

The validity of screening based on spot morning urine samples to detect subjects with microalbuminuria in the general population

RON T. GANSEVOORT, JACOBIE C. VERHAVE, HANS L. HILLEGE, JOHANNES G.M. BURGERHOF, STEPHAN J.L. BAKKER, DICK DE ZEEUW, and PAUL E. DE JONG, FOR THE PREVEND STUDY GROUP

Division of Nephrology, Trial Coordination Center, Department of Epidemiology and Statistics, and Department of Clinical Pharmacology, Groningen University Medical Center, Groningen (GUMC), The Netherlands

The validity of screening based on spot morning urine samples to detect subjects with microalbuminuria in the general population.

Background. No study has yet investigated the validity of prescreening by albumin measurements in a spot morning urine sample to identify in the general population subjects with microalbuminuria. We therefore tested the diagnostic performance of urinary albumin concentration (UAC) and albumin-creatinine ratio (ACR), measured in a spot morning urine sample, in predicting a urinary albumin excretion (UAE) ≥ 30 mg in subsequent 24-hour urines (microalbuminuria).

Methods. Subjects (2527) participating in the PREVEND study, a representative sample from the general population, collected a spot morning urine sample and, on average, 77 days later, two 24-hour urine collections.

Results. The ROC curve of UAC in predicting microalbuminuria has an area-under-the-curve of 0.92 with a discriminator value of 11.2 mg/L. Using this cut-off value for UAC, sensitivity in predicting microalbuminuria is 85.0%, and specificity 85.0%. For ACR these values are, respectively: area-under-the-curve 0.93, discriminator value 9.9 mg/g, sensitivity 87.6%, and specificity 87.5%. Sensitivity for UAC in predicting microalbuminuria does not differ significantly from the sensitivity for ACR, whereas the difference between the specificities of UAC and ACR reaches statistical significance, but is numerically very small. In various subgroups characterized by differences in urinary creatinine excretion, the area-under-the-ROC curve, sensitivity, as well as specificity, do not increase relevantly compared to the results in the overall study population. This holds true for ACR as well as UAC.

Conclusion. The diagnostic performance of measuring UAC in a spot morning urine sample in predicting microalbuminuria in subsequent 24-hour urine collections is satisfactory, and, moreover, comparable to that of measuring ACR. In order to keep the burden and costs involved in population screening for microalbuminuria as low as possible, we therefore propose prescreening by measuring UAC in a spot morning urine sample. Those subjects with a UAC above a certain predefined level (e.g., 11 mg/L) should be asked to collect timed urine samples.

Key words: albuminuria, microalbuminuria, creatinine, screening, sensitivity, specificity, PREVEND.

In patients with type 1, as well as type 2 diabetes mellitus, the presence of a urinary albumin excretion ≥ 30 mg/24-hour is highly predictive for later occurrence of cardiovascular disease [1–4]. Evidence is accumulating that in the general population a similar association exists [5–7]. The risk for cardiovascular events entailed by albuminuria seems at least partly independent from serum cholesterol and blood pressure [3, 7]. These results indicate that in the general population mass screening for the presence of abnormal urinary albumin excretion may be a useful strategy to identify people at high risk for cardiovascular events who may benefit from preventive strategies.

The reference method to measure urinary albumin excretion is a 24-hour urine collection (UAE) [8, 9]. In mass screening, however, such a method is impractical. This would imply that huge numbers of individuals would have to undergo the cumbersome procedure of a 24-hour urine collection. A solution to this problem would be that first a spot morning urine collection is performed. In this spot morning urine collection, albumin concentration (UAC) or albumin-creatinine ratio (ACR) can be determined. Subsequently, only those people with an UAC or ACR above a certain predefined value would be invited to collect a 24-hour urine. To our knowledge, no study has yet investigated the validity of albumin measurements from a spot morning urine sample to identify in the general population subjects with abnormal urinary albumin excretion in a subsequent 24-hour urine collection.

The PREVEND study has collected in the general population spot morning urine samples and 24-hour urines on separate occasions. We tested the diagnostic performance of measuring UAC and ACR in the spot morning urine samples to predict albuminuria in the subsequent 24-hour urine collections. In addition, we tested whether UAC and ACR in this respect behave differently in subgroups known for higher creatinine production rate.

METHODS

Study population

This study was performed in the subjects participating in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study. The PREVEND study is designed to prospectively investigate the natural course of increased levels of urinary albumin excretion and its relation to renal and cardiovascular disease in a large cohort drawn from the general population. Details of this protocol have been described elsewhere [10, 11]. In summary, in the period 1997 to 1998, all inhabitants of the city of Groningen, The Netherlands, aged 28 to 75 years, were sent a 1-page postal questionnaire and a vial to collect an early morning urine sample ($N = 85,421$). Of these subjects, 40,856 responded (47.8%) and sent a vial to a central laboratory where urinary albumin and creatinine concentrations were measured. After exclusion of subjects with type 1 DM (defined as the use of insulin) and pregnant women, all subjects with a UAC of ≥ 10 mg/L ($N = 6000$) and a randomly selected control group with UAC < 10 mg/L ($N = 2592$) were invited for further investigations in an outpatient clinic and to collect two consecutive 24-hour urines. These 8592 subjects form the PREVEND cohort. Because estimation of the diagnostic performance of the proposed tests would be biased by the fact that the PREVEND cohort is enriched for subjects with albuminuria, we reweighted the oversampled part (UAC of ≥ 10 mg/L) by proportionally taking a computer-generated random subset. Subjects were excluded when leukocyturia or erythrocyturia was present because this makes albumin measurement unreliable (leukocytes $> 75/\mu\text{L}$, or erythrocytes > 50 erythrocytes/ μL , or leukocytes = 75, and erythrocytes $> 5/\mu\text{L}$ measured by dipstick in the 24-hour urines), and when subjects were known with proteinuria or renal disease. Thus, a study population of 2527 subjects was created that is a representative sample of the general population.

Study design

The screening program in the outpatient clinic consisted of two visits [10, 11]. At the first visit, participants completed a self-administered extended questionnaire regarding demographics. Furthermore, blood pressure and anthropometric measurements (weight and height) were performed, blood was drawn in fasting condition, and subjects were asked to collect 24-hour urine on two consecutive days. Oral and written instructions on how to collect 24-hour urine were given, and subjects were instructed to postpone urine collection in case of urinary tract infection or menstruation, and to refrain as far as possible from heavy exercise during the collection period. Furthermore, the subjects were asked to store the urine cold (4°C) for a maximum of 4 days prior to the

second visit. Measurements of urinary volume, albumin, and creatinine concentration were performed on each collection. All subjects gave written informed consent. The PREVEND study was approved by the local medical ethics committee, and is conducted in accordance with the guidelines of the Declaration of Helsinki.

Analytical methods

Urinary albumin excretion was determined by nephelometry, with a threshold of 2.3 mg/L and intra- and interassay coefficients of variation of 2.2% and 2.6%, respectively (BNII, Dade Behring Diagnostica, Marburg, Germany). UAE was calculated as the average urinary albumin excretion in the two consecutive 24-hour urine collections. Creatinine assessment in urine was determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY, USA), an automatic enzymatic method. The intra- and interassay coefficients of variation were 0.9% and 2.9%, respectively. Urinary leukocyte and erythrocyte measurements were performed by Nephur-test and leuko-sticks (Boehringer Mannheim, Mannheim, Germany).

Statistical analysis

Sensitivity and specificity were calculated to determine the diagnostic properties of ACR and UAC (measured in the spot morning urine collection) in predicting a UAE ≥ 30 mg/24-hour (measured in 24-hour urine collections). Determination of the confidence intervals for sensitivity and specificity was performed using the guidelines of Gardner and Altman [12]. ROC curves were calculated to compare the discriminative power of ACR and UAC. The ROC curve analysis was also used to determine discriminator values for ACR and UAC. The value lying nearest to the point on intersection of the ROC curve and the 100%-to-100% diagonal was chosen as discriminator value. For UAC and ACR, the true positive rate (TPR) was calculated as $a/(a+b)$, the false positive rate as $b/(a+b)$, and the false negative rate as $c/(c+d)$, where a is the number of positive tests with subsequent UAE ≥ 30 mg/24-hour, b is the number of positive test results with UAE < 30 mg/24-hour, c is the number of negative test results with UAE ≥ 30 mg/24-hour, and d is the number of negative test results with UAE < 30 mg/24-hour [13].

It is known from literature that some anthropomorphic/demographic variables influence muscle mass, and thus, urinary creatinine excretion, which is included in the ACR [14–17]. Therefore, multiple regression analysis was performed with 24-hour urinary creatinine excretion as dependent variable, to test whether, and if so, which of these variables had a statistically significant impact on 24-hour urinary creatinine excretion in our study. The independent variables tested were gender, age, weight, and

Table 1. Characteristics of participating subjects

Number	2527
Gender (male, %)	47.1
Age years	48.8 (48.3–49.3)
Weight kg	77.2 (76.7–77.7)
Height cm	172.9 (172.5–173.3)
Race (Caucasian, %)	95.4
Smoking %	34.3
CVD history %	11.4
Type 2 DM %	2.6
Use of BP lowering agents %	9.5
SBP mm Hg	126.2 (125.5–126.9)
DBP mm Hg	72.8 (72.4–73.2)
Use of lipid lowering agents %	6.6
Serum cholesterol mmol/L	5.63 (5.59–5.66)
Serum creatinine μ mol/L	83.2 (82.6–83.8)
Spot morning UAC mg/L	5.9 (3.6–9.8)
Spot morning ACR mg/g	4.9 (3.7–7.6)
24-hr UAE mg/24-hr	7.0 (5.4–10.5)

Data are given as means with 95% confidence intervals, with the exception of spot morning urinary albumin concentration (UAC), albumin-creatinine ratio (ACR), and 24-hour urinary albumin excretion (UAE), which are given as medians with interquartile range. Other abbreviations are: CVD, cardiovascular disease; DM, diabetes mellitus; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

race. Subsequently, it was analyzed whether these anthropomorphic variables influence the discriminator values of ACR and UAC. For continuous variables, the overall population was divided in two subgroups, equal to or above the median value and under the median value. Student *t* test (or Welch *t* test in case SDs were statistically significantly different) was used to test differences of sensitivity/specificity of ACR versus UAC in predicting UAE ≥ 30 mg/24-hour. Data are given as means plus 95% confidence intervals (95% CI). In case of skewed distribution (UAC, ACR, and UAE), medians are given with interquartile range. A value of $P < 0.05$ (two-sided) was used as the nominal level of statistical significance. Calculations were performed using the statistical package SPSS, version 11.5, for Windows (Statistical Package for the Social Sciences, Chicago, IL, USA).

RESULTS

Altogether, 2527 subjects were included. Table 1 shows the characteristics of the study population. The prevalence of a UAE ≥ 30 mg/24-hour was 6.1%. The mean time between the spot morning urine collection and the collection of the 24-hour urines was 77 days.

Figure 1 shows the diagnostic performance of a spot morning urine UAC in predicting a UAE ≥ 30 mg in subsequent 24-hour urine collections. The ROC curve has an area-under-the-curve of 0.92, and the discriminator value is 11.2 mg/L. Using this cut-off value for UAC, sensitivity in predicting a UAE ≥ 30 mg/24-hour is 85.0% (79.3–90.6), and specificity 85.0% (83.5–86.4). For ACR these values are, respectively: area-under-the-curve 0.93, discriminator value 9.9 mg/g, sensitivity 87.6% (82.4–92.8), and specificity 87.5% (86.2–88.9) (Fig. 2). Sensitivity for

UAC in predicting UAE ≥ 30 mg/24-hour does not differ significantly from the sensitivity for ACR, whereas the difference between the specificities of UAC and ACR is numerically small, but does reach statistical significance (Table 2).

Multiple regression analysis revealed that, in order of significance, gender, age, weight, and race were statistically significantly associated with urinary creatinine excretion (R^2 0.55, $P < 0.001$). Table 2 shows the results for diagnostic performance of UAC and ACR in a spot morning urine sample in predicting a 24-hour urinary albumin excretion ≥ 30 mg. Data are given for both the overall study population, as well as for various subgroups when subdivided according to these anthropomorphic/demographic variables. Because diabetic subjects have a higher prevalence of elevated urinary albumin excretion, we also calculated the diagnostic performance of UAC and ACR for diabetic and nondiabetic subjects separately. Using subgroup-specific discriminator values, it appears that in these subgroups, the area-under-the-ROC curve, sensitivity, as well as specificity, does not increase relevantly compared to the results in the overall study population. This holds true for both ACR, as well as UAC. Of note, subgroup-specific discriminator values differ less for UAC when compared to ACR.

The robustness of our results was tested by generating a second data set. From our overall population, another random sample representative for the general population was drawn. In this second sample, the prevalence of albuminuria in excess of 30 mg/24-hour is 6.0% (versus 6.1% in the first data set, $P = \text{NS}$). The diagnostic performance of UAC in a spot morning urine sample in predicting UAE ≥ 30 mg/24-hour is similar: the area under the ROC-curve being 0.92 (versus 0.92 in the first data set, $P = \text{NS}$), and the discriminator value 12.4 mg/L (versus 11.2 mg/L in the first data set). Sensitivity and specificity for UAC at the discriminator value is 86.3% (80.8–91.7%) and 86.3% (84.9–87.6%), respectively. Both values are not statistically different from values obtained in the first data set. For ACR, the area under the ROC curve in the second data set is 0.93 (versus 0.93 in the first data set, $P = \text{NS}$), and the discriminator value 9.9 mg/g (versus 9.9 mg/g in the first data set). Sensitivity and specificity for ACR at the discriminator value is 86.3% (80.8–91.7%) and 86.3% (85.0–87.7%), respectively. Both values are, again, not statistically different from values obtained in the first data set.

Traditionally, a cut-off value for UAC of ≥ 20 mg/L has been used to indicate a UAE ≥ 30 mg/24-hour. Using this cut-off value in our data set we obtain low sensitivity, but high specificity (Table 3). For ACR, the traditionally used cut-off value indicating a UAE ≥ 30 mg/24-hour has been 30 mg/g. For this cut-off value, sensitivity again is low, whereas specificity is high (Table 3). Later, based on the observation that there are differences between males and

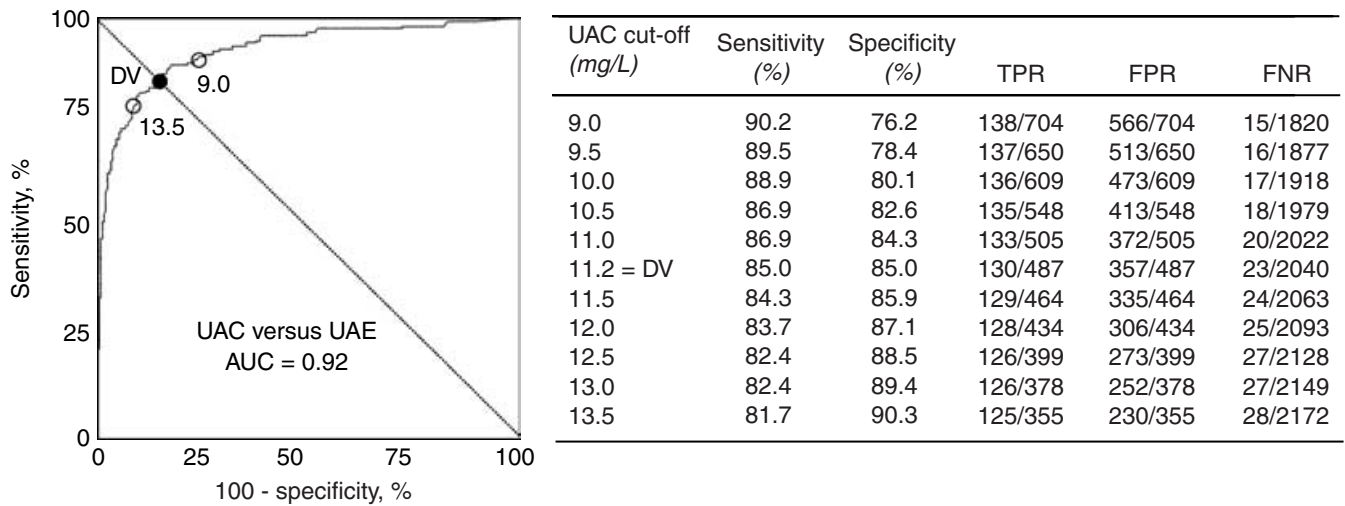


Fig. 1. Diagnostic performance of urinary albumin concentration in a spot morning urine sample (UAC) in predicting microalbuminuria in subsequent 24-hour urines excretion of ≥ 30 mg (UAE). A receiver operating characteristics (ROC) curve is shown on the left. Two arbitrary cut-off values for UAC (in mg/L) are shown by markers and values. The value lying on the intersection of the ROC curve and the 100%-to-100% diagonal is defined “discriminator value” (DV). Sensitivity and specificity for a number of UAC cut-off values are shown on the right (Table). Other abbreviations are: AUC, area-under-the-curve; TPR, true positive rate; FPR, false positive rate; FNR, false negative rate.

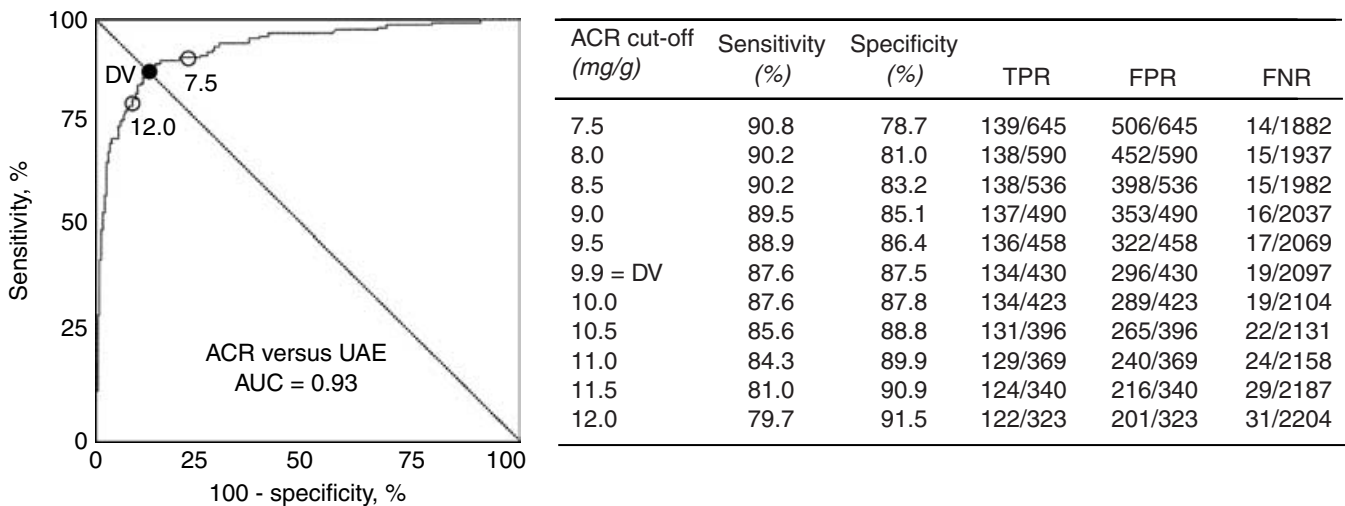


Fig. 2. Diagnostic performance of albumin-creatinine ratio in a spot morning urine sample (ACR) in predicting microalbuminuria in subsequent 24-hour urines. A receiver operating characteristics (ROC) curve is shown on the left. Two arbitrary cut-off values for ACR (in mg/g) are shown by markers and values. The value lying on the intersection of the ROC curve and the 100%-to-100% diagonal is defined “discriminator value” (DV). Sensitivity and specificity for a number of ACR cut-off values are shown on the right (Table). Other abbreviations are: AUC, area-under-the-curve; TPR, true positive rate; FPR, false positive rate; FNR, false negative rate.

females in urinary creatinine excretion, gender specific cut-off values for ACR were proposed by Warram et al: for males, an ACR ≥ 17 mg/g and for females an ACR ≥ 25 mg/g [18]. Using these gender specific cut-off values, sensitivity in males and females increases, but remains low, whereas specificity is hardly affected (Table 3).

DISCUSSION

Our data indicate that in the general population UAC and urinary ACR measured in a spot morning urine sample have satisfying, and numerically similar, power

to predict which individuals will have a 24-hour UAE ≥ 30 mg/24-hour in subsequent 24-hour urine collections. Furthermore, our data suggest that applying traditionally used cut-off values for UAC and ACR results in low sensitivity, and thus, in a relatively large percentage of false-negative test results for predicting microalbuminuria.

In the general population, only few studies have been devoted to the evaluation of UAC and ACR versus timed urine collection procedures [14, 19–23]. Most of these involved only small numbers of subjects, with the consequence that confidence intervals for sensitivity and specificity are wide [14, 19, 21–23]. More important, nearly all

Table 2. Diagnostic performance of albumin-creatinine ratio (ACR) and urinary albumin concentration (UAC) in a spot morning urine collection in predicting a 24-hour urinary albumin excretion of ≥ 30 mg (UAE)

	Number	UAE ≥ 30 mg/24h %	Albumin-creatinine ratio mg/g				Urinary albumin concentration mg/L			
			ROC AUC	DV mg/g	Sensitivity %	Specificity %	ROC AUC	DV mg/L	Sensitivity %	Specificity %
Overall	2527	6.1	0.93	9.9	87.6 (82.4–92.8)	87.5 (86.2–88.9)	0.92	11.2	85.0 (79.3–90.6)	85.0 (83.5–86.4) ^a
Subgroups										
Gender										
Men	1189	8.2	0.95	9.6	88.7 (82.3–95.0)	89.8 (88.0–91.6) ^b	0.95	12.1	86.6 (79.8–93.4)	86.8 (84.8–88.8) ^a
Women	1338	4.2	0.91	10.1	83.9 (74.3–93.5)	85.8 (83.9–87.7)	0.88	10.4	83.9 (74.3–93.5)	81.6 (79.5–83.7) ^{a,b}
Age, years										
<48	1246	3.0	0.90	7.3	83.8 (71.9–95.7)	83.6 (81.5–85.7) ^b	0.88	10.6	83.8 (71.9–95.7)	83.7 (81.6–85.8)
≥ 48	1281	9.1	0.94	11.1	88.8 (83.1–94.5)	87.1 (85.2–89.0)	0.94	11.6	85.3 (78.9–91.8)	85.2 (83.2–87.3)
Weight, kg										
≥ 76.0	1287 ^c	8.3	0.95	10.2	88.8 (82.8–94.8)	88.8 (87.0–90.6)	0.94	12.1	87.9 (81.7–94.0)	88.1 (86.2–89.9) ^b
< 76.0	1197 ^c	3.8	0.91	9.0	84.4 (73.9–95.0)	84.7 (82.6–86.8) ^b	0.88	10.6	82.2 (71.1–93.4)	82.1 (79.9–84.3) ^{a,b}
Race										
Caucasian	2386 ^c	5.9	0.94	10.1	87.9 (82.6–93.3)	88.2 (86.9–89.5)	0.93	11.2	85.1 (79.2–91.0)	85.3 (83.9–86.8) ^a
Non-Caucasian	115 ^c	7.0	0.89	7.8	87.5 (64.6–100)	81.3 (73.9–88.7)	0.87	11.1	75.0 (45.0–100)	77.6 (69.7–85.5)
Type 2 DM										
No	2437 ^c	5.7	0.93	9.6	87.0 (81.3–92.6)	87.3 (86.0–88.7)	0.92	11.1	84.8 (78.8–90.8)	85.0 (83.6–86.5) ^a
Yes	66 ^c	19.7	0.93	16.3	84.6 (65.0–100)	84.9 (75.3–94.5)	0.91	16.1	76.9 (54.0–99.8)	75.5 (63.9–87.1)

Abbreviations are: UAE, 24-hr urinary albumin excretion; ROC, receiver operating curve; AUC, area under the curve; DV, discriminatory value. Values for sensitivity and specificity (means and 95% confidence interval) are given for the discriminator value in the overall group and in several subgroups. Subgroups for age and weight are defined as $<$ or \geq the median value.

^a $P < 0.05$ ACR value versus corresponding UAC value.

^b $P < 0.05$ subgroup value versus overall value.

^c Information on weight, race, and type 2 DM is not available in all subjects.

of these studies are hampered by the fact that they, unlike the procedure to be followed in mass screening, used a portion of a 24-hour urine collection to measure UAC or ACR and the same 24-hour urine collection for determination of the reference value UAE. This way of analyzing data addresses another question, that being whether a spot morning urine sample can replace a 24-hour urine collection. It is expected to result in falsely high values for sensitivity and specificity because it does not take into account day-to-day variability in albuminuria. Thus, to our knowledge, our study is the first to investigate the validity of albumin measurements from a spot morning urine sample to identify in the general population subjects with abnormal urinary albumin excretion in subsequent 24-hour urine collections.

Theoretically, mass screening to identify subjects with a UAE ≥ 30 mg/24-hour by measuring UAC has the disadvantage that this latter parameter is influenced by variations in urinary volume. When urine is more concentrated, the concentration of albumin is higher and vice versa. Therefore, a loss of specificity and sensitivity might be expected. For this reason, the urinary albumin concentration can be divided by the urinary creatinine concentration (ACR ratio), thus correcting for variations in urinary volume. The disadvantage of the use of ACR is, however, that additional measurement of urinary creatinine is needed at the expense of extra costs and additional variability, the amount depending on the creatinine measurement, per se, and on interindividual differences in urinary creatinine excretion. Our data suggest that there is hardly any difference in power of UAC versus ACR in predicting a UAE ≥ 30 mg/24-hour: the areas under both ROC curves are good and nearly similar (0.92 versus 0.93, respectively, $P = \text{NS}$). Moreover, sensitivity and specificity for both indicators are acceptable (Figs. 1 and 2). When we defined specific subgroups according to differences in creatinine generation rate in order to try to improve the diagnostic performance of ACR in predicting an abnormal 24-hour urinary albumin, the AUC, sensitivity, and specificity for ACR in each subgroup was not relevantly higher than in the overall population. These results were corroborated in our second data set. Determination of creatinine in large numbers of spot morning urine samples obtained in mass screening will result in substantial costs, the exact amount of which will vary per laboratory. In order to keep costs and the burden involved in mass screening for microalbuminuria as low as possible, we therefore propose prescreening by measuring in a spot morning urine sample only urinary albumin concentration. Those subjects with a urinary albumin concentration above a certain predefined level should be asked to collect 24-hour urines.

We want to emphasize that the use of UAC over ACR is a cheaper test with a comparable ability to screen for disease. Its utility is purely as a screening tool. Monitoring

Table 3. Diagnostic performance of traditionally used cut-off values for urinary albumin concentration (UAC) and albumin-creatinine ratio (ACR) in predicting microalbuminuria in subsequent 24-hour urines

	(Sub)group	Cut-off value	Sensitivity %	Specificity %	TPR	FPR	FNR
UAC	All	≥20 mg/L	69.3 (62.0–76.6)	95.8 (95.0–96.6)	106/205 (52%)	99/205 (48%)	47/2322 (2.0%)
ACR	All	≥30 mg/g	49.0 (71.1–56.9)	98.7 (98.2–99.1)	75/107 (70%)	32/107 (30%)	78/2420 (3.2%)
	Male specific	≥17 mg/g	73.2 (64.4–82.0)	97.8 (96.9–98.7)	71/95 (75%)	24/95 (25%)	26/1094 (2.4%)
	Female specific	≥25 mg/g	51.8 (38.7–64.9)	97.7 (96.8–98.5)	29/59 (49%)	30/59 (51%)	27/1279 (2.1%)
	All gender specific		65.4 (57.8–72.9)	97.7 (97.1–98.3)	100/154 (65%)	54/154 (35%)	53/2373 (2.1%)

Abbreviations are: TPR, true positive rate; FPR, false positive rate; FNR, false negative rate. Values for sensitivity and specificity are given as means and 95% confidence intervals.

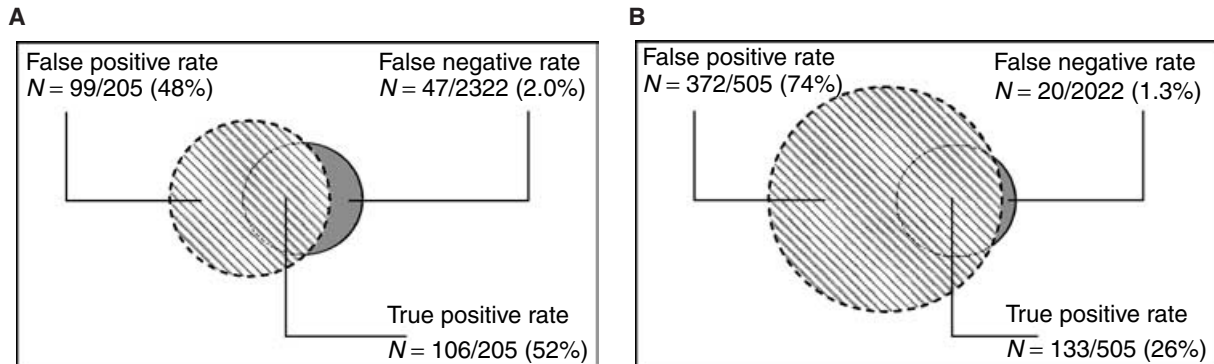


Fig. 3. Venn diagrams for screening on urinary albumin concentration (UAC) in a spot morning urine collection to identify subjects with microalbuminuria in subsequent 24-hour urine collections. Diagram A shows the situation in the general population ($N = 2527$), with the traditionally used cut-off value of 20 mg/L. The hatched circle represents individuals with a positive test result (spot morning UAC ≥ 20 mg/L, $N = 205$), whereas the solid gray circle represents individuals with a positive “gold standard” (24-hour urine collection UAE ≥ 30 mg, $N = 153$). Diagram B shows the situation when in the same population the cut-off value 11 mg/L is chosen. Now, 505 people have a positive test result (UAC ≥ 11 mg/L).

individual patients over time is another issue. It may well be that in this case UAC may be not useful due to variations caused by changes in urinary volume, whereas ACR due to relatively parallel changes in urinary creatinine concentration may be more helpful in patient monitoring.

The next question to be addressed is which cut-off value for UAC to use. Traditionally, the cut-off value indicating a UAE ≥ 30 mg/24-hour has been 20 mg/L [8, 9]. This specific value has been derived from studies performed in diabetic subjects that plotted UAC versus UAE [24]. Regression analysis in these studies showed that a UAE of 30 mg/24-hour corresponded with a UAC of approximately 20 mg/L. It is questionable whether this value, derived from studies in diabetic individuals, will be similar to the one in the general population. More important, it should again be noted that these studies used the same urine collection to measure UAE and UAC, not taking into account day-to-day variability in albuminuria [24]. In contrast, in our study, the spot morning urine sample is used to predict which individuals have an abnormal urinary albumin excretion in a subsequent 24-hour urine collection. In this setting, using the traditional UAC cut-off value of 20 mg/L to identify subjects “at risk” for abnormal albuminuria, specificity appears high (95.8%), whereas sensitivity is low (69.3%). Consequently, the number of false-negative test results is unacceptably high (47 out of 153 subjects with a UAE ≥ 30 mg/24-hour would

not be detected, Fig. 3). In order to meet the requirements for mass screening, the number of false negatives should be as low as possible. On the other hand, decreasing the percentage of false-negative test results is expected to result in increases in the percentage of false positives. Since the “penalty” of being false positive is merely that a 24-hour urine collection has to be performed, we think that a relatively large number of false-positive test results is acceptable. Based on our findings, we therefore propose that an UAC cut-off value of 11 mg/L should be used for mass screening in the general population to identify subjects that will have a UAE ≥ 30 mg/24-hour. Using this cut-off value, the percentage of false-negative test results drops. Now only 20 out of 153 subjects with a UAE ≥ 30 mg/24-hour are not detected (Fig. 3).

The concept of screening for abnormal urinary albumin excretion is only worthwhile when interventions to reduce the high number cardiovascular events in subjects with this condition are possible and of proven clinical benefit. Of interest, subgroup analysis of the HOPE study, a recent large-scale, randomized, controlled trial, showed that in those subjects with higher baseline levels of albuminuria, intervention with an ACE inhibitor is of particular value. This held true both in diabetic and nondiabetic patients [25, 26]. Furthermore, we recently completed a randomized, controlled trial that was especially designed to investigate this issue: the PREVEND IT study [27]. In

this study, 864 normotensive, normocholesterolemic subjects with a UAE ≥ 30 mg/24-hour were treated in a 2 \times 2 factorial design with the ACE inhibitor fosinopril or placebo, and the HMG CoA reductase inhibitor pravastatin or placebo. It was shown that the ACE inhibitor lowered albuminuria by 30% and reduced the relative risk for the combined primary outcome parameter of cardiovascular morbidity and mortality by 44% ($P = 0.07$). In this study, the beneficial effect of the ACE inhibitor was dependent of the baseline value of albuminuria: the higher albuminuria, the more protective the effect of the ACE inhibitor [26]. Further studies to confirm the clinical benefit of intervention based on the presence of albuminuria are needed.

Such studies should also address the issue of cost effectiveness of mass screening of the general population with subsequent intervention. Recently, Boulware et al concluded that a strategy of annual screening for proteinuria by primary care physicians, with follow-up testing and treatment with ACE inhibitors, would not be cost effective to slow progression of kidney disease [28]. However, the results of this study are strongly influenced by the low yield of the screening test (looking only for dipstick positive proteinuria), the high costs for the screening by the primary care physicians, and the fact that they only took into account benefits with regard to the prevention of end-stage renal disease. Our screening approach, measuring UAC in a spot morning urine samples that are sent in vials by post, looking for microalbuminuria, will result in more cases per 1000 persons screened, and is moreover less expensive [29]. Such a screening program may help to tackle not only the epidemic of end-stage renal disease, but at the same time, also to lower cardiovascular morbidity and mortality. We hope that such an approach will be cost effective. A formal analysis is planned.

One should realize that subjects using insulin, pregnant women, and subjects with leukocyturia and/or erythrocyturia were excluded. Screening for albuminuria is already accepted clinical practice for insulin-treated diabetics. Therefore, there is no need for such subjects to take part in screening of the general population. The same holds true for pregnant women, in whom albuminuria may increase because of pregnancy-related hyperfiltration, and may indicate the onset of (pre-)eclampsia. It is generally accepted that the presence of leukocyturia and/or erythrocyturia may indicate a urinary tract infection or bleeding. In such cases, the amount of albuminuria is not thought to reflect endothelial damage, but merely the result of infection/bleeding. Such urine samples should not be used as risk indicators [9, 10]. We therefore are convinced that our results are as robust as possible, of course, keeping in mind that these results are valid for the Dutch situation, and should be corroborated in other populations that may differ in (socio)demographics.

CONCLUSION

We found that the diagnostic performance of measuring urinary albumin concentration in a spot morning urine sample in predicting an albumin excretion ≥ 30 mg in subsequent 24-hour urine collections is satisfactory and comparable to that of albumin-creatinine ratio. In order to keep the burden and costs involved in mass screening of the general population as low as possible, we therefore propose to measure UAC in a spot morning urine sample as prescreening. Those subjects with a UAC above a certain predefined level (e.g., 11 mg/L) should be asked to collect timed urine samples.

Reprint requests to R.T. Gansevoort, M.D., Ph.D., Division of Nephrology, Department of Medicine, University Hospital Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands.
E-mail: R.T.Gansevoort@INT.AZG.NL

REFERENCES

1. MOGENSEN CE: Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 310:356–360, 1984
2. ROSSING P, HOUGAARD P, BORCH-JOHNSEN K, PARVING HH: Predictors of mortality in insulin dependent diabetes: 10 year observational follow up study. *BMJ* 313:779–384, 1996
3. GERSTEIN HC, MANN JF, YI Q, et al: Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 286:421–426, 2001
4. VIBERTI GC, HILL RD, JARRETT RJ, et al: Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet* 1:1430–1432, 1982
5. ROMUNDSTAD S, HOLMEN J, KVENILD K, et al: Microalbuminuria and all-cause mortality in 2,089 apparently healthy individuals: A 4.4-year follow-up study. The Nord-Trøndelag Health Study (HUNT), Norway. *Am J Kidney Dis* 42:466–473, 2003
6. JAGER A, KOSTENSE PJ, RUHE HG, et al: Microalbuminuria and peripheral arterial disease are independent predictors of cardiovascular and all-cause mortality, especially among hypertensive subjects: Five-year follow-up of the Hoorn Study. *Arterioscler Thromb Vasc Biol* 19:617–624, 1999
7. HILLEGE HL, FIDLER V, DIERCKX GF, et al: Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 106:1777–1782, 2002
8. AMERICAN DIABETES ASSOCIATION: Diabetic nephropathy. *Diabetes Care* 25:S85–S89, 2002
9. KEANE WF, EKNOYAN G: Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): A position paper of the National Kidney Foundation. *Am J Kidney Dis* 33:1004–1010, 1999
10. PINTO-SIETSMA SJ, JANSSEN WM, HILLEGE HL, et al: Urinary albumin excretion is associated with renal functional abnormalities in a nondiabetic population. *J Am Soc Nephrol* 11:1882–1888, 2000
11. HILLEGE HL, JANSSEN WM, BAK AA, et al: Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. *J Intern Med* 249:519–526, 2001
12. GARDNER MJ, ALTMAN DG: Calculating confidence intervals for proportions and their differences, in *Statistics with Confidence: Confidence Intervals and Statistical Guidelines*, edited by Gardner MJ, Altman DG, London, BMJ, 1989, pp 28–33
13. ALTMAN DG (editor): *Practical Statistics for Medical Research*, London, 1999, pp 415
14. CONNELL SJ, HOLLIS S, TIESZEN KL, et al: Gender and the clinical usefulness of the albumin:creatinine ratio. *Diabet Med* 11:32–36, 1994
15. HOULIHAN CA, TSALAMANDRIS C, AKDENIZ A, JERUMS G: Albumin

- to creatinine ratio: A screening test with limitations. *Am J Kidney Dis* 39:1183–1189, 2002
16. JACOBS DR, MURTAUGH MA, STEFFES M, et al: Gender- and race-specific determination of albumin excretion rate using albumin-to-creatinine ratio in single, untimed urine specimens. *Am J Epidemiol* 155:1114–1119, 2002
 17. MATTIX HJ, HSU CY, SHAYKEVICH S, CURHAN G: Use of the albumin/creatinine ratio to detect microalbuminuria: Implications of sex and race. *J Am Soc Nephrol* 13:1034–1039, 2002
 18. WARRAM JH, GEARIN G, LAFFEL L, KROLEWSKI AS: Effect of duration of type 1 diabetes on the prevalence of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio. *J Am Soc Nephrol* 7:930–937, 1999
 19. DERHASCHNIG U, KITTLER H, WOISETSCHLAGER C, et al: Microalbumin measurement alone or calculation of the albumin/creatinine ratio for the screening of hypertension patients? *Nephrol Dial Transplant* 17:81–85, 2002
 20. JENSEN JS, CLAUSEN P, BORCH-JOHNSEN K, et al: Detecting microalbuminuria by urinary albumin/creatinine concentration ratio. *Nephrol Dial Transplant* 12(Suppl 2):6–9, 1997
 21. TOWNSEND JC: Albumin to creatinine ratio: An unreliable index of 24 h albumin excretion in healthy adults. *N Z Med J* 100:66–67, 1987
 22. MOORE RR, JR., HIRATA-DULAS CA, KASISKE BL: Use of urine specific gravity to improve screening for albuminuria. *Kidney Int* 52:240–243, 1997
 23. NEWMAN DJ, PUGIA MJ, LOTT JA, et al: Urinary protein and albumin excretion corrected by creatinine and specific gravity. *Clin Chim Acta* 294:139–155, 2000
 24. BAKKER AJ: Detection of microalbuminuria. Receiver operating characteristic curve analysis favors albumin-to-creatinine ratio over albumin concentration. *Diabetes Care* 22:307–313, 1999
 25. HEART OUTCOMES PREVENTION EVALUATION STUDY INVESTIGATORS: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. *Lancet* 355:253–259, 2000
 26. HEART OUTCOMES PREVENTION EVALUATION STUDY INVESTIGATORS: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high risk patients. *N Engl J Med* 342:145–153, 2000
 27. ASSELBERGS FW, DIERCKS GFH, HILLEGE HL, et al, ON BEHALF OF THE PREVEND IT INVESTIGATORS: Effects of fosinopril and pravastatin on cardiovascular events in microalbuminuric subjects without hypertension and hypercholesterolemia: A single-center, double-blind, randomised, placebo-controlled trial with 2 × 2 factorial design (PREVEND IT). *Circulation* 108:2723(A), 2003
 28. BOULWARE LE, JAAR BG, TARVER-CARR ME, et al: Screening for proteinuria in US adults. A cost-effectiveness analysis. *JAMA* 290:3101–3114, 2003
 29. GANSEVOORT RT, DE JONG PE, POSTMA MJ: Cost-effectiveness of screening for proteinuria. *JAMA* 291:1442–1443, 2004

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.

Copyright of *Kidney International Supplement* is the property of Nature Publishing Group and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.