

Microalbuminuria and Cardiovascular Disease

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To reduce the burden of cardiovascular disease (CVD), management strategies are increasingly focusing on preventive measures following early detection of markers of atherosclerosis. This review focuses on microalbuminuria, which is gaining recognition as a simple marker of an atherogenic milieu. Prospective and epidemiologic studies have found that microalbuminuria is predictive, independently of traditional risk factors, of all-cause and cardiovascular mortality and CVD events within groups of patients with diabetes or hypertension, and in the general population. The pathophysiologic mechanism underlying the association between albumin excretion and CVD is not fully defined. One hypothesis is that microalbuminuria may be a marker of CVD risk because it reflects subclinical vascular damage in the kidneys and other vascular beds. It may also signify systemic endothelial dysfunction that predisposes to future cardiovascular events. Based on this theory, periodic screening for microalbuminuria could allow early identification of vascular disease and help stratify overall cardiovascular risk, especially in patients with risk factors such as hypertension or diabetes. A positive test for urinary albumin excretion could signify the need for an intensive multifactorial intervention strategy, including behavior modification and targeted pharmacotherapy, aimed at preventing further renal deterioration and improving the overall CVD risk factor profile. Data from intervention studies suggest that treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, statins, and/or strict glycemic control (in diabetics) offer significant reductions in cardiovascular and/or renal morbidity in patients with albuminuria. Use of this (old) marker may allow improved use of medications and strategies for secondary prevention.

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Statistics for the United States indicate that 71.3 million people in 2003 had some form of cardiovascular disease (CVD), that 13.2 million had coronary artery disease (CAD), and that CVD was responsible for 37.3% (910,614) of all deaths (1). This contribution of CVD to morbidity and mortality has directed attention to early atherosclerosis detection coupled with appropriate preventive intervention. Several atherosclerotic risk factors have been identified and have shown utility in predicting CVD. This review focuses on microalbuminuria, which is gaining recognition as a marker of an atherogenic milieu, owing to its association with several atherosclerotic risk factors and early systemic vascular (endothelial) damage (2).

Epidemiology

Microalbuminuria is a persistent, increased urinary excretion of albumin (Table 1 shows diagnostic thresholds) (3–5). Data from the 1999 to 2000 National Health and Nutrition Examination Survey (NHANES) indicated that 8.8% of US adults had microalbuminuria (6). Older age, female gender, and non-Hispanic black ethnicity were associated with a higher prevalence (6). Population surveys also demonstrate an excess of microalbuminuria among individuals with diabetes and hypertension, the prevalence increasing with disease duration (6,7).

In NHANES III (conducted 1988 to 1994), 28.8% of participants with diabetes and 16.0% with hypertension had microalbuminuria *versus* 5.1% of the subpopulation with no risk factors (7).

Microalbuminuria and Clinical Outcomes

Recent investigations demonstrate a continuous positive relationship between urinary albumin excretion (UAE) and adverse clinical outcomes (Figure 1) (8). Epidemiologic and experimental data show that microalbuminuria is associated with an increased risk for all-cause and cardiovascular mortality, cardiac abnormalities, cerebrovascular disease, and, possibly, peripheral arterial disease (PAD) (Table 2). The association between UAE and adverse clinical outcomes is observed at levels below the current microalbuminuria threshold (8–10). For example, in a 6-yr examination of 1568 seemingly healthy individuals (without hypertension, diabetes, or CVD), the risk for cardiovascular events increased continuously with the level of UAE not only in the whole study population but also in the subgroup of patients with albuminuria below the threshold for a definition of microalbuminuria (10).

Mortality

The correlation between microalbuminuria and mortality was apparent from studies that involved high-risk patients (11). In a Heart Outcomes Prevention Evaluation (HOPE) substudy, UAE predicted mortality in patients who were at high cardiovascular risk (≥ 55 yr of age with CVD or diabetes plus at least one other cardiovascular risk factor) (8). All-cause mortality

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Table 1. Classification of abnormal UAE^a

	24-H Urine Albumin (mg/24 h)	Overnight Urine Albumin (μ g/24 h)	Albumin (mg/L)	Spot Urine		
				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

^aUAE, urinary albumin excretion. Reprinted from reference (3), with permission.

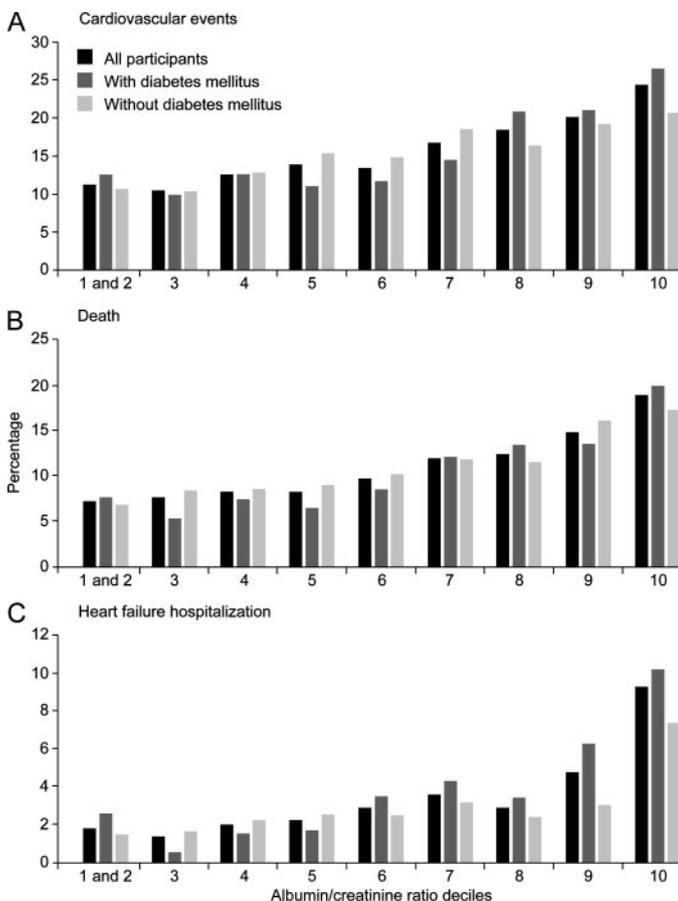


Figure 1. Cardiovascular outcomes in the Heart Outcomes Prevention Evaluation (HOPE) by degree of albuminuria. (A through C) Major cardiovascular events (myocardial infarction, stroke, or cardiovascular death; (A), all-cause mortality (B), and hospitalization for congestive heart failure (C) in each albumin-to-creatinine ratio decile for all participants, participants with diabetes, and participants without diabetes. Deciles 1 and 2 are combined because of very low incidence rates in these two deciles. Decile 8 includes an albumin-to-creatinine ratio decile of 2 mg/mmol, the microalbuminuria threshold. Reproduced from reference (8), with permission.

was 9.4% among patients without microalbuminuria versus 18.2% among those with microalbuminuria (relative risk [RR] 2.09; 95% confidence interval [CI] 1.84 to 2.38). A linear relationship was also observed between the microalbuminuria level and cardiovascular events, extending below the traditional microalbuminuria threshold. In a prospective study that involved individuals who were aged 50 to 75 yr, microalbuminuria was associated with an increased risk for cardiovascular death after adjustment for other risk factors (RR 3.22; 95% CI 1.28 to 8.06; Figure 2) (12). The risk for all-cause mortality in patients with microalbuminuria was also elevated (RR 1.70; 95% CI 0.86 to 3.34), especially among those with concomitant hypertension (RR 2.87; 95% CI 1.22 to 6.33).

The presence of microalbuminuria also seems to predict all-cause mortality in the general population (9,13–15). This was initially shown in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study, in which inhabitants of Groningen, The Netherlands, who were aged 28 to 75 yr were sent a questionnaire and a vial to collect an early-morning urine sample for measurement of UAE (9). A total of 40,548 participants who were followed for 2.6 yr were included in an analysis of mortality by baseline UAE. A clear positive relationship was observed between UAE and all-cause, cardiovascular, and noncardiovascular death. A two-fold increase in UAE was associated with a 1.29 (95% CI 1.18 to 1.40) higher RR for cardiovascular death and a 1.12 (95% CI 1.04 to 1.21) higher RR for noncardiovascular death. Importantly, the relationship was apparent at levels of albuminuria that are considered normal.

Cardiac Disease

Microalbuminuria seems to correlate with various cardiac abnormalities and diseases, including left ventricular (LV) dysfunction and hypertrophy, electrocardiographic abnormalities, and ischemic heart disease (IHD) (16). The Strong Heart Study demonstrated a significant association between microalbuminuria and echocardiographic parameters of LV systolic and diastolic function in a cohort of 1576 Native Americans with diabetes (17). Furthermore, a correlation has been noted between UAE and echocardiographic measures of LV mass index,

Table 2. Clinical studies reporting the risks associated with a positive microalbuminuria result^a

Study	Population	Microalbuminuria Definition	Risk Associated with a Positive Microalbuminuria Result (95% CI)
Prospective studies			
HOPE (7)	Subjects at high cardiovascular risk (≥ 55 yr with CVD or with diabetes + ≥ 1 CVD risk factor; $n = 9043$)	ACR ≥ 2 mg/mmol in a first-morning spot urine sample	All-cause mortality: RR 2.09 (1.84 to 2.38)
PREVEND (8)	Residents of Groningen, the Netherlands, 28 to 75 yr ($n = 40,548$)	UAE 20 to 200 mg/L in an early-morning spot urine sample	Cardiovascular death: RR 1.29 (1.18 to 1.40) Noncardiovascular death: RR 1.12 (1.04 to 1.21)
PREVEND (21)	Residents of Groningen, the Netherlands, 28 to 75 yr ($n = 7330$)	UAE 30 to 300 mg in a 24-h urine sample	All-cause mortality: HR 3.3 (1.5 to 7.1) for patients with ST-T segment changes + microalbuminuria <i>versus</i> 0.9 (0.4 to 1.9) for ST-T segment changes alone Cardiovascular death: HR 10.4 (2.5 to 43.6) for patients with ST-T segment changes + microalbuminuria <i>versus</i> 2.7 (0.6 to 12.3) for ST-T segment changes alone
Hoom Study (11)	Population-based: White individuals, 50 to 75 yr ($n = 631$)	ACR ≥ 2 mg/mmol in a first-morning spot urine sample	Cardiovascular death: RR 3.22 (1.28 to 8.06) All-cause mortality: RR 1.70 (0.86 to 3.34) All-cause mortality in patients with hypertension: RR 2.87 (1.22 to 6.33)
HUNT (12)	Nondiabetic, nonhypertensive residents of Nord-Trøndelag, Norway, ≥ 20 yr ($n = 2089$)	ACR ≥ 0.76 mg/mmol (>60 th percentile) in a first-morning spot urine sample	All-cause mortality: RR 2.3 (1.0 to 5.4)
EPIC-Norfolk (13)	Residents of Norfolk, UK, 40 to 79 yr ($n = 20,911$)	ACR 2.5 to 25 mg/mmol in a random spot urine sample	All-cause mortality: HR 1.48 (1.20 to 1.79) Cardiovascular death: HR 2.03 (1.55 to 2.67) Fatal stroke: HR 1.58 (1.10 to 3.0) Coronary heart disease death: HR 2.01 (1.40 to 2.90)
EPIC-Norfolk (24)	Residents of Norfolk, UK, 40 to 79 yr ($n = 23,630$)	ACR 2.5 to 25 mg/mmol in a random spot urine sample	Stroke: HR 1.49 (1.13 to 2.14)
Third Copenhagen City Heart Study (14)	Residents of Copenhagen, Denmark, 30 to 70 yr, without coronary heart disease	UAE >4.8 $\mu\text{g}/\text{min}$ (>3 rd quartile) in a timed overnight urine sample	All-cause mortality: RR 1.9 (1.5 to 2.4) Coronary heart disease: RR 2.0 (1.4 to 3.0)
Danish MONICA (22)	Population-based: Individuals without ischemic heart disease, renal disease, urinary tract infection, or diabetes ($n = 2085$)	ACR >0.65 mg/mmol (>90 th percentile) in a first-morning spot urine sample	Ischemic heart disease: RR 2.3 (1.3 to 3.9)
Shibata Study (25)	Residents of Shibata, Japan, ≥ 40 yr ($n = 2651$)	Positive albumin dipstick test	Stroke: RR in men 2.5 (1.1 to 5.7)
Portland Study (26)	Older residents of Portland, Oregon, with previous stroke or transient ischemic attack ($n = 121$)	UAE 20 to 200 mg/L in a first-morning spot urine sample	Recurrent stroke: HR 4.9 (1.4 to 17.6)
Slowik <i>et al.</i> (27)	Patients admitted within 24 h of a first ischemic stroke ($n = 60$)	UAE 30 to 300 mg in a 24-h urine sample	Mortality: OR 6.0 (1.3 to 27.7)
Cross-sectional studies			
Zander <i>et al.</i> (29)	Patients with type 2 diabetes ($n = 1060$)	UAE 20 to 200 $\mu\text{g}/\text{min}$ in a timed overnight urine sample	PAD: OR 2.1 (1.4 to 3.2)
PREVEND (20)	Nondiabetic residents of Groningen, the Netherlands, 28 to 75 yr ($n = 7579$)	UAE 30 to 300 mg in a 24-h urine sample	Electrocardiographic abnormalities: Infarct patterns: OR 1.61 (1.12 to 2.32) Major ischemia: OR 1.43 (1.08 to 1.91) Minor ischemia: OR 1.32 (1.03 to 1.68)
PREVEND (28)	Nondiabetic residents of Groningen, the Netherlands, 28 to 75 yr ($n = 6669$)	UAE 30 to 300 mg in a 24-h urine sample	PAD: OR 0.98 (0.68 to 1.41) in multivariate analysis
Earle <i>et al.</i> (19)	Patients with type 1 diabetes and without CVD	UAE 20 to 200 $\mu\text{g}/\text{min}$ in a timed overnight urine sample	Silent myocardial ischemia: OR 6.3 (1.2 to 37.8)

^aACR, albumin-to-creatinine ratio; CI, confidence interval; CVD, cardiovascular disease; EPIC-Norfolk, European Prospective Investigation into Cancer in Norfolk; HOPE, Heart Outcomes Prevention Evaluation; HR, hazard ratio; HUNT, Nord-Trøndelag Health Study; OR, odds ratio; PAD, peripheral artery disease; PREVEND, Prevention of Renal and Vascular End Stage Disease; RR, relative risk.

LV hypertrophy, and concentric hypertrophy in untreated hypertensive patients (18). The larger Losartan Intervention For Endpoint reduction in hypertension (LIFE) study confirmed this finding (19).

A study that involved 64 asymptomatic patients with type 1 diabetes revealed a higher incidence of myocardial ischemia,

detected by stress echocardiography and electrocardiography, in the presence of microalbuminuria *versus* normoalbuminuria (25 *versus* 6.3%; OR 6.3; 95% CI 1.2 to 37.8; $P = 0.03$) (20). Electrocardiographic recordings from 7579 PREVEND participants without diabetes showed an independent association between microalbuminuria and infarct patterns (odds ratio

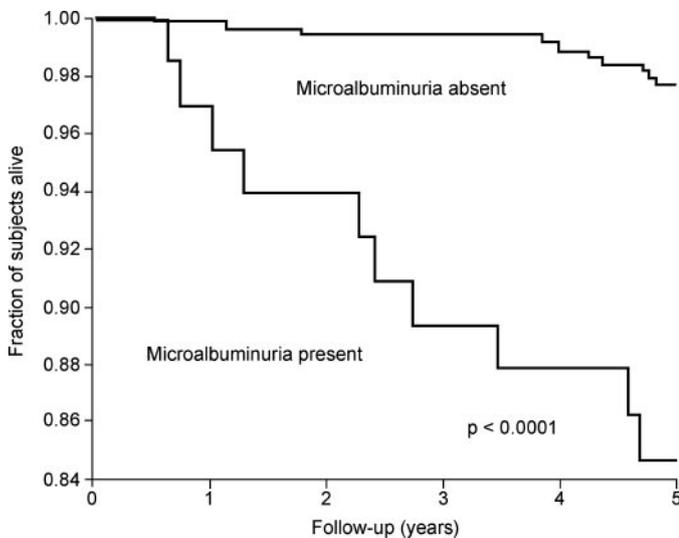


Figure 2. Cardiovascular survival (Kaplan-Meier) according to microalbuminuria status in a population-based cohort aged 50 to 70 yr. Reproduced from reference (12), with permission.

[OR] 1.61; 95% CI 1.12 to 2.32), major ischemia (OR 1.43; 95% CI 1.08 to 1.91), and minor ischemia (OR 1.32; 95% CI 1.03 to 1.68) (21). This group subsequently reported that, in patients with electrocardiographic ST-T segment changes, microalbuminuria could identify those who were at increased risk for all-cause and cardiovascular mortality (22).

Microalbuminuria was also associated with a 2.3-fold (95% CI 1.3 to 3.9) higher RR of IHD in a population-based study of 2085 individuals without previous IHD, renal disease, or diabetes (23). Survival free from IHD during follow-up was 97% among patients with normoalbuminuria *versus* 91% among those with microalbuminuria ($P < 0.0001$). It is interesting that the IHD risk that was associated with other conventional CVD factors more than doubled in the presence of microalbuminuria (23).

Elevated UAE also correlates directly with angiographic evidence of CAD. A study of 308 patients who underwent elective coronary angiography revealed that patients with angiographic evidence of CAD had significantly higher urinary albumin levels than disease-free individuals (28 *versus* 10 mg/g; $P < 0.001$) and that UAE increased progressively with CAD severity (24).

Cerebrovascular Disease

Microalbuminuria is common among patients with cerebrovascular disease and correlates with an increased stroke risk even after correction for confounding clinical risk factors. In the European Prospective Investigation into Cancer in Norfolk population, microalbuminuria was independently associated with a 50% increased risk for stroke (hazard ratio [HR] 1.49; 95% CI 1.13 to 2.14); the association with macroalbuminuria was even greater (HR 2.43; 95% CI 1.11 to 6.26) (25). In addition, a 15.5-yr cohort study that examined stroke risk factors in Japan showed that urinary albumin was an independent risk factor

for stroke in men (RR 2.5; 95% CI 1.1 to 5.7) but not in women (26).

An association between microalbuminuria and recurrent stroke has also been reported. Among a population of older (median age 65 yr) Americans with previous ischemic stroke or transient ischemic attack, microalbuminuria independently predicted future stroke (HR 4.9; 95% CI 1.4 to 17.6; $P < 0.01$ *versus* patients with normoalbuminuria) (27).

Other reported cerebrovascular clinical correlates with microalbuminuria include cerebral ischemic lacunae, middle cerebral artery stenosis, impaired carotid arterial blood flow and vasomotor reactivity on Doppler ultrasonography, and increased carotid artery intima-media thickness. In addition, patients who have had an acute stroke and have microalbuminuria have a poorer outcome than those without microalbuminuria (28).

PAD

Studies to explore the risk for PAD in patients with microalbuminuria are limited, and additional investigations are warranted to clarify the relationship. In PREVEND, the presence of microalbuminuria increased the risk for PAD in an unadjusted model (OR 1.51; 95% CI 1.09 to 2.10) but not in multivariate analysis (OR 0.98; 95% CI 0.68 to 1.41) (29). A second study reported a significant association between UAE and PAD among patients with type 2 diabetes (OR 2.1; 95% CI 1.4 to 3.2; $P < 0.01$) but not those with type 1 diabetes (30).

Pathophysiology

The pathophysiologic processes that link microalbuminuria and CVD are unclear. Microalbuminuria could be a cause or a consequence of vascular disease. In the STENO hypothesis put forward by Deckert *et al.* (31), albumin leakage into the urine is a reflection of widespread vascular damage. In a sense, the kidney is the window of the vasculature. In view of these considerations, endothelial function and chronic inflammation have been suggested as possible candidates to explain the association between microalbuminuria and CVD (32,33). However, there are many inconsistencies in the literature. It is true that low-grade inflammation can be both a cause and a consequence of endothelial dysfunction, and some studies used markers of inflammation such as C-reactive protein, IL-6, and TNF- α , which indicate that low-grade inflammation is associated with the occurrence and the progression of microalbuminuria and with an associated increased risk for atherosclerotic disease (34–36). However, other studies indicate that although microalbuminuria, endothelial dysfunction, and low-grade inflammation are linked, they all are independently associated with risk for cardiovascular death (37,38). The inconsistency of these observations may reflect, in part, inadequate precision of the measurements of endothelial function and inflammation, or these markers may not be relevant to CVD risk in people with microalbuminuria.

Although many cross-sectional and a few prospective studies indicated that microalbuminuria is associated with several cardiovascular risk factors such as aging, male gender, hypertension, diabetes, smoking, obesity, and dyslipidemia, it is clear that these explain, at most, a very small part of the association

between microalbuminuria and atherosclerotic events. As with measures of endothelial function and inflammation, it is possible that this is related to inadequate quantification of these exposures, or there could be confounding by other risk factors that might cause both the microalbuminuria and the associated CVD.

Another interesting theory is that some individuals are born with varying degrees of vascular function within a physiologic range and, therefore, excrete a variable amount of microalbumin (39). This inherent variability of the vascular state as determined by urine microalbumin excretion may be associated with susceptibility to subsequent organ damage (39). This could also explain why microalbuminuria is a predictor of not only CVD but also new-onset hypertension and diabetes (9). If this proves to be the case, then it may be desirable to identify these individuals to consider early interventional strategies to provide primary prevention. This hypothesis also raises the question about individualizing BP, cholesterol, and glucose goals in patients with microalbuminuria and associated increased susceptibility to organ damage. In a sense, the kidney may serve as a barometer of an appropriate BP goal; that is, the level of BP at which normalization of UAE occurs. Similarly, intensification of glycemic control and intensive reduction of LDL cholesterol if associated with normalization of UAE may represent a biomeasure of therapeutic success. Future clinical trials will need to address these considerations given what is known and not known about the relationship between microalbuminuria and CVD.

Reducing the Risk Associated with Microalbuminuria

Screening

Because microalbuminuria precedes the appearance of hypertension and diabetes and independently predicts CVD risk (39), screening for UAE, a relatively simple process, should facilitate early vascular disease detection. Traditionally, a dipstick test has been used to measure protein in the urine. However, it is semiquantitative and insensitive, particularly when detecting albumin concentrations <300 mg/d. A variety of antibody-based methods are available to measure urinary albumin. These include RIA, nephelometry, immunoturbidimetry, and ELISA. A more modern HPLC method that is more sensitive to detect microalbuminuria has been developed (40). Whether this method helps to identify patients who are at increased risk for CVD compared with the traditional antibody-based methods is unknown. However, because there is a continuous relationship between the amount of UAE in the urine and cardiovascular events, it is likely that more sensitive measures may assist in the earlier identification of patients who are at risk.

Preferably, an albumin-to-creatinine ratio that uses an overnight or first-morning void urine sample or measurement of albumin excretion per unit of time should be used for screening. With the latter method, a timed overnight urine collection avoids the complicating factors of a 24-h urine collection. For an untimed sample, the albumin-to-creatinine ratio is preferred but must be corrected for the gender difference in creatinine

production between men and women (Table 1) (3). In addition, creatinine excretion in the urine depends not only on gender but also on age and race (41,42).

The National Kidney Foundation guidelines recommend a front-end UAE screen in all patients who are at risk for renal disease, including those with diabetes, hypertension, family history of chronic kidney disease, age >60 yr, and racial and ethnic minorities (43). The American Diabetes Association (ADA) recommends an annual UAE test in all patients with type 1 diabetes of >5 yr duration and in all patients with type 2 diabetes starting at time of diagnosis as a prognostic indicator of CVD risk (44).

Risk Stratification

UAE testing improves the accuracy of cardiovascular risk assessment in patients with hypertension (45,46). It also may be as reliable as an ultrasound evaluation of cardiac and carotid structure in predicting cardiovascular risk in hypertensive patients (45) (Figure 3), and combined ultrasound and microalbuminuria screening can improve the accuracy of target organ damage detection by 10-fold compared with routine investigation (46). Therefore, it seems reasonable to consider screening all patients who present with hypertension for UAE, as is recommended for patients with diabetes.

UAE testing may also help to stratify risk in patients who are admitted for acute myocardial infarction and in directing acute and chronic care of patients with CAD. The presence of microalbuminuria during the first week of hospitalization for acute myocardial infarction is a strong prognostic marker for in-hospital mortality, particularly among patients with hypertension, and of long-term recurrent coronary events or mortality (47). Moreover, in the HOPE study, in a cohort of more than 9000 patients with substantial cardiovascular comorbidity or risk factors, there was a continuous relationship between urinary microalbumin excretion and cardiovascular events regardless of whether the patients had diabetes (8). This relationship extended well below the microalbuminuria threshold, emphasizing the continuous relationship between microalbuminuria and CVD events.

Treatments

Intensive and multifactorial interventions are recommended for patients with microalbuminuria to delay progression of CVD (Table 3). Despite the clear association of microalbuminuria with cardiovascular risk, limited studies have been performed to evaluate strategies to reduce microalbuminuria and evaluate the impact on cardiovascular events. The Prevention of REnal and Vascular ENdstage Disease Intervention Trial (PREVEND IT) is the only randomized trial to study the effect of albuminuria lowering in microalbuminuric, otherwise healthy individuals (48). In this clinical trial, the lowering of albuminuria with an angiotensin-converting enzyme (ACE) inhibitor only tended to be cardioprotective. One problem with this trial may have been an insufficient number of patients to be followed for a sufficient period of time to have enough events to evaluate the impact of treatment. A prespecified secondary analysis of the LIFE trial (patients with hypertension and LVH)

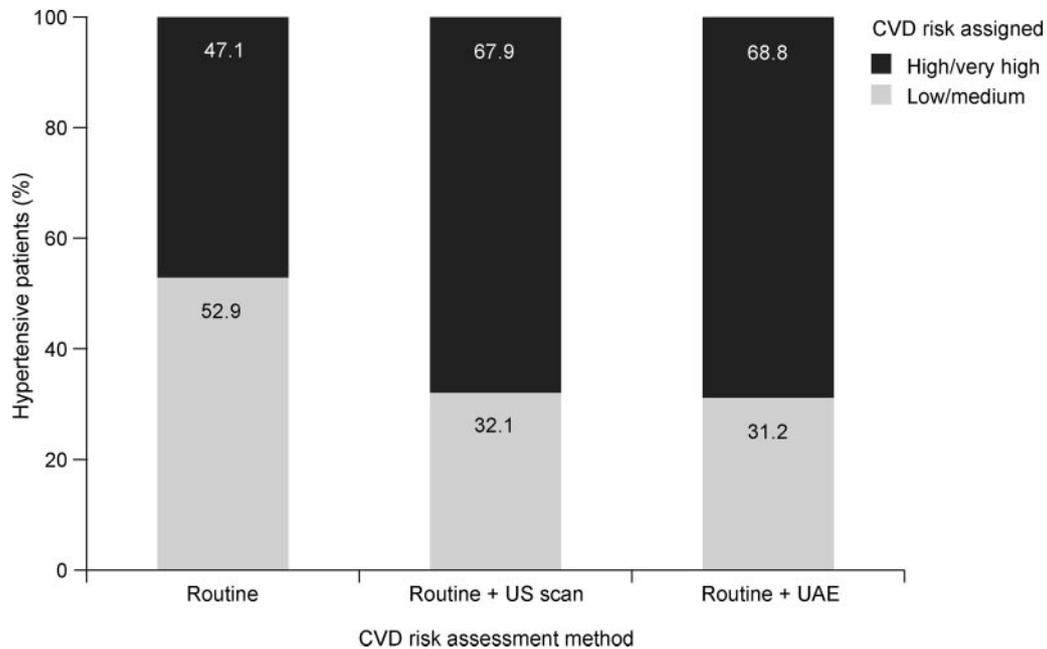


Figure 3. Cardiovascular disease (CVD) risk stratification in patients with hypertension using routine diagnostic methods alone or coupled with either ultrasound (US) detection of left ventricular hypertrophy and/or carotid plaque or with urinary albumin excretion (UAE).

Table 3. Summary of recommendations for patients with microalbuminuria^a

Renoprotection with ACE inhibitors or angiotensin receptor blockers for patients with diabetes
BP control
<140/90 mmHg for the general population
<130/80 mmHg for patients with diabetes
Glycemic control: hemoglobin A _{1c} <7%
Consider screening in patients with diabetes
LDL cholesterol control for diabetes in the general population
<100 mg/dl (<2.6 mmol/L) for patients with or without diabetes
<70 mg/dl (<1.8 mmol/L) for patients with CVD
Correct disturbances in triglyceride, HDL, and non-HDL levels
Smoking cessation
Dietary limitation of salt (<3 g/d) and saturated fat
Regular exercise and weight control
Antiplatelet therapy

^aACE, angiotensin-converting enzyme.

noted that time-varying albuminuria was associated with cardiovascular events, suggesting that therapeutic strategies that are associated with a reduction of albuminuria may be cardioprotective (49).

Smaller clinical trials in patients with microalbuminuria are illustrative of the advantage of ACE inhibition or angiotensin receptor blockade in limiting the progression from microalbuminuria to clinical proteinuria in patients with either type 1 or

type 2 diabetes. However, whether limiting the progression from micro- to macroalbuminuria will result in fewer cardiovascular events is unknown. In clinical trials of patients with chronic kidney disease as a result of type 2 diabetes and clinical proteinuria, such as Irbesartan Diabetic Nephropathy Trial (IDNT) and Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) (50–52), it is evident that therapeutic strategies that are associated with reduction of proteinuria are associated with fewer cardiovascular and kidney disease end points (53,54). However, whether one can extrapolate these observations to microalbuminuric patients is unknown.

Strategies to reduce microalbuminuria are available in clinical practice. Perhaps the most important is the reduction of BP. In the Irbesartan Microalbuminuria-2 trial, normalization of microalbuminuria in patients with type 2 diabetes and hypertension occurred in approximately 20% of patients who attained traditional BP goals of 140/90 mmHg with medications such as diuretics, β blockers, and vasodilators (50). An improvement of the normalization rate to approximately 33% occurred when the full dosage (300 mg) of the renin-angiotensin system blocking drug irbesartan (an angiotensin II receptor blocker) was used as part of the BP-lowering regimen to 140/90 mmHg. However, even lower BP goals may be advantageous for reducing UAE, and both the ADA and the Joint National Committee 7 recommend a lower BP goal of <130/80 mmHg in patients with diabetes (44,55).

Higher dosage angiotensin receptor blocker or using both an ACE inhibitor and an angiotensin receptor blocker together in full dosage may facilitate an even greater reduction in microalbuminuria (56,57). Thiazide diuretics also help to reduce proteinuria (58), and dietary salt restriction may also be helpful in reducing UAE (59).

Strict glycemic control also delays the onset of microalbuminuria, the progression of microalbuminuria to clinical proteinuria, and the development of nephropathy in patients with either type 1 or type 2 diabetes (5,44,60). Glycosaminoglycans have also been demonstrated to reduce albuminuria (61). Whether these specific therapeutic strategies will prevent progression of CVD because they reduce microalbuminuria is unknown. The Steno-2 trial demonstrated that intensified BP, cholesterol, and glycemic control in patients with type 2 diabetes was associated with decreased risk for cardiovascular events (62). However, this was not correlated with reduction in UAE.

There is some debate in the literature as to whether statins reduce UAE (63–65). Regardless, these drugs are important given the CVD risk. Both the National Kidney Foundation and the ADA recommend an LDL cholesterol goal of <100 mg/dl for patients with advanced renal disease or diabetes (5,60). For patients with diabetes and CVD, an LDL goal of <70 mg/dl is appropriate. Disturbances in triglyceride, HDL, and non-HDL levels should also be addressed (5,60). Moreover, one needs to consider strategies to improve diet by reducing saturated and trans fats and dietary salt. In addition, efforts to assist in smoking avoidance, proper exercise, and weight control should be encouraged.

Cost-Effectiveness

Annual screening for UAE is recommended in people with diabetes (66). In part, this recommendation is based on the evidence that long-term cost-effectiveness is more favorable when treatment is started earlier in preventing ESRD (67), but there are no data when it comes to preventing CVD. The evidence for screening the general population without diabetes for UAE to prevent ESRD is limited. Only in the past year was a study that evaluated the cost-effectiveness of screening for UAE in the general population published. In this analysis, patients with increased UAE were treated with an ACE inhibitor. The authors demonstrated that this approach was cost-effective to prevent cardiovascular events (68). Although evidence is accruing to indicate that individuals with hypertension and increased cardiovascular risk should be screened for UAE, more studies are needed to confirm that systematic screening is cost-effective in the general population.

Conclusion

Epidemiologic and clinical evidence has established a pathophysiologic link between microalbuminuria and CVD in patients with diabetes and hypertension and in the general population. This correlation is observed even at levels of albuminuria below the conventional threshold for microalbuminuria (10). Screening for UAE can help clinicians estimate a patient's CVD risk and, if positive, should prompt the early introduction of a multifactorial intervention strategy that aim to improve the overall CVD risk factor profile as well as prevent further loss of renal function.

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Disclosures

None.

References

1. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, Zheng ZJ, Flegal K, O'Donnell C, Kittner S, Lloyd-Jones D, Goff DC Jr, Hong Y, Adams R, Friday G, Furie K, Gorelick P, Kissela B, Marler J, Meigs J, Roger V, Sidney S, Sorlie P, Steinberger J, Wasserthiel-Smoller S, Wilson M, Wolf P: Heart disease and stroke statistics—2006 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 113: e85–e151, 2006
2. Ray KK, Cannon CP, Cairns R, Morrow DA, Rifai N, Kirtane AJ, McCabe CH, Skene AM, Gibson CM, Ridker PM, Braunwald E: Relationship between uncontrolled risk factors and C-reactive protein levels in patients receiving standard or intensive statin therapy for acute coronary syndromes in the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol* 46: 1417–1424, 2005
3. de Jong PE, Curhan GC: Screening, monitoring, and treatment of albuminuria: Public health perspectives. *J Am Soc Nephrol* 17: 2120–2126, 2006
4. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* 43: S1–S290, 2004
5. Standards of medical care in diabetes—2006. *Diabetes Care* 29[Suppl 1]: S4–S42, 2006
6. 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, 1999 to 2000. *J Am Soc Nephrol* 16: 180–188, 2005
7. Jones CA, Francis ME, Eberhardt MS, Chavers B, Coresh J, Engelgau M, Kusek JW, Byrd-Holt D, Narayan KM, Herman WH, Jones CP, Salive M, Agodoa LY: Microalbuminuria in the US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 39: 445–459, 2002
8. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Halle JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S: Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 286: 421–426, 2001
9. Brantsma AH, Bakker SJ, Hillege HL, de Zeeuw D, de Jong PE, Gansevoort RT: Urinary albumin excretion and its relation with C-reactive protein and the metabolic syndrome in the prediction of type 2 diabetes. *Diabetes Care* 28: 2525–2530, 2005
10. Arnlov J, Evans JC, Meigs JB, Wang TJ, Fox CS, Levy D, Benjamin EJ, D'Agostino RB, Vasan RS: Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: The Framingham Heart Study. *Circulation* 112: 969–975, 2005
11. Weir MR: Microalbuminuria in type 2 diabetics: An important, overlooked cardiovascular risk factor. *J Clin Hypertens (Greenwich)* 6: 134–141, 2004
12. Jager A, Kostense PJ, Ruhe HG, Heine RJ, Nijpels G, Dekker JM, Bouter LM, Stehouwer CD: 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
13. Romundstad S, Holmen J, Kvenild K, Hallan H, Ellekjaer H: 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
 14. Yuyun MF, Khaw KT, Luben R, Welch A, Bingham S, Day NE, Wareham NJ: Microalbuminuria independently predicts all-cause and cardiovascular mortality in a British population: The European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. *Int J Epidemiol* 33: 189-198, 2004
 15. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen G, Clausen P, Scharling H, Appleyard M, Jensen JS: Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation* 110: 32-35, 2004
 16. Karalliedde J, Viberti G: Microalbuminuria and cardiovascular risk. *Am J Hypertens* 17: 986-993, 2004
 17. Liu JE, Robbins DC, Palmieri V, Bella JN, Roman MJ, Fabsitz R, Howard BV, Welty TK, Lee ET, Devereux RB: Association of albuminuria with systolic and diastolic left ventricular dysfunction in type 2 diabetes: The Strong Heart Study. *J Am Coll Cardiol* 41: 2022-2028, 2003
 18. Pontremoli R, Ravera M, Bezante GP, Viazzi F, Nicoletta C, Berruti V, Leoncini G, Del SM, Brunelli C, Tomolillo C, Deferrari G: Left ventricular geometry and function in patients with essential hypertension and microalbuminuria. *J Hypertens* 17: 993-1000, 1999
 19. Wachtell K, Palmieri V, Olsen MH, Bella JN, Aalto T, Dahlof B, Gerds E, Wright JT Jr, Papademetriou V, Mogensen CE, Borch-Johnsen K, Ibsen H, Devereux RB: Urine albumin/creatinine ratio and echocardiographic left ventricular structure and function in hypertensive patients with electrocardiographic left ventricular hypertrophy: The LIFE study. Losartan Intervention for Endpoint Reduction. *Am Heart J* 143: 319-326, 2002
 20. Earle KA, Mishra M, Morocutti A, Barnes D, Stephens E, Chambers J, Viberti GC: Microalbuminuria as a marker of silent myocardial ischaemia in IDDM patients. *Diabetologia* 39: 854-856, 1996
 21. Diercks GF, van Boven AJ, Hillege HL, Janssen WM, Kors JA, de Jong PE, Grobbee DE, Crijns HJ, van Gilst WH: Microalbuminuria is independently associated with ischaemic electrocardiographic abnormalities in a large nondiabetic population. The PREVEND (Prevention of Renal and Vascular ENdstage Disease) study. *Eur Heart J* 21: 1922-1927, 2000
 22. Diercks GF, Hillege HL, van Boven AJ, Kors JA, Crijns HJ, Grobbee DE, de Jong PE, van Gilst WH: Microalbuminuria modifies the mortality risk associated with electrocardiographic ST-T segment changes. *J Am Coll Cardiol* 40: 1401, 2002
 23. 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
 24. Tuttle KR, Puhlman ME, Cooney SK, Short R: Urinary albumin and insulin as predictors of coronary artery disease: An angiographic study. *Am J Kidney Dis* 34: 918-925, 1999
 25. Yuyun MF, Khaw KT, Luben R, Welch A, Bingham S, Day NE, Wareham NJ: Microalbuminuria and stroke in a British population: The European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. *J Intern Med* 255: 247-256, 2004
 26. Nakayama T, Date C, Yokoyama T, Yoshiike N, Yamaguchi M, Tanaka H: A 15.5-year follow-up study of stroke in a Japanese provincial city. The Shibata Study. *Stroke* 28: 45-52, 1997
 27. Beamer NB, Coull BM, Clark WM, Wynn M: Microalbuminuria in ischemic stroke. *Arch Neurol* 56: 699-702, 1999
 28. Slowik A, Turaj W, Iskra T, Strojny J, Szczudlik A: Microalbuminuria in nondiabetic patients with acute ischemic stroke: Prevalence, clinical correlates, and prognostic significance. *Cerebrovasc Dis* 14: 15-21, 2002
 29. Stuveling EM, Hillege HL, Bakker SJ, Asselbergs FW, de Jong PE, Gans RO, de Zeeuw D; PREVEND study group: C-reactive protein and microalbuminuria differ in their associations with various domains of vascular disease. *Atherosclerosis* 172: 107-114, 2004
 30. Zander E, Heinke P, Reindel J, Kohnert KD, Kairies U, Braun J, Eckel L, Kerner W: Peripheral arterial disease in diabetes mellitus type 1 and type 2: Are there different risk factors? *Vasa* 31: 249-254, 2002
 31. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A: Albuminuria reflects widespread vascular damage. The Steno hypothesis. *Diabetologia* 32: 219-226, 1989
 32. Stehouwer CD, Henry RM, Dekker JM, Nijpels G, Heine RJ, Bouter LM: Microalbuminuria is associated with impaired brachial artery, flow-mediated vasodilation in elderly individuals without and with diabetes: Further evidence for a link between microalbuminuria and endothelial dysfunction—The Hoorn Study. *Kidney Int Suppl* 92: S42-S44, 2004
 33. Stehouwer CD, Smulders YM: Microalbuminuria and risk for cardiovascular disease: Analysis of potential mechanisms. *J Am Soc Nephrol* 17: 2106-2111, 2006
 34. Jager A, van H, V, Kostense PJ, Emeis JJ, Nijpels G, Dekker JM, Heine RJ, Bouter LM, Stehouwer CD: C-reactive protein and soluble vascular cell adhesion molecule-1 are associated with elevated urinary albumin excretion but do not explain its link with cardiovascular risk. *Arterioscler Thromb Vasc Biol* 22: 593-598, 2002
 35. Stehouwer CD, Gall MA, Twisk JW, Knudsen E, Emeis JJ, Parving HH: Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: Progressive, interrelated, and independently associated with risk of death. *Diabetes* 51: 1157-1165, 2002
 36. Schram MT, Chaturvedi N, Schalkwijk CG, Fuller JH, Stehouwer CD: Markers of inflammation are cross-sectionally associated with microvascular complications and cardiovascular disease in type 1 diabetes: The EURODIAB Prospective Complications Study. *Diabetologia* 48: 370-378, 2005
 37. Jensen JS, Borch-Johnsen K, Jensen G, Feldt-Rasmussen B: Microalbuminuria reflects a generalized transvascular al-

- bumin leakiness in clinically healthy subjects. *Clin Sci (Lond)* 88: 629–633, 1995
38. Nosadini R, Velussi M, Brocco E, Abaterusso C, Piarulli F, Morgia G, Satta A, Faedda R, Abhyankar A, Luthman H, Tonolo G: Altered transcapillary escape of albumin and microalbuminuria reflects two different pathogenetic mechanisms. *Diabetes* 54: 228–233, 2005
 39. de Zeeuw D, Parving HH, Henning RH: Microalbuminuria as an early marker for cardiovascular disease. *J Am Soc Nephrol* 17: 2100–2105, 2006
 40. 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
 41. 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
 42. 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
 43. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 39: S1–266, 2002
 44. American Diabetes Association: Nephropathy in diabetes. *Diabetes Care* S79–S83, 2004
 45. Leoncini G, Sacchi G, Viazzi F, Ravera M, Parodi D, Ratto E, Vettoretti S, Tomolillo C, Deferrari G, Pontremoli R: Microalbuminuria identifies overall cardiovascular risk in essential hypertension: An artificial neural network-based approach. *J Hypertens* 20: 1315–1321, 2002
 46. Cuspidi C, Meani S, Salerno M, Severgnini B, Fusi V, Valerio C, Catini E, Magrini F, Zanchetti A: Cardiovascular risk stratification according to the 2003 ESH-ESC guidelines in uncomplicated patients with essential hypertension: Comparison with the 1999 WHO/ISH guidelines criteria. *Blood Press* 13: 144–151, 2004
 47. Koulouris S, Lekatsas I, Karabinos I, Ioannidis G, Katostaras T, Kranidis A, Triantafyllou K, Thalassinos N, Anthopoulos L: Microalbuminuria: A strong predictor of 3-year adverse prognosis in nondiabetic patients with acute myocardial infarction. *Am Heart J* 149: 840–845, 2005
 48. Asselbergs FW, Diercks GF, Hillege HL, van Boven AJ, Janssen WM, Voors AA, de Zeeuw D, de Jong PE, van Veldhuisen DJ, van Gilst WH: Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation* 110: 2809–2816, 2004
 49. Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlof B, Devereux RB, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wan Y: Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: Losartan intervention for endpoint reduction in hypertension study. *Hypertension* 45: 198–202, 2005
 50. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P: The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 345: 870–878, 2001
 51. Viberti G, Mogensen CE, Groop LC, Pauls JF: Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. European Microalbuminuria Captopril Study Group. *JAMA* 271: 275–279, 1994
 52. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 355: 253–259, 2000
 53. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345: 861–869, 2001
 54. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345: 851–860, 2001
 55. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 42: 1206–1252, 2003
 56. Rossing K, Jacobsen P, Pietraszek L, Parving HH: Renoprotective effects of adding angiotensin II receptor blocker to maximal recommended doses of ACE inhibitor in diabetic nephropathy: A randomized double-blind crossover trial. *Diabetes Care* 26: 2268–2274, 2003
 57. Rossing K, Schjoedt KJ, Jensen BR, Boomsma F, Parving HH: Enhanced renoprotective effects of ultrahigh doses of irbesartan in patients with type 2 diabetes and microalbuminuria. *Kidney Int* 68: 1190–1198, 2005
 58. Buter H, Hemmelder MH, Navis G, de Jong PE, de Zeeuw D: The blunting of the antiproteinuric efficacy of ACE inhibition by high sodium intake can be restored by hydrochlorothiazide. *Nephrol Dial Transplant* 13: 1682–1685, 1998
 59. Heeg JE, de Jong PE, van der Hem GK, de Zeeuw D: Efficacy and variability of the antiproteinuric effect of ACE inhibition by lisinopril. *Kidney Int* 36: 272–279, 1989
 60. Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T: Diabetic nephropathy: Diagnosis, prevention, and treatment. *Diabetes Care* 28: 164–176, 2005
 61. Gambaro G, Kinalska I, Oksa A, Pont'uch P, Hertlova M, Olsovsky J, Manitius J, Fedele D, Czekalski S, Perusicova J, Skrha J, Taton J, Grzeszczak W, Crepaldi G: Oral sulodexide reduces albuminuria in microalbuminuric and macroalbuminuric type 1 and type 2 diabetic patients: The Di.N.A.S. randomized trial. *J Am Soc Nephrol* 13: 1615–1625, 2002
 62. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 348: 383–393, 2003
 63. Tonelli M, Isles C, Craven T, Tonkin A, Pfeffer MA, Shepherd J, Sacks FM, Furberg C, Cobbe SM, Simes J, West M, Packard C, Curhan GC: Effect of pravastatin on rate of kidney function loss in people with or at risk for coronary disease. *Circulation* 112: 171–178, 2005
 64. Tonolo G, Ciccarese M, Brizzi P, Puddu L, Secchi G, Calvia P, Atzeni MM, Melis MG, Maioli M: Reduction of albumin

- excretion rate in normotensive microalbuminuric type 2 diabetic patients during long-term simvastatin treatment. *Diabetes Care* 20: 1891-1895, 1997
65. Nakamura T, Ushiyama C, Hirokawa K, Osada S, Shimada N, Koide H: Effect of cerivastatin on urinary albumin excretion and plasma endothelin-1 concentrations in type 2 diabetes patients with microalbuminuria and dyslipidemia. *Am J Nephrol* 21: 449-454, 2001
66. Rippin JD, Barnett AH, Bain SC: Cost-effective strategies in the prevention of diabetic nephropathy. *Pharmacoeconomics* 22: 9-28, 2004
67. 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 (standard antihypertensive medications excluding ACE inhibitors, other angiotensin-2 receptor antagonists, and dihydropyridine calcium channel blockers) or late irbesartan treatment in patients with type 2 diabetes, hypertension, and renal disease. *Diabetes Care* 27: 1897-1903, 2004
68. Atthobari J, Asselbergs FW, Boersma C, de VR, Hillege HL, van Gilst WH, Gansevoort RT, de Jong PE, de Jong-van den Berg LT, Postma MJ: Cost-effectiveness of screening for albuminuria with subsequent fosinopril treatment to prevent cardiovascular events: A pharmacoeconomic analysis linked to the Prevention of Renal and Vascular Endstage Disease (PREVEND) study and the Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT). *Clin Ther* 28: 432-444, 2006