Frontiers in Nephrology

Screening, Monitoring, and Treatment of Albuminuria: Public Health Perspectives

Paul E. de Jong* and Gary C. Curhan†

**Division of Nephrology, Department of Medicine, University Medical Center Groningen, Groningen, The Netherlands; and †Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts*

Microalbuminuria is an early sign of progressive cardiovascular and renal disease in individuals with and without diabetes. Despite compelling data, at present only a minority of patients with diabetes and rarely individuals without diabetes are screened for albuminuria in a systematic way. All of the criteria to implement systematic albuminuria screening are fulfilled in diabetes, and most are nearly fulfilled for microalbuminuria screening in individuals without diabetes. Because of the growing evidence that treatment of microalbuminuria in individuals without diabetes may offer a cost-effective benefit to prevent cardiovascular disease, nephrologists and other health care providers should pay more attention to the early detection and subsequent treatment of individuals with microalbuminuria.

J Am Soc Nephrol 17: 2120–2126, 2006. doi: 10.1681/ASN.2006010097

Microalbuminuria is an early sign of progressive cardiovascular and renal disease. We discuss whether screening for albuminuria is warranted and, if so, how screening and subsequent monitoring could be carried out.

The criteria that a screening program should fulfill have been described by Wilson and Jungner (1) and are given in Table 1. As more data are available on the impact of elevated albuminuria on renal and cardiovascular prognosis in individuals with diabetes than in individuals without diabetes, we discuss separately the evidence that is available for the need for albuminuria testing in these two groups.

Screening for Albuminuria to Prevent Chronic Kidney Disease and Cardiovascular Disease

Albuminuria screening first may be used as a tool to detect individuals with undiagnosed chronic kidney disease (CKD). Elevated albuminuria (30 to 300 mg/d albumin is the definition of microalbuminuria) is an early predictor of progressive renal function loss in type 1 (2,3) and type 2 diabetes (4,5). At the time that microalbuminuria becomes manifest, GFR typically is normal or elevated or only modestly impaired (stage 1 or 2 CKD). Increased urinary albumin excretion (UAE) also may indicate a worse renal prognosis in individuals without diabetes. In a Japanese study, >100,000 individuals were tested for dipstick proteinuria. After a period of >17 yr, the likelihood of being on dialysis increased according to the degree of dipstick proteinuria at baseline (6). A similar finding was reported from the Prevention of Renal and Vascular End Stage Disease (PREVEND) study: After a 4.2-yr follow-up, the number of individuals who *de novo* had developed stage 3 or worse CKD was related to baseline albuminuria (7) (Figure 1). By screening for elevated albuminuria, one of course will not only detect individuals with microalbuminuria but also individuals with macroalbuminuria (>300 mg/d), who most likely are already in stage 3 or 4 CKD.

The benefits of screening for albuminuria in the short term are to detect individuals who are at risk for cardiovascular disease in individuals with diabetes (8) and individuals without diabetes (9,10). We should keep this in mind in view of the pros and cons for screening for albuminuria in the general population. Especially in individuals without diabetes, the short-term benefits will be to prevent cardiovascular events; only in the long term might it be found to prevent ESRD.

Does Screening for Albuminuria Help Detect Individuals at Risk for CKD and CVD in an Early Phase?

The time course of albuminuria in relation to progressive renal function loss has been well described. When microalbuminuria becomes manifest, the phase of glomerular hyperfiltration is shifting to that of progressive renal function loss. This has been shown in type 1 (11) and type 2 diabetes (5). This loss of GFR ultimately leads to ESRD. Evidence is accumulating that the same holds true for individuals who do not have diabetes and have microalbuminuria (12,13). It is a great benefit that we may detect individuals who are at risk for progressive disease in an early phase, because it is widely known that CKD typically becomes symptomatic only in stages 4 and 5 CKD. In that

Published online ahead of print. Publication date available at www.jasn.org.

Address correspondence to: Dr. Paul E. de Jong, Division of Nephrology, Department of Medicine, University Medical Center Groningen, Groningen University, Hanzeplein 1, 9713 GZ Groningen, The Netherlands. Phone: +31-50-3612955; Fax: +31-50-3619310; E-mail p.e.de.jong@int.umcg.nl

ISSN: 1046-6673/1708-2120

Table 1. The Wilson-Jungner criteria

	Individuals with Diabetes	General Population
1. The disease for which the screening test could be used is an important health problem.	Yes	Yes
2. The natural course of the disease should be well described.	Yes	Yes
3. The disease should be detectable in an early phase.	Yes	Yes
4. Treatment in an early phase should offer benefit.	Yes	Probably
5. A suitable test should be available to indicate the early phase of the disease.	Yes	Yes
6. The test should be acceptable, and there should be a well-defined cutoff.	Yes	Yes
7. The interval at which it should be tested should be well known.	Yes	Not yet
8. The extra workload needed in case of a positive test should be possible and acceptable.	Yes	Yes
9. The risk of screening, both somatic and psychiatric, should outweigh the benefits.	Yes	Yes
10. Screening and subsequent treatment in case of positive tests should be cost-effective.	Yes	Probably

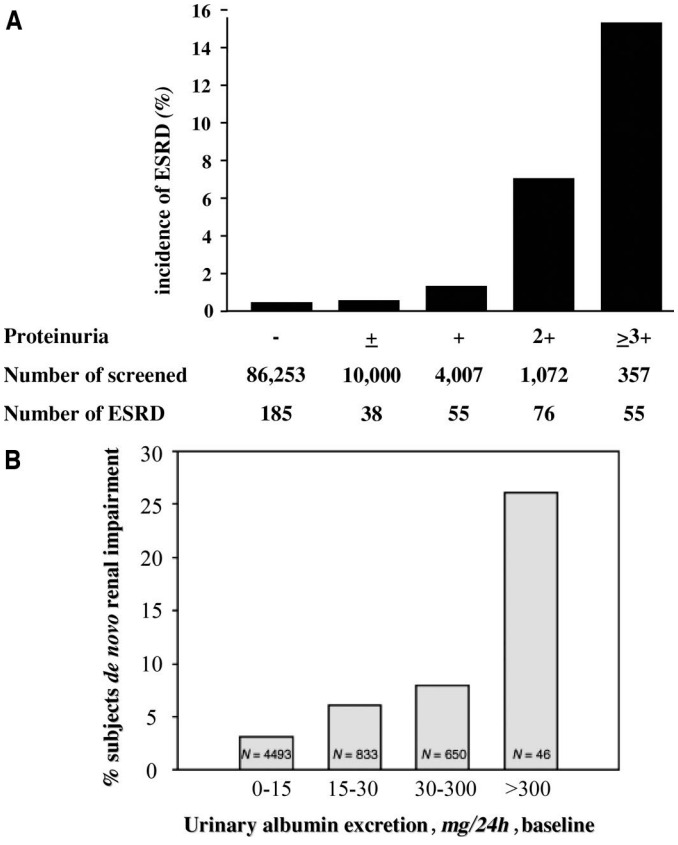

Figure 1. The incidence of new ESRD after 17 yr of follow-up (A) and of new stage 3 chronic kidney disease after 4.2 yr of follow-up (B) according to dipstick proteinuria (A) or albuminuria (B) in a community-based screening in Japan (A) or the Netherlands (B) (references [6] and [7], respectively).

respect, it is noteworthy that most patients with CKD are not aware of having diseased kidneys (14). Patients with earlier stages of CKD need increased attention because they are at increased risk for cardiovascular disease. Because nephrologists presently are focusing predominantly on renal replacement therapy programs for patients with ESRD, the International Society of Nephrology issued a call to action to pay attention to patients with earlier CKD. Remuzzi and Weening (15) drew the parallel with an iceberg. What we are looking for presently is only the tip of what we should look for in the future.

Is Lowering of Albuminuria, Started at an Early Phase, Associated with Better Renal and Cardiovascular Outcomes?

The trials in individuals with macroalbuminuria (16–19) showed that lowering of albuminuria by either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) was associated with a better renal (20) and cardiovascular (21) outcome. Moreover, it has been shown that the renoprotective and cardioprotective effects were related to the extent to which albuminuria was lowered. These trials all were performed in patients with stage 3 or 4 CKD. Recently, however, a few trials have been carried out in individuals with earlier stages of renal disease. The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA) study in patients with type 2 diabetes and microalbuminuria (GFR $>$ 90 ml/min) showed that treatment with an ARB effectively prevented progression from micro- to macroalbuminuria (22). The Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) showed that an ARB even effectively prevented progression from normo- to microalbuminuria, again in type 2 diabetes (23). There are few data to show that lowering of albuminuria in individuals with still normal GFR results in a better cardiovascular outcome. Gaede *et al.* (24) recently showed that an intervention that aimed to correct multiple risk factors in type 2 diabetes and microalbuminuria reduced the risk for cardiovascular and microvascular events by approximately 50%. In the Prevention of Renal and Vascular Endstage Disease Inter-

vention Trial (PREVEND IT), who did not have diabetes but had UAE of 15 to 300 mg/d and a normal GFR were treated for 4 yr with fosinopril and/or pravastatin. There was a trend for fewer cardiovascular events in the fosinopril-treated group, in which albuminuria was lowered by 30% persistently during the 4-yr period. Pravastatin, in contrast, did not lower albuminuria and had no effect on cardiovascular events (25). The group with the higher baseline albuminuria (50 to 300 mg/d) showed the most benefit from fosinopril for preventing cardiovascular events.

Is the Screening Test Acceptable and Reliable?

The albuminuria screening debate is hampered by differences in laboratory methods used, urine samples studied, and definitions of microalbuminuria, which lead to different conclusions. The best approach depends on the number of individuals to be screened and the way the screening will be organized.

Which Laboratory Method Should We Use?

Traditionally, the dipstick test was used to detect protein in the urine. The test is semiquantitative, however, and insensitive to detect reliably albumin concentrations in ranges <300 mg/d albumin. At present, various antibody-based methods are used to measure lower levels of urinary albumin. These include RIA, nephelometry, immunoturbidimetry, and ELISA. It is beyond the scope of this review to evaluate these different techniques in detail. Recently, an HPLC method was developed by which not only immunoreactive but also immunounreactive albumin is measured (26). Using this method, more patients are found to have an albumin excretion in the microalbuminuric range (27). Whether patients who are detected as having microalbuminuria by HPLC are equally at risk for progressive renal and cardiovascular disease as those who are detected by the traditional antibody-based methods has yet to be determined. Whichever method is chosen, it is preferable to measure albumin in fresh samples (28).

These methods all require laboratory facilities. Antibody-based dipstick tests for microalbuminuria also are available (29,30). Although only semiquantitative, these tests have the advantage that they can be used easily by the general practitioner or the patient at home. A recent study in hypertensive patients found a sensitivity of 88%, a specificity of 80%, a positive predictive value of 69%, and a negative predictive value of 92% (30). The development of point-of-care testing systems may provide in the near future a quantitative urine albumin value within seconds.

Which Sample Should We Collect?

For the diagnosis of microalbuminuria, a 24-h urine collection is the gold standard. Because of the effort involved, it is not the method of choice for screening. The second best is a timed overnight urine collection. Again, because this requires collection of urine over a given time period, this may be acceptable for screening specific patient groups such as patients with diabetes or hypertension, but it is less feasible for population screening. The next best is a first-morning urine sample. This has the advantage over a spot-urine sample because it is always performed at the same time of the day, and it is least influenced by hydration status and physical activity of the patient, reducing the variability that is caused by these factors. This may be a good choice for population screening if the patient is asked to mail a urine sample, as was done in the PREVEND study (31). In clinical practice, however, a spot-urine sample is collected when the patient visits either the general practitioner or the health care office, where the screening takes place. Some of the variability in timing of collection can be overcome by correcting urinary albumin concentration for urinary creatinine concentration.

Taking these considerations together, the best approach is to use a spot-urine sample (either the first-morning void or at the time of the visit to the medical office) as a prescreening. The patients whose urine is found positive then either should deliver two more samples to confirm whether the first value indeed was abnormal or, preferably, should collect two 24-h urine samples. This latter approach was tested in the PREVEND study. After using just one first-morning urine sample for measurement of urinary albumin concentration, patients with a urinary albumin concentration above a certain cutoff were invited for two 24-h urine collections. It was suggested that a cutoff value of 10 mg albumin/L could be used for mass screening to identify individuals who are more likely to have a UAE >30 mg/24 h (32).

How Should We Express Albuminuria, and Which Definition Should be Used for Abnormally Elevated Albuminuria?

Preferably, the excretion of albumin per unit of time should be used: UAE per 24 h or per minute (in case of timed overnight collections). For untimed samples, the albumin-to-creatinine ratio is advocated most (33). Because it corrects albumin for creatinine concentration, it may be more reliable than just a urinary albumin concentration. The albumin-to-creatinine ratio, however, introduces the need to use different definitions for an abnormal value for men and women (Table 2). Moreover, creatinine excretion in the urine depends not only on gender but also on age and race (34,35). This may explain why urinary albumin concentration from a spot sample performs equally well for the definition of microalbuminuria as albumin-to-creatinine ratio (32). In case a specific individual is followed over time with serial urine samples, the albumin-to-creatinine ratio may offer an advantage over albumin concentration alone.

The definitions for microalbuminuria and macroalbuminuria are given in Table 2. Because the relation between albuminuria and an increased cardiovascular (or renal) risk is continuous, it is difficult to conclude what is a normal level. In general, it is desirable to define specific cutoff values that could be used in clinical guidelines. The lower cutoff value may change over the years, as has been seen for BP and cholesterol values in the past decades. In fact, cutoff levels are defined depending the cost-effectiveness of screening for albuminuria and treatment to lower albuminuria in an attempt to prevent cardiovascular disease and CKD. If it is found to be cost-effective to lower

Table 2. Classification of abnormal urinary albumin excretion

	24-H Urine Albumin (mg/24 h)	Overnight Urine Albumin (μg/min)	Spot Urine			
			Albumin (mg/L)	Albumin/Creatinine Ratio		
				Gender	mg/mmol	mg/g
Normal	<15	<10	<10	M	<1.25	<10
				F	<1.75	<15
High normal	15 to <30	10 to <20	10 to <20	M	1.25 to <2.5	10 to <20
				F	1.75 to <3.5	15 to <30
Microalbuminuria	30 to <300	20 to <200	20 to <200	M	2.5 to <25	20 to <200
				F	3.5 to <35	30 to <300
Macroalbuminuria	>300	>200	>200	M	>25	>200
				F	>35	>300

albuminuria from levels >15 mg/L, then it is wise to set the definition of abnormal albuminuria at that level. It may be appropriate to use a lower albuminuria cutoff in case of concomitant morbidities, such as diabetes.

What Extra Work Should Be Done When an Individual Is Found to Be Positive?

When someone is found to be positive for microalbuminuria, one first should confirm the positive test by repeated testing. It has been argued that two of the three tests need to be positive. After confirmation, one should look for a potential cause underlying the albuminuria, especially in case of macroalbuminuria. One should ascertain whether there is any classical renal disease, such as glomerulonephritis or interstitial nephritis. If medical history for such a disease is negative, then a urinary sediment and measurement of renal function may be sufficient. In addition, cardiovascular risk factors (BP, cholesterol, and glucose) should be screened.

Is Screening to Detect Microalbuminuria Followed by Appropriate Treatment of Positive Individuals Cost-Effective?

In diabetes, it has been shown that ACE inhibitor or ARB treatment is cost-effective (36) for preventing ESRD. Moreover, it has been shown that, in the long term, cost-effectiveness is even more favorable when treatment is started earlier (37). The evidence for individuals without diabetes is limited. Boulware *et al.* (38) showed that screening for dipstick proteinuria by primary care providers followed by treatment of those who were positive was not cost-effective in terms of preventing ESRD. This is not surprising, because it generally takes many years before a who does not have diabetes but has dipstick-positive proteinuria will reach ESRD. There are alternatives to the Boulware approach, however (39). First, the use of a dipstick would require screening of many individuals to find the few who were positive, whereas screening for microalbuminuria would detect more positive individuals; the prevalence of microalbuminuria is approximately 30 times higher than that of macroalbuminuria (31). Although the costs of an albuminuria measurement are higher than those of a dipstick test, the higher yield of the test will outweigh that difference. Second, screening *via* the general practitioner is labor-intensive, whereas the delivery of a urine sample to a central laboratory facility will be cheaper. Third, although it takes many years for an individual with microalbuminuria to develop stage 5 CKD, cardiovascular events may be manifest already within a few years. We therefore studied the cost-effectiveness of screening for albuminuria and subsequent treatment of individuals with an elevated UAE with an ACE inhibitor. This approach was cost-effective to prevent cardiovascular events (40).

How Can a Screening Program for Albuminuria Be Organized?

Taking the evidence together, we can conclude that screening for albuminuria and treatment of those who are found to be positive is well accepted in individuals with diabetes. Indeed, annual screening for albuminuria in individuals with diabetes is recommended in the guidelines of the American Diabetes Association (41). At present, it seems too early to recommend such an approach for the general population: More studies to examine the beneficial effect of albuminuria lowering are needed. It seems sensible to screen individuals who are at higher risk for cardiovascular disease and CKD. Besides individuals with diabetes, attention should focus on individuals with hypertension (42), hyperlipidemia, and obesity and those who smoke. However, a focused approach will overlook many individuals with an elevated UAE. First, many individuals are not aware that they have diabetes, hypertension, or hyperlipidemia. Indeed, in the PREVEND study, two thirds of those screened were found to have previously undiagnosed hypertension and/or diabetes (43). Second, it has been shown that UAE gradually increases with increasing plasma glucose level or systolic or diastolic BP even within the normal ranges (44). This suggests that individuals with higher but still normal levels of plasma glucose and systolic or diastolic BP are at risk for having microalbuminuria. They will not be detected when the screening is limited only to those with manifest diabetes and/or hypertension. It is of interest that the presence of microalbuminuria may even precede manifest diabetes (45,46) and hypertension (47,48). Microalbuminuria may be considered

one of the earliest manifestations of the insulin resistance syndrome. Indeed, it has been shown that the prevalence of microalbuminuria increases according to the number of components of the metabolic syndrome present (49). The aforementioned data raise doubt whether we should limit our screening strategies to those with known risk factors or preferably should screen the general population.

The composition of the population and the type of health care delivery system will dictate the optimal design of the screening program. The components to consider include who will do the testing (*e.g.*, physician, nurse, technician), where the screening will take place (*e.g.*, clinic, health fair), and how it will be financially supported.

How Should a Patient with Microalbuminuria Be Monitored in the Long Term?

Screening for albuminuria in individuals with diabetes has been advocated to be performed once every year. In case of a positive test, it is advocated to repeat testing twice within 3 to 6 mo. If two of the three tests are positive, then treatment to lower albuminuria should be started (41). Thus far, no hard data are available for the optimal time interval for albuminuria testing in individuals with hypertension or in other groups. As progression of albuminuria may be slower in individuals without diabetes than in individuals with diabetes, it seems acceptable to perform albuminuria testing in individuals with hypertension or other risk categories every 3 yr.

Both in type 1 diabetes (50) and in the general population (51), progression and regression of albuminuria can be observed. After 4.2 yr, UAE had regressed in 9.8% individuals in the general population, whereas progression was found in 11.4%. Progression and regression of albuminuria were most prevalent in the group of individuals with a UAE of 15 to 30 mg/d (21.3 and 47.4%, respectively). This suggests that especially in individual with a borderline elevation in UAE, repeated testing every 3 to 5 yr is indicated.

Lowering of BP with agents that interfere with the renin-angiotensin-aldosterone system, such as ACE inhibitors or ARB is most effective for lowering UAE. It has been shown in patients with manifest renal disease (*i.e.*, those with overt proteinuria of >300 mg/d) that the extent to which proteinuria is lowered during treatment predicts the prevention of both CKD and progressive cardiovascular disease (20,21). It is highly likely but not proved that the same will hold true for individuals with microalbuminuria. Thus far, however, we cannot define a certain cutoff level below which albuminuria should be lowered; we suggest use of the same cutoff as for the definition of microalbuminuria: <30 mg/d.

Conclusion

There is compelling evidence that screening for albuminuria should be carried out in individuals with diabetes. Evidence is accumulating that it also should be implemented in individuals with hypertension and in individuals with increased cardiovascular and renal risk. Further studies are needed to confirm that systematic screening for albuminuria also is cost-effective in the general population. The short-term benefits for prevention of cardiovascular disease may outweigh those of the long-term prevention of ESRD.

References

1. Wilson JMG, Jungner F: *Principles and Practice of Screening for Disease. Public Health Papers, No 34*, Geneva, World Health Organization, 1968
2. Mogensen CE, Christensen CK: Predicting diabetic nephropathy in insulin-dependent patients. *N Engl J Med* 311: 89–93, 1984
3. Parving H-H, Oxenboll B, Svendsen PA, Christiansen JS, Andersen AR: Early detection of patients at risk of developing diabetic nephropathy. *Acta Endocrinol* 100: 550–555, 1982
4. Mogensen CE: Microalbuminuria predicts clinical proteinuria and early mortality in maturity onset diabetes. *N Engl J Med* 310: 356–360, 1986
5. Nelson RG, Bennet PH, Beck GJ, Tan M, Knowler WC, Mitch WE, Hirschman GH, Myers BD: Development and progression of renal disease in Pima Indians with non-insulin-dependent diabetes mellitus. *N Engl J Med* 335: 1636–1642, 1996
6. Iseki K, Ikemiya Y, Iseki C, Takishita S: Proteinuria and the risk of developing end-stage renal disease. *Kidney Int* 63: 1468–1474, 2003
7. Verhave JC, Gansevoort RT, Hillege HL, Bakker SJ, De Zeeuw D, de Jong PE; PREVEND Study Group: An elevated urinary albumin excretion predicts de novo development of renal function impairment in the general population. *Kidney Int Suppl* 92: S18–S21, 2004
8. Damsgaard EM, Froland A, Jorgensen OD, Mogensen CE: Microalbuminuria as predictor of increased mortality in elderly people. *BMJ* 300: 297–300, 1990
9. Borch-Johnsen K, Feldt-Rasmussen B, Strandgaard S, Schroll M, Jensen JS: Urinary albumin excretion. An independent predictor of ischemic heart disease. *Arterioscler Thromb Vasc Biol* 19: 1992–1997, 1999
10. Hillege HL, Fidler V, Diercks GFH, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, Gans RO, Janssen WM, Grobbee DE, de Jong PE; Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group: Urinary albumin excretion predicts cardiovascular and non-cardiovascular mortality in general population. *Circulation* 606: 1777–1782, 2002
11. Mogensen CE: Prediction of clinical diabetic nephropathy in IDDM patients. Alternatives to microalbuminuria? *Diabetes* 39: 761–767, 1990
12. Pinto-Sietsma SJ, Janssen WMT, Hillege HL, Navis G, De Zeeuw D, De Jong PE: Urinary albumin excretion is associated with renal functional abnormalities in a nondiabetic population. *J Am Soc Nephrol* 11: 1882–1888, 2000
13. De Jong PE, Brenner BM: From secondary to primary prevention of progressive renal disease: The case for screening for albuminuria. *Kidney Int* 66: 2109–2118, 2004
14. Coresh J, Byrd-Holt D, Astor BC, Briggs JP, Eggers PW, Lacher DA, Hostetter TH: Chronic kidney disease awareness, prevalence, and trends among US adults. *J Am Soc Nephrol* 16: 180–188, 2005
15. Remuzzi G, Weening JJ: Albuminuria as early test for vascular disease. *Lancet* 365: 556–557, 2005
16. The Gruppo Italiano di Studi Epidemiologici in Nephrolo-

gia (GISEN): Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric non-diabetic nephropathy. *Lancet* 349: 1857–1863, 1997
17. Lewis EJ, Hunsicker LG, Bain RP, Rhode RD: The effect of angiotensin converting enzyme inhibition on diabetic nephropathy. *N Engl J Med* 329: 1456–1462, 1993
18. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I; Collaborative Study Group: Renoprotective effects of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345: 851–860, 2001
19. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S; RENAAL Study Investigators: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345: 861–869, 2001
20. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, de Zeeuw D, Shahinfar S, Toto R, Levey AS; AIPRD Study Group: Progression of chronic kidney disease: The role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition—A patient-level meta-analysis. *Ann Intern Med* 139: 244–252, 2003
21. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, Snapinn S, Brenner BM: Albuminuria therapeutic target for cardiovascular protection in type 2 nephropathy. *Circulation* 110: 921–927, 2004
22. Parving HH, Lehnert H, Brochner-Mortensen J: The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 345: 870–878, 2001
23. Ruggenenti P, Fassi A, Ilieva AP, Bruno S, Iliev IP, Brusegan V, Rubis N, Gherardi G, Arnoldi F, Ganeva M, Ene-Iordache B, Gaspari F, Perna A, Bossi A, Trevisan R, Dodesini AR, Remuzzi G; Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators: Preventing microalbuminuria in type 2 diabetes. *N Engl J Med* 351: 1941–1951, 2004
24. Gaede P, Vedel P, Larsen N, Jensen GV, Parving H-H, Pedersen O: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 348: 383–393, 2003
25. Asselbergs FW, Diercks GFH, Hillege HL, van Boven AJ, Janssen WM, Voors AA, de Zeeuw D, de Jong PE, van Veldhuisen DJ, van Gilst WH; Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) Investigators: Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation* 110: 2809–2816, 2004
26. Comper WD, Jerums G, Osicka TM: Differences in urinary albumin detected by four immunoassays and high-performance liquid chromatography. *Clin Biochem* 37: 105–111, 2004
27. Brinkman JW, Bakker SJL, Gansevoort RT, Hillege HL, Kema IP, Gans RO, de Jong PE, de Zeeuw D: Which method for quantifying urinary albumin excretion gives what outcome? A comparison of immunonephelometry with HPLC. *Kidney Int Suppl* 92: S69–S75, 2004
28. Brinkman JW, Bakker SJL, Gansevoort RT de Jong PE, de Zeeuw D: Falsely low urinary albumin concentrations after prolonged frozen storage of urine samples. *Clin Chem* 51: 2181–2183, 2005
29. Mogensen CE, Viberti GC, Peheim E, Kutter D, Hasslacher C, Hofmann W, Renner R, Bojestig M, Poulsen PL, Scott G, Thoma J, Kuefer J, Nilsson B, Gambke B, Mueller P, Steinbiss J, Willamowski KD: Evaluation of the Micral-Test II strip, an immunologic rapid test for the detection of microalbuminuria. *Diabetes Care* 20: 1642–1646, 1997
30. Parikh CR, Fischer MJ, Estacio R, Schrier RW: Rapid microalbuminuria screening in type 2 diabetes mellitus: Simplified approach with Micral test strips and specific gravity. *Nephrol Dial Transplant* 19: 1881–1885, 2004
31. Hillege HL, Janssen WM, Bak AA, Diercks GF, Grobbee DE, Crijns HJ, Van Gilst WH, De Zeeuw D, De Jong PE; PREVEND Study Group: 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
32. Gansevoort RT, Verhave JC, Hillege HL, Burgerhof JG, Bakker SJ, de Zeeuw D, de Jong PE; for the PREVEND Study Group: The validity of screening based on spot morning urine samples to detect subjects with microalbuminuria in the general population. *Kidney Int Suppl* 94: S28–S35, 2005
33. Levey AS, Eckardt KU, Tsukumato Y, Levin A, Coresh J, Rossert J, Zeeuw D, Hostetter TH, Lameire N, Eknoyan G: Definition and classification of chronic kidney disease: A global position statement from Kidney Disease: Improving Global Outcome (KDIGO). *Kidney Int* 67: 2089–2100, 2005
34. 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
35. Verhave JC, Hillege HL, de Zeeuw D, de Jong PE: How to measure the prevalence of microalbuminuria in relation to age and gender? *Am J Kidney Dis* 40: 436–437, 2002
36. Rippin JD, Barnett AH, Bain CS: Cost-effective strategies in the prevention of diabetic nephropathy. *Pharmacoeconomics* 22: 9–28, 2004
37. Palmer AJ, Annemans L, Roze S, Lamotte M, Lapuerta P, Chen R, Gabriel S, Carita P, Rodby RA, de Zeeuw D, Parving HH: Cost-effectiveness of early irbesartan treatment versus control or late irbesartan treatment in patients with type 2 diabetes, hypertension and renal disease. *Diabetes Care* 27: 1897–1903, 2004
38. Boulware LE, Jaar BG, Tarver-Carr ME, Brancati FL, Powe NR: Screening for proteinuria in US adults: A cost-effectiveness analysis. *JAMA* 290: 3101–3114, 2003
39. Gansveoort RT, de Jong PE, Postma MJ: Cost effectiveness of screening for proteinuria. *JAMA* 291: 1442–1443, 2004
40. Atthobari J, Asselbergs FW, Boersma C, de Vries R, Hillege HL, van Gilst WH, Gansevoort RT, de Jong PE, de Jong van den berg LTW: Cost-effectiveness of screening for albuminuria and subsequent treatment with an ACE inhibitor to prevent cardiovascular events: A pharmacoeconomic analysis linked to the PREVEND and the PREVEND IT studies. *Clin Ther* 28: 432–444, 2006
41. American Diabetes Association: Diabetic nephropathy, position statement. *Diabetes Care* 25[Suppl 1]: S85–S89, 2002
42. Cerasola G, Cottone S, Mule G, Nardi E, Mangano MT, Andronico G, Contorno A, Li Vecchi M, Galione P, Renda F, Piazza G, Volpe V, Lisi A, Ferrara L, Panepinto N,

Riccobene R: Microalbuminuria, renal dysfunction and cardiovascular complication in essential hypertension. *J Hypertens* 14: 915–920, 1996
43. Ozyilmaz A, Brantsma AH, Bakker SJL, de Zeeuw D, de Jong PE, Gansevoort RT: Mass screening for albuminuria enhances the efficacy of screening for cardiovascular and renal risk factors [Abstract]. *J Am Soc Nephrol* 16: 321A, 2005
44. Verhave JC, Hillege HL, Burgerhof JGM, Navis G, de Zeeuw D, de Jong PE; PREVEND Study Group: Cardiovascular risk factors are differently associated with urinary albumin excretion in men and women. *J Am Soc Nephrol* 14: 1330–1335, 2003
45. Mykkanen L, Haffner SM, Kuusisto J, Pyorala K, Laakso M: Microalbuminuria precedes the development of NIDDM. *Diabetes* 43: 552–557, 1994
46. Brantsma AH, Bakker SJL, Hillege HL, de Zeeuw D, de Jong PE, Gansevoort RT; PREVEND Study Group: Urinary albumin excretion and C-reactive protein and the risk to develop type 2 diabetes. *Diabetes Care* 28: 2525–2530, 2005
47. Wang TJ, Evans JC, Meigs JB, Rifai N, Fox CS, D'Agostino RB, Levy D, Vasan RS: Low-grade albuminuria and the risks of hypertension and blood pressure progression. *Circulation* 111: 1370–1376, 2005
48. Brantsma AH, Bakker SJL, de Zeeuw D, de Jong PE, Gansevoort RT: Albuminuria and only a mild decrease in GFR predict already development of hypertension. *J Am Soc Nephrol* 17: 331–335, 2006
49. Chen J, Muntner P, Hamm LL, Jones DW, Batuman V, Fonseca V, Whelton PK, He J: The metabolic syndrome and chronic kidney disease in US adults. *Ann Intern Med* 140: 167–174, 2004
50. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS: Regression of microalbuminuria in type 1 diabetes. *N Engl J Med* 348: 2285–2293, 2003
51. Brantsma AH, Bakker SJL, de Zeeuw D, de Jong PE, Gansevoort RT: What causes progression or regression of albuminuria in the general population? [Abstract]. *J Am Soc Nephrol* 16: 324A, 2005