbidity and mortality. However, macroalbuminuria is a better risk marker than low eGFR or erythrocyturia to identify in population screening of individuals who are at risk for accelerated GFR loss.
**INTRODUCTION**

Worldwide, the number of people who have ESRD and require dialysis is increasing [1]. In the United States, for instance, the number of new patients with ESRD is expected to increase between 2000 and 2010 by 48% [2]. This development shows the need for preventive strategies. During the past two decades, several therapeutic options have been developed and proved efficacious in slowing the rate of renal function decline. Among these therapeutic treatments are low-protein diets, BP reduction, especially with angiotensin- converting enzyme inhibitors and angiotensin II antagonists [3–6], and lipid lowering. However, for such treatments to be most efficacious with the least societal economic burden, it is necessary to identify patients in an early stage of their disease, before significant loss of renal function has occurred. Unfortunately, such identification is difficult because many renal diseases for which preventive strategies can be started do not cause early symptoms and therefore often are diagnosed late, when there is already advanced renal failure. The National Health and Nutrition Examination Survey (NHANES) indeed showed a low awareness of chronic kidney disease (CKD) among patients with Kidney Disease Outcomes Quality Initiative (KDOQI) stages 1 through 4 for CKD. Only in the last stage of CKD, which is characterized by a GFR 15 ml/min, were most patients aware of their illness [7,8]. Considering this, it is necessary to develop screening strategies for the early identification of people who are at risk for accelerated renal function loss and may benefit from preventive treatment strategies.

Such screening has proved to be effective in high-risk populations, such as diabetics or hypertensive populations, or in family members of patients who require dialysis [9–12]. Unfortunately, there are few data on the yield of screening programs to identify patients who are at risk for accelerated renal function loss in the general population. Putative renal risk markers could be high albuminuria, erythrocyturia, and low estimated GFR (eGFR), because in patients with renal disease, these variables have been proved to be strong predictors of renal outcome [13,14].

For this study, we used the data of the Prevention of Renal and Vascular End-stage Disease (PREVEND) Study to evaluate the changes in renal function as well as total mortality and cardiovascular mortality and morbidity over time in patients with macroalbuminuria, erythrocyturia, and impaired renal function. We also calculated the prevalence of these classical renal risk markers in the general population and evaluated whether these individuals were known to have these laboratory abnormalities before screening took place.

**MATERIALS AND METHODS**

**Study Population**

This study was performed in the individuals who participated in the PREVEND Study. This study is designed to investigate prospectively the natural course of albuminuria and its relation to renal and cardiovascular disease (CVD) in a large cohort drawn from the general population. Details of the study protocol have been described elsewhere [15,16].

In summary, in the period 1997 to 1998, all 85,421 inhabitants of the city of Groningen, The Netherlands, who were aged 28 to 75 yr were sent a one-page postal questionnaire (regarding demographics, use of medication, and presence of pregnancy) and a vial to collect an early-morning urine sample; 40,856 (47.8%) individuals responded. Their vials were sent to a central laboratory, where urinary albumin and creatinine concentrations were measured. After exclusion of individuals who were using insulin (possibly) and pregnant women and those who were not able or willing to participate, all individuals with a urinary albumin concentration (UAC) of ≥ 10 mg/L (group A; n = 7,768) and an SPSS-generated (SPSS,
Inc., Chicago, IL) random sample of individuals with a UAC < 10 mg/L (group B; n = 3.395 of a total of 30.890) were invited for further detailed investigations in an outpatient clinic and to collect two consecutive 24-h urine samples. This procedure was followed to obtain a cohort that was enriched for the presence of albuminuria, the primary parameter under investigation in the PREVEND study. Of group A, 6.000 (77.2%) individuals completed the screening protocol of those who were invited, and of group B, 2.592 (76.3%) individuals did. These 8.592 individuals form the PREVEND baseline cohort. The 8.592 individuals were seen twice at an outpatient clinic, where anthropometric measurements were performed and BP was measured. Blood was drawn after an overnight fast. Participants were asked to perform 24-h urine collections on two consecutive days before the second visit. For this study, three subgroups were defined:

1. Macroalbuminuria: A 24-h urinary albumin excretion (UAE) ≥ 300 mg/24 h
2. Erythrocyturia: ≥ 250 erythrocytes/µl, without leukocyturia
3. Renal function impairment: A creatinine clearance below the 5% age- and gender-matched lowest values of both 24-h urinary creatinine clearance and Modification of Diet in Renal Disease (MDRD) eGFR. We used this latter combined approach to define renal function impairment to be sure not to include falsley individuals with either incomplete 24-h urine collections or extremes of body composition. We similarly did not use a fixed cutoff value of < 60 ml/min, because that would have led to an overrepresentation of elderly and of female individuals.

Approximately 4 yr later, from 2001 through 2003, all PREVEND participants were invited for follow-up investigations at an outpatient clinic. A total of 240 participants had died, and 1.452 declined participation. Therefore, 6.894 (80.2%) participants completed the follow-up investigations. The PREVEND study is approved by the local medical ethics committee and conducted in accordance with the guidelines of the declaration of Helsinki. All participants who attended the outpatient clinic gave written informed consent.

Measurements and Definitions

After the screening, both the participants and their general practitioners received a report of the test results, together with therapeutic advice to treat hypertension, hypercholesterolemia, and diabetes according to standard guidelines. For our study, the general practitioners of the individuals with macroalbuminuria, erythrocyturia, and/or impaired renal function were sent a questionnaire to evaluate whether they were known to have these laboratory abnormalities before the screening.

Plasma and urinary creatinine, plasma cholesterol, and glucose were determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY), an automated enzymatic method. Urinary leukocyte and erythrocyte measurements were done by Nephur-test leuco sticks (Boehringer Mannheim, Mannheim, Germany). Urinary albumin concentration (UAC) 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 (Dade Behring Diagnostic, Marburg, Germany).

Systolic and diastolic BP was calculated as the mean of the last two BP measurements of the two visits. UAE is given as the mean of the two 24-h urine excretions. GFR was assessed by calculating creatinine clearance (mean of two 24-h urinary creatinine excretions divided by plasma creatinine and corrected for body surface area); furthermore, eGFR was estimated by using the four-variable MDRD formula [17].

Smoking was defined as current smoking or cessation of smoking < 1 yr before the study. A history of CVD was defined as a self-assessed history of myocardial infarction, cerebrovascular
Macroalbuminuria is a better risk marker than low estimated GFR accident, or peripheral vascular disease. Information on the use of antihypertensive medications in general and for angiotensin-converting enzyme inhibitors or angiotensin II antagonists specifically was obtained for approximately 80% of the population under investigation by linking the database with pharmacy data. The change in medication use is calculated as the percentage of patients who started or stopped using their medication during follow-up.

Mortality data were obtained from the National Central Bureau of Statistics, a registry for all deaths, subdivided in cardiovascular, malignancies, and other causes. Information on morbidity was obtained from PRISMANT, a database that collects information on hospitalizations on the basis of the International Classification of Diseases, 9th Revision; cardiovascular events are defined as the following codes; 410, 411, 413, 414, 430 to 438, 440 to 442, and 444. Of note, mortality and morbidity data are known for all participants, including those who were lost to follow-up.

Statistical Analyses

All calculations were performed with SPSS version 12.0. Continuous data are reported as means ± SD or as medians with the interquartile range in case of skewed data distribution. All subgroups were compared with the total population minus the specific subgroup under investigation (called the control group) for possible differences in baseline characteristics. Differences in baseline characteristics were tested for statistical significance with t test for continuous data. Glucose and UAE were transformed into their natural logarithm because of skewed distribution. Considering that the selection of individuals into the PREVEND cohort is based on the UAC (with enrichment for individuals with a UAC > 10 mg/L), the prevalence rates of the classical renal risk markers in our cohort may not be comparable to those in the general population. Therefore, we assessed prevalence rates in a subsample of 3,432 individuals that has been formed by reweighing the “oversampled” group A, thereby accounting for the enrichment procedure. These individuals form a representative sample of the general population. Detailed information about how reweighing was achieved has been published previously [18]. Comparison between prevalence rates was carried out with χ² analysis. Multivariate analysis of survival was performed using Cox proportional hazards regression to calculate hazard ratios that were unadjusted as well as adjusted for age and gender. All P values are two tailed, and P < 0.05 was considered statistically significant. Sensitivity analyses were performed to account for the possibility of “competing” risks (e.g., participants who died during follow-up could have experienced renal function deterioration before they died). Such sensitivity analysis also was performed to investigate whether imbalance with respect to the number of participants with diabetes among the three study groups would be responsible for differences in observed rates in renal function decline. For this sensitivity analysis, diabetes was defined as a fasting plasma glucose ≥ 7.0 mmol/l or the use of oral glucose-lowering agents.

RESULTS

Overall, 134 participants in this study had macroalbuminuria, 128 had erythrocyturia, and 103 had impaired renal function. Table 1 shows the characteristics of the various groups under investigation. Participants with macroalbuminuria or impaired renal function generally had an increased cardiovascular risk profile, as reflected by, for example, a higher body mass index, BP, and serum cholesterol. Participants with erythrocyturia differed from the control group insofar as they more often were female and had a higher level of albuminuria. The prevalence of macroalbuminuria, erythrocyturia, and impaired renal
function in our study population is presented in Figure 1. This Venn diagram shows that only a minority of participants had two or three overlapping symptoms. To calculate the prevalence of the three renal risk markers in the general population, we used a subsample that was representative of the general population as explained in the Materials and Methods section. The prevalence of macroalbuminuria, erythrocyturia, and impaired renal function in the general population was calculated to be 0.6, 1.3, and 0.9%, respectively. Information from the general practitioners was received on 110 (82%) of the 134 participants with macroalbuminuria, on 89 (70%) of the 128 participants with erythrocyturia, and on 59 (57%) of the 103 participants with impaired renal function. It was found that only 25, 20, and 27% of the participants with macroalbuminuria, erythrocyturia, and impaired renal function were already known to have this laboratory abnormality before the screening.

Of the total population, 2.8% died, whereas for participants with macroalbuminuria, erythrocyturia, and impaired renal function the percentages of participants who died were

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total population</th>
<th>Macroalbuminuria</th>
<th>Erythrocyturia</th>
<th>Impaired Renal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>8,592</td>
<td>134</td>
<td>128</td>
<td>103</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>49 (13)</td>
<td>58 (13)**</td>
<td>51 (13)</td>
<td>61 (11)**</td>
</tr>
<tr>
<td>Male (%)</td>
<td>50</td>
<td>66**</td>
<td>34**</td>
<td>51</td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
<td>26.1 (4.2)</td>
<td>28.9 (4.6)**</td>
<td>25.9 (4.4)</td>
<td>27.1 (4.4)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>38.0</td>
<td>32.6</td>
<td>48.0*</td>
<td>28.2</td>
</tr>
<tr>
<td>History of CVD (%)</td>
<td>9.4</td>
<td>29.7**</td>
<td>13.9</td>
<td>30.5**</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>129 (20)</td>
<td>152 (25)**</td>
<td>129 (23)</td>
<td>142 (24)**</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>74 (10)</td>
<td>83 (10)**</td>
<td>75 (12)</td>
<td>79 (11)**</td>
</tr>
<tr>
<td>Anti-hypertensive Tx (%)</td>
<td>16.8</td>
<td>46.2**</td>
<td>23.0</td>
<td>57.3**</td>
</tr>
<tr>
<td>ACEI or A2A (%)</td>
<td>5.8</td>
<td>20.8**</td>
<td>8.8</td>
<td>28.1**</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.65 (1.13)</td>
<td>6.13 (1.30)**</td>
<td>5.77 (1.18)</td>
<td>6.09 (1.49)**</td>
</tr>
<tr>
<td>Lipid-lowering Tx (%)</td>
<td>6.9</td>
<td>18.2**</td>
<td>12.5**</td>
<td>29.4**</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.9 (1.2)</td>
<td>5.8 (2.4)**</td>
<td>4.8 (0.8)</td>
<td>5.0 (1.1)</td>
</tr>
<tr>
<td>Oral antidiabetic Tx (%)</td>
<td>2.1</td>
<td>9.7**</td>
<td>1.6</td>
<td>2.9</td>
</tr>
<tr>
<td>UAC &lt;10 mg/L (%)±</td>
<td>30.2</td>
<td>0**</td>
<td>21.9*</td>
<td>16.5*</td>
</tr>
<tr>
<td>Median UAE (mg/day)</td>
<td>9.5 (6.3-17.8)</td>
<td>549 (371-1011)**</td>
<td>23.7 (10.2-91.5)</td>
<td>37.6 (8.2-157.3)**</td>
</tr>
<tr>
<td>Macroalbuminuria (%)¶</td>
<td>1.6</td>
<td>100**</td>
<td>7.0**</td>
<td>17.5**</td>
</tr>
<tr>
<td>Erythrocyturia (%)</td>
<td>1.5</td>
<td>6.7**</td>
<td>100**</td>
<td>7.8**</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>80.8 (14.7)</td>
<td>68.4 (20.4)**</td>
<td>74.9 (15.6)**</td>
<td>44.6 (11.6)**</td>
</tr>
</tbody>
</table>

Means (S.D.) are given for continuous variables. Because of skewed distribution for UAE the median and interquartile range is given.

* P<0.05 versus total population minus the specific group under investigation
** P<0.01 versus total population minus the specific group under investigation
± Prescreening
¶ Screening
Macroalbuminuria is a better risk marker than low estimated GFR

Cardiovascular mortality was high in the participants with macroalbuminuria and in the participants with impaired renal function (4.5 and 5.8%, respectively), compared with 0.8% in the control group. The same was true for cardiovascular morbidity, with 21.6 and 23.3%, respectively, in the macroalbuminuria and impaired renal function groups, compared with 6.1% in the control population and 8.6% in the erythrocyturia group. Hazard ratios are shown in Table 2.

Overall, 6.894 individuals participated in the second screening 4.2 yr later, including 86 participants with macroalbuminuria, 97 with erythrocyturia, and 68 with impaired renal function (Table 3). Numbers decreased because participants died or withdrew consent before the second screening. Baseline characteristics of the participants who were lost to follow-up in the three different renal risk groups were not statistically different, compared with participants who completed the second screening. BP had fallen more in the group with macroalbuminuria and the group with impaired renal function (8.0 and 8.3 mmHg systolic and 3.6 and 4.8 mmHg diastolic, respectively) than in the control group (1.7 mmHg systolic and 0.3 mmHg diastolic). This probably is due to the use of more antihypertensive drugs in these groups. At the second screening, however, both systolic and diastolic BP still were higher in the macroalbuminuria group than in the impaired renal function group. During follow-up, renal function had fallen more in participants with macroalbuminuria (7.2 ml/min per 1.73 m² [10.6%]) than in the control group (2.3 ml/min per 1.73 m² [2.8%]) and in the participants with erythrocyturia (2.6 ml/min per 1.73 m² [3.5%]). It is interesting that eGFR fell by only 0.2 ml/min per 1.73 m² (0.4%) in participants with impaired renal function. Participants who at baseline had both macroalbuminuria and impaired renal function (n = 18) experienced a rate of renal function decline of 9.0 ml/min per 1.73 m².

Various sensitivity analyses were performed. First, there were more participants with diabetes in the macroalbuminuria group when compared with the overall population and the two other groups under investigation. After exclusion of individuals with diabetes, the observed renal function decline in the macroalbuminuria group was 7.1 ml/min per 1.73 m², whereas it was 7.2 ml/min per 1.73 m² when individuals with diabetes were included. For cardiovascular morbidity and mortality, the incidence rates were similar in the macroalbuminuria group when individuals with diabetes were excluded or included (mortality 4.4 versus 4.5%, respectively [NS]; morbidity 21.1 versus 21.6%, respectively [NS]). Second, we investigated “competing” risks as a potential source of bias (e.g., participants who died during follow-up or were lost to follow-up for other reasons could have experienced renal function deterioration before they died).

We observed a difference in mortality rates between the macroalbuminuria and impaired renal function groups (9.7 versus 16.5%, respectively). If it is assumed that the difference in
GFR decline between these two groups is due to the difference in mortality rates, then this suggests that a relatively small number of participants who died would be responsible for this difference. For the difference of 7.0 ml/min per 1.73 m² between the macroalbuminuria and impaired renal function groups to be explained fully by the participants who died during follow-up, this would mean that the 6.8% more participants who died in the impaired renal function group should have had a renal function decline of almost 120 ml/min per 1.73 m² each. If such sensitivity analysis takes into account not only “overmortality” but also all 17 participants who died in the macroalbuminuria group and assuming that the deceased participants in the impaired renal function group had a neutral effect size (i.e., 7.2 ml/min per 1.73 m² renal function loss, as in the participants from this group for whom follow-up is available), then this would mean that these 17 participants should have experienced a renal function decline of 35.2 ml/min per 1.73 m². If such sensitivity analysis takes into account not only the 17 participants who died during follow-up but also all 35 participants who were lost to follow-up, again assuming a neutral effect size in the macroalbuminuria group, then this would mean that these 35 participants should have experienced a renal function decline of 21 ml/min per 1.73 m².

**DISCUSSION**

In this study, we investigated whether the putative renal risk markers macroalbuminuria, impaired renal function, and erythrocyturia can be used for population screening to identify individuals who are at risk for accelerated renal function loss. We found that both individuals with macroalbuminuria and individuals with impaired renal function have increased cardiovascular mortality and morbidity compared with individuals in the control population.
Table 3: Results with regard to patient characteristics and renal function of subjects with follow-up

<table>
<thead>
<tr>
<th></th>
<th>Total population</th>
<th>Macroalbuminuria</th>
<th>Erythrocyturia</th>
<th>Impaired Renal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>6894</td>
<td>86</td>
<td>97</td>
<td>68</td>
</tr>
</tbody>
</table>

**Systolic Blood Pressure (mmHg)**
- **baseline**: 128 (20) 151 (23)** 127 (23) 142 (22)**
- **follow-up**: 127 (19) 143 (23)** 125 (20) 134 (21)**
- **change**: -1.7 (13.1) -8.0 (2.2)** -2.1 (1.6) -8.3 (2.3)**

**Diastolic Blood Pressure (mmHg)**
- **baseline**: 74 (10) 82 (10)** 74 (11) 79 (10)**
- **follow-up**: 73 (9) 79 (10)** 73 (10) 74 (9)
- **change**: -0.3 (6.6) -3.6 (1.0)** -0.6 (0.8) -4.8 (1.1)**

**Antihypertensive treatment (%)**
- **baseline**: 15.7 37.1** 17.9 53.9**
- **follow-up**: 24.8 67.1** 33.3 72.3**
- **change**: 12.6 36.8** 18.8 22.6**

**Number of antihypertensives**
- **baseline**: 0.22 0.60** 0.27 0.97**
- **follow-up**: 0.39 1.18** 0.49 1.40**
- **change**: 0.17 0.58** 0.22 0.43**

**ACEi or A2A treatment (%)**
- **baseline**: 5.2 15.7** 7.1 23.1**
- **follow-up**: 11.1 49.4** 13.6 44.6**
- **change**: 7.9 36.8** 9.3 24.2**

**Serum cholesterol (mmol/L)**
- **baseline**: 5.64 (1.13) 6.10 (1.34)** 5.74 (1.11) 5.99 (1.52)*
- **follow-up**: 5.43 (1.05) 5.55 (1.10) 5.39 (1.10) 5.41 (1.10)
- **change**: -0.21 (0.93) -0.55 (0.13) -0.35 (0.10) -0.58 (0.17)

**Lipid lowering drugs (%)**
- **baseline**: 5.1 12.9** 4.8 18.2**
- **follow-up**: 11.8 28.0** 10.7 33.3**
- **change**: 8.0 17.2** 8.7 12.1**

**Urinary Albumin Excretion (mg/d)**
- **baseline**: 9.2 (6.3-16) 510.5 (359.2-1075)** 19.3 (9.2-85) 24.7 (7.9-85)**
- **follow-up**: 8.7 (6.1-16) 468.7 (171.5-1042)** 16.3 (7.4-43) 23.4 (9.3-163)**
- **change**: 0.2 (2.4-2.8) -77.0 (-295.2-303.9)** -1.2 (-11.4-5.9) 0.1 (-7.2-22.2)

**Erythrocyturia positive (%)**
- **baseline**: 1.4 5.8* 100** 2.9
- **follow-up**: 1.7 5.8* 18** 0
- **change**: 0.3 0 -82** -2.9

**eGFR (mL/min/1.73m²)**
- **baseline**: 80.8 (14) 67.8 (19)** 76.5 (13)** 45.5 (10)**
- **follow-up**: 78.5 (17) 60.5 (20)** 73.8 (15)** 45.3 (14)**
- **change**: -2.3 (12.3) -7.2 (1.2)** -2.6 (1.0) -0.2 (1.1)**

* P<0.05 versus total population minus the specific group under investigation
** P<0.01 versus total population minus the specific group under investigation
In contrast, only individuals with macroalbuminuria but not those with impaired renal function at baseline had a greater loss of renal function during follow-up than the control population. Individuals with erythrocyturia do not show a worse cardiovascular and renal prognosis, although they - just as the individuals with macroalbuminuria and with impaired renal function - have a higher noncardiovascular mortality. The prevalence of these three renal risk markers is low in the general population, and there is little overlap among the three. Last, only a minority of the individuals who were found positive were already known to have the abnormality.

Our finding of an increased cardiovascular morbidity and mortality in individuals with macroalbuminuria as well as in individuals with an impaired renal function is in agreement with literature: several studies reported a high cardiovascular morbidity and mortality among individuals with albuminuria [19–21] and among individuals with impaired renal function [22]. The finding that macroalbuminuria is predictive of accelerated renal function loss also is compatible with data from other studies. Iseki et al. [13] showed in a large cohort of Japanese individuals who were followed for 17 yr that proteinuria as measured by dipstick was predictive of later risk to reach ESRD. It also is in line with data in patients with known primary renal disease, in whom proteinuria has been found to be a strong risk marker for progressive loss of renal function [23]. Surprising, however, eGFR did not fall in the group with impaired renal function at baseline. This finding is in line with a recent study in England in individuals with a median eGFR of 28.5 ml/min per 1.73 m². The majority of these individuals had stable renal function over 31 mo [24]. An explanation for the unexpected finding of stable renal function in a group of individuals who were selected on the basis of impaired renal function at baseline can be the phenomenon of “regression to the mean.” This phenomenon contains two aspects. First, regression to the mean can be caused by day-to-day variations of renal function in a given individual and, second, to imprecision in the measurement. For instance, individuals who collected 24-h urine inadequately at the baseline study well may deliver a better collected sample at the second screening. We tried to overcome this bias by requiring not only a low 24-h creatinine clearance but also a low eGFR according to the MDRD formula, the latter not being dependent on urinary values. This leaves us with the possibility of an imprecise measurement of plasma creatinine (which is included in both measures of GFR). Therefore, regression to the mean cannot be ruled out. The influence of this source of bias can be investigated by checking renal function on several occasions over time. Fortunately, the PREVEND study is an ongoing cohort study. Participants are seen at our outpatient clinic at a 3- to 4-yr interval. We were able to do an interim analysis with data of the 4,772 individuals.
Macroalbuminuria is a better risk marker than low estimated GFR

who already participated in the third screening. eGFR of the individuals with impaired renal function stayed nearly constant, even between the second and third screenings, whereas eGFR deteriorated along a straight line in individuals with macroalbuminuria (Figure 2). Individuals with impaired renal function at baseline experienced less renal function decline during follow-up compared with the overall population. Although these individuals used more interfering medication, BP, glucose, and cholesterol levels at baseline and during follow-up still were higher (or equal) to values in the total population. This suggests that the low rate of renal function loss in this group is not due to better medical management of this group. Consequently, we conclude from our data that screening on the basis of determination of renal function impairment and subsequent treatment may be useful to prevent cardiovascular events. It is unlikely, however, that such screening may be helpful to prevent progressive renal function deterioration.

The individuals with erythrocyturia showed no significant renal function decline compared with the control population. This finding seems at odds with a previous epidemiologic study that was performed in the Okinawa region of Japan. Iseki et al. [13,25] used a dipstick to identify people with proteinuria and erythrocyturia. They found that both parameters predicted long-term renal function outcome, as assessed by the incidence of ESRD. Of note, in this study, only men with erythrocyturia showed a higher risk for ESRD. This is in contrast with our data, which do not show a negative impact of erythrocyturia. These contradictory findings may be explained by the fact that the study by Iseki et al. was performed in a Japanese population, which is known for a relatively high incidence of lupus nephritis and IgA nephropathy, both diseases that are characterized in general by erythrocyturia and progressive renal function loss [26,27]. Most likely, our data on erythrocyturia do not point to a specific renal disease. First, two thirds of the individuals with erythrocyturia at first screening consisted of relatively younger women. Second, the presence of erythrocyturia showed almost no overlap with the two other risk markers for renal disease, proteinuria, and renal function impairment. Third, only in 18% of the individuals with erythrocyturia did this abnormality persist at the second screening. Although individuals were asked specifically to refrain from urine collection during menstruation, we hypothesize that, at least in part, erythrocyturia may be due to menses or to urologic disorders. In concordance with our observation, another Japanese study showed that erythrocyturia indicated a higher risk for development of renal insufficiency only in combination with proteinuria [28]. On the basis of these data, it can be concluded that screening for erythrocyturia is not effective for identifying patients who are at risk for rapid renal function decline in a white population. Although our data argue that screening for macroalbuminuria may help to prevent better CVD and renal disease, we should realize that the prevalence of this renal abnormality is low in our population. The prevalence that we found is nearly similar to the low prevalence of macroalbuminuria that was found in the NHANES III population [29]. The low prevalence, of course, is related to the strict cutoff value that is used: UAE ≥ 300 mg/d in two 24-h urine collections. In prospective studies, renal function decline and UAE are associated in a continuous way [30,31]. It follows, then, that more individuals may be identified when the cutoff value for elevated UAE is lowered. The cutoff to be preferred is the value above which screening and intervention will be cost-effective [32]. The yield of screening to identify individuals who are at risk for renal function deterioration also may be increased by taking into account other risk factors, such as high BP, cholesterol, and glucose. The aim of our study, however, is not to design an integrated renal risk score but merely to investigate which of the three classical renal risk markers performs best in predicting renal function prognosis. Of note, the prevalence of impaired renal function also was found to be low, and lower than
that described in the NHANES study [33] and in a previous publication of the PREVEND study [14]. In those reports, however, a fixed cutoff value of < 60 ml/min per 1.73 m² was used. As described in the Materials and Methods section, we chose a more strict approach, aiming to identify individuals with the worst renal function, independent of the age- and gender-related influence on GFR.

Most of the individuals who were positive for these putative renal risk markers were not known to have that abnormality. This is in line with data that most individuals with minor renal damage are not aware of this [7]. Of note, we found little overlap among the three groups with putative renal risk markers. A similar finding was reported from the NHANES III study, in which screening for albuminuria and renal failure resulted in the identification of two different segments of the population [29]. In this study, 37% of the individuals with renal insufficiency (defined as GFR < 30 ml/min) demonstrated no microalbuminuria or macroalbuminuria. The authors suggested that their results confirmed that comprehensive screening initiatives may need to integrate a number of different criteria to identify individuals who are at risk for ESRD and that different criteria may be valuable in different age groups or at-risk populations (e.g., individuals with hypertension or diabetes).

Our study has some limitations. First, not all questionnaires were returned by the general practitioners, and objective follow-up data were available in only 80% of participants. However, the baseline characteristics of the participants who were lost to follow-up were not significantly different from the participants for whom follow-up was available. It is likely, however, that loss to follow-up will be encountered especially in those who are in poor health. It therefore can be expected that, if anything, our results will underestimate health care outcome, whereas our main message is that the presence of macroalbuminuria heralds bad renal and cardiovascular prognosis. Second, in our study, we used a dipstick test to measure erythrocyturia. Complementary microscopic analyses perhaps could increase the ability to predict renal disease, because it is possible to distinguish a nephrologic from a urologic origin of erythrocyturia [26,34]. Another solution could be to screen for erythrocyturia more than once to separate persistent erythrocyturia from erythrocyturia that is caused by, for example, menses. In large-scale screening projects, however, neither option is feasible. Third, our results with regard to mortality, morbidity, and renal function loss probably are an underestimation of the natural course. After the identification of individuals with a laboratory abnormality in our screening program, some of them were treated with antihypertensive medication. Intervention can have a biasing effect on follow-up data. However, this is the same for all three groups under investigation. For this reason, it is not likely that these effects influence the notion of our conclusion that only macroalbuminuria heralds a poor renal prognosis. Fourth, “competing” risk bias may have influenced our results (e.g., participants who died or were lost to follow-up in the impaired renal function group may have experienced more renal function decline than the participants for whom follow-up data are available, thus resulting in a lower rate of renal function decline in this group of participants in comparison with the participants with macroalbuminuria). We therefore performed sensitivity analyses on the basis of worst-case scenarios. These analyses provide figures that are highly unlikely from a clinical point of view, suggesting that competing risk bias, if present, cannot explain fully the observed difference in rate of renal function decline between the groups with macroalbuminuria and impaired renal function at baseline. Finally, the PREVEND study is performed in a predominantly white population. Our results therefore may not be valid for other, nonwhite populations.
**CONCLUSION**

Most individuals who were identified by this screening were not known to have or were treated for their laboratory abnormality. Individuals with impaired renal function or macroalbuminuria are at risk for both cardiovascular morbidity and mortality. However, screening for macroalbuminuria is a better strategy than screening for low eGFR to identify individuals who are at risk for accelerated GFR loss in population screening. Although the prevalence of macroalbuminuria is low, the outcome with regard to renal function decline and cardiovascular morbidity and mortality justify screening, because these individuals are likely to benefit from early cardio- and renoprotective strategies.
REFERENCES


Garg AX, Kiberd BA, Clark WF, Haynes RB, Clase CM: Albuminuria and renal insufficiency prevalence guides population screening: Results from the NHANES III. Kidney Int 61: 2165–2175, 2002


Brantsma AH, De Zeeuw D, Hilleges HL: Letter regarding article by Klausen et al., “very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes.” Circulation 111: e110 – e111, 2005

