Monitoring Kidney Function and Albuminuria in Patients With Diabetes

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It is beyond doubt that patients with diabetes are at high risk of developing renal and cardiovascular disease. Both outcomes have significant clinical implications and are associated with high additional costs. Several traditional (blood pressure, HbA_{1c}, cholesterol) and novel cardiovascular biomarkers (C-reactive protein, pro-brain natriuretic peptide) are at hand to identify those individuals who will develop end-stage renal or cardiovascular disease, as early as possible. The traditional biomarkers have been successfully applied in clinical practice and have proven their clinical usefulness. Renal biomarkers, in particular, albuminuria and estimated glomerular filtration rate (eGFR), have been added to the biomarker armamentarium. Both are indeed associated with renal and cardiovascular disease in individuals with diabetes and may be used to identify individuals at risk of long-term complications. Although identifying individuals at risk is important, even more important is the question whether we can lower this risk by changing renal biomarkers through pharmacological (or other) intervention. This overview describes the performance of albuminuria and eGFR in predicting renal and cardiovascular disease. In the second part, the relationship between treatment-induced changes in these two renal biomarkers and renal and cardiovascular outcome will be described.

ALBUMINURIA AND eGFR AS PREDICTORS FOR RENAL AND CARDIOVASCULAR DISEASE

Albuminuria

The relationship between albuminuria and renal and cardiovascular disease has been well established. Its association was first described in patients with type 1 diabetes (1,2). Several studies followed these initial reports and confirmed the significance of albuminuria in predicting long-term renal prognosis. Data from prospective trials showed that patients with type 2 diabetes appear to progress from micro- to macroalbuminuria to end-stage renal disease (ESRD), similar to the earlier reports of patients with type 1 diabetes. The Reduction in End Points in Non-Insulin Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan (RENAAL) showed that albuminuria is the most critical baseline predictor for ESRD (3). Similar data were observed in type 2 diabetic patients participating in the Irbesartan Diabetic Nephropathy Trial (4). A recent study provides further evidence of the importance of albuminuria as a renal risk predictor in type 2 diabetes. Lorenzo et al. (5) illustrate that the rate of renal function loss was higher in diabetic compared with nondiabetic patients. Interestingly, after adjustment for the difference in albuminuria between the two groups of patients, the difference in eGFR decline was annihilated. These data confirm that patients with diabetes show faster renal function decline, but this is explained, at least to a large extent, by the higher levels of albuminuria. Prospective studies in different populations have shown that increased albuminuria is associated with increased renal risk (Fig. 1*A*) (6).

After the discovery of increased albuminuria as a renal risk marker, it soon became clear that increased albuminuria predicts cardiovascular disease as well. In patients with and without diabetes participating in the Heart Outcomes Prevention Evaluation (HOPE) trial, the presence of microalbuminuria was independently associated with increased risk for cardiovascular disease and mortality (7). In a prospective study of subjects with type 2 diabetes, it was shown that individuals with microalbuminuria had a 1.8-fold increased risk for cardiovascular mortality during 12 years of follow-up compared with individuals with normoalbuminuria (8). Because of these studies, microalbuminuria was evidently associated with cardiovascular and renal risk in diabetes. However, in the 1990s, studies followed demonstrating that the predictive capacity of microalbuminuria goes beyond diabetes. Prospective cohort studies in hypertensive individuals and in the general population showed that increased albuminuria is associated with increased cardiovascular risk (Fig. 1*B*). Interestingly, the slope of relation between albuminuria and renal and cardiovascular risk is similar in different populations and disease conditions, albeit at a different risk level.

Glomerular filtration rate

Although the best measure for glomerular filtration rate (GFR) is obtained by techniques that involve infusion of exogenous substances, GFR is usually estimated in clinical practice by various formulae based on serum creatinine concentration, since this is much less invasive and time-consuming. However, serum creatinine is also affected by factors other than glomerular filtration such as diet, muscle mass, and tubular secretion (9). To circumvent these limitations, several equations have been developed to estimate GFR from serum creatinine concentration.

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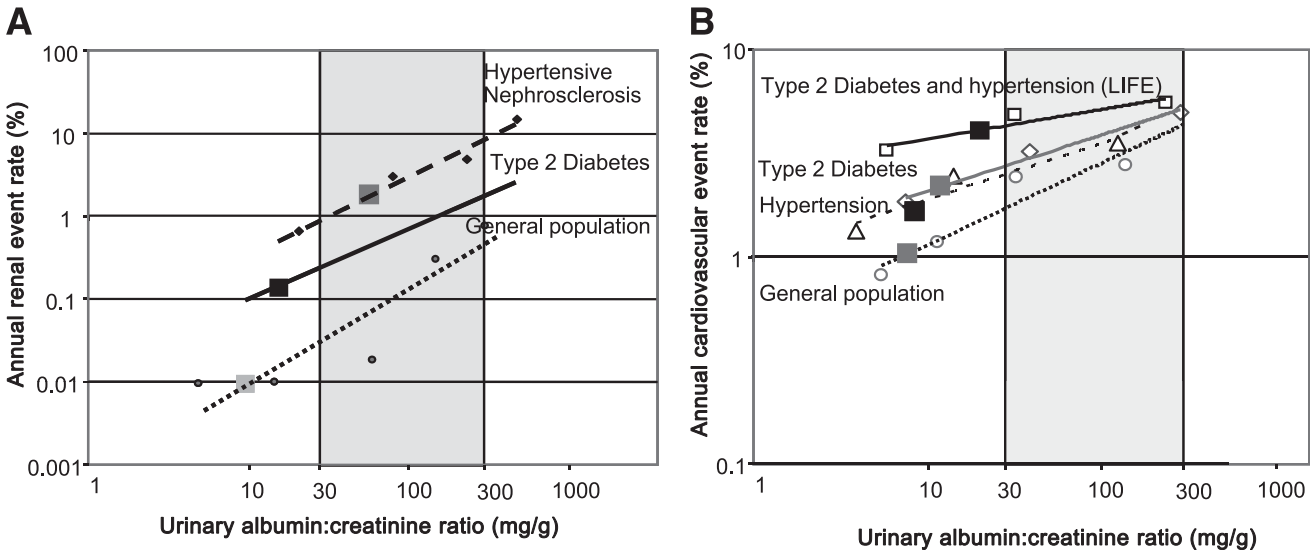

Figure 1—A: *Association between albuminuria level and the risk for renal outcomes in different populations. Data show the risk for ESRD for the general population (Prevention of Renal and Vascular Endstage Disease [PREVEND]), individuals with type 2 diabetes (ADVANCE), and individuals with hypertensive nephrosclerosis (African American Study of Kidney Disease and Hypertension [AASK]). The protein-to-creatinine ratio, measured in the AASK trial, was converted to albumin-to-creatinine ratio. The center of the squares are placed on the average albuminuria level in each population. Adapted with permission from Lambers Heerspink et al. (6).* B: *Associations between albuminuria level and the risk for cardiovascular outcomes in different populations. Data show the risk for cardiovascular event in the type 2 diabetic population (ADVANCE), hypertensive population (LIFE), and general population (PREVEND). The centers of the squares are placed on the average albuminuria level in each population.*

The most popular equation used today is the Modification of Diet in Renal Disease (MDRD) equation (10).

It is known that next to albuminuria, a reduction in eGFR is also associated with a higher risk to develop end-stage renal or cardiovascular disease. As early as 1989, minor increases in serum creatinine (reduction in eGFR) were found to predict mortality (11). This study included 10,940 hypertensive individuals and demonstrated that individuals with a serum creatinine >1.7 mg/dL had a more than threefold increased risk for 8-year mortality. Minor reductions in eGFR are linked to increased risk for renal and cardiovascular disease in patients with diabetes as well. Keane et al. (12) demonstrated that baseline serum creatinine was among the strongest risk predictors for ESRD in patients with type 2 diabetes and nephropathy. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial enrolled a broad range of type 2 diabetic patients with different degrees of renal impairment. In this population, every halving of eGFR measured at the start of the trial was associated with a 1.5- and 1.9-fold increased risk for cardiovascular disease and cardiovascular death, respectively (13). These effects were independent of other baseline renal/cardiovascular risk markers, including albuminuria. Interestingly, the combined effects of baseline albuminuria and eGFR for cardiovascular events and cardiovascular death were independent of each other (Fig. 2). The finding that albuminuria and eGFR are independent additive risk markers was recently confirmed in older adults with diabetes in the Cardiovascular Health study (14). This study illustrated that both an increase in albuminuria and a reduction in eGFR almost doubled the risk for all-cause mortality compared with individuals with either a reduction in eGFR or elevation in albuminuria. The large proportion of patients with impaired eGFR but normal albuminuria (62% in the ADVANCE trial and 53% in the Cardiovascular Health study) in addition to the data that each marker of kidney disease independently predicts renal or cardiovascular risk further supports the concept that both eGFR and albuminuria are independent but complimentary manifestations of different pathology that is associated with cardiovascular risk. Albuminuria may reflect a certain disease state of the microvasculature (endothelial dysfunction), whereas a decrease in GFR may reflect activation of certain hormonal systems, such as the renin-angiotensin-aldosterone system (RAAS), to maintain GFR at an adequate level. These data provide an alternative concept to the traditional paradigm describing albuminuria and eGFR as serial manifestations of kidney disease, whereby albuminuria precedes the decline in GFR. The independent additive value of albuminuria and eGFR supports guideline recommendations advocating the regular measurement of both albuminuria and eGFR to identify patients early at risk for renal and cardiovascular complications (15).

TREATMENT-INDUCED CHANGES IN ALBUMINURIA OR eGFR AND ASSOCIATION WITH RENAL AND CARDIOVASCULAR PROTECTION

—Albuminuria and eGFR are useful biomarkers in predicting the risk for renal and cardiovascular events. However, to have any meaning in clinical practice, it is necessary to show that short-term treatment–induced reductions in albuminuria or changes in eGFR are associated with long-term renal and cardiovascular protection.

Albuminuria

Several studies found that the extent of albuminuria reduction by inhibition of the RAAS has been associated with renal protection. In advanced diabetes and nephropathy, each 50% decrease in albuminuria during the first 6 months, induced by treatment with the angiotensin receptor blocker losartan, was associated with a 45% decrease in the long-term risk

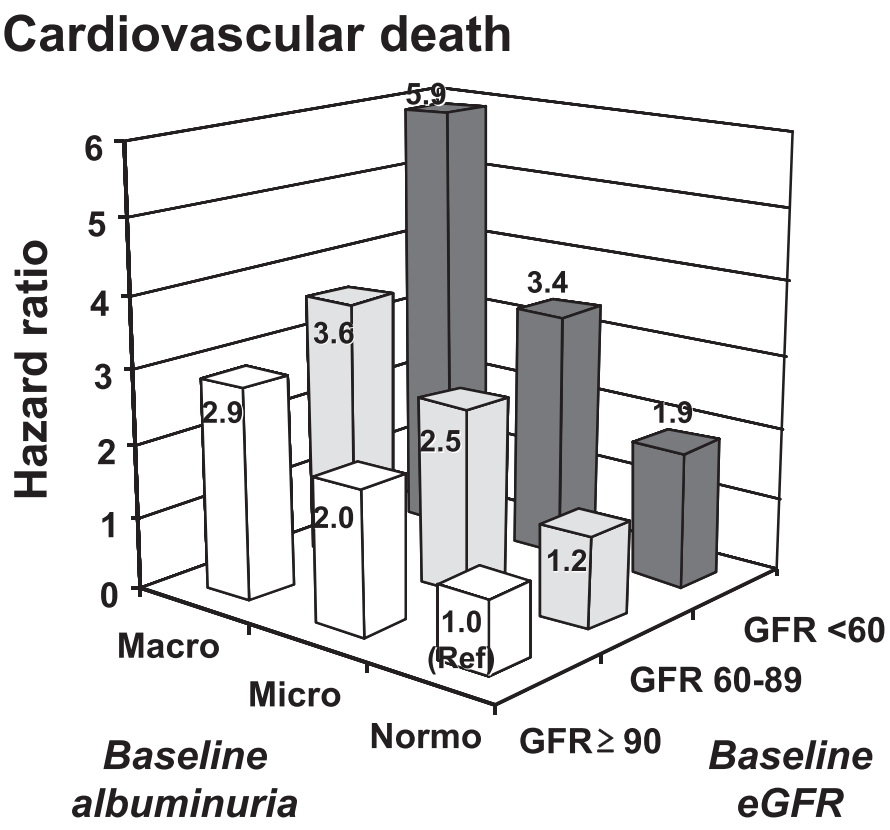

Figure 2—*Combined effects of albuminuria and eGFR levels at baseline on the risk for adverse outcomes. The estimates are adjusted for baseline covariates, including age, sex, duration of diabetes, systolic blood pressure, history of currently treated hypertension, history of macrovascular disease, HbA_{1c}, LDL cholesterol, HDL cholesterol, log-transformed triglycerides, BMI, electrocardiogram abnormalities, current smoking, and current drinking. Adapted with permission from Ninomiya et al. (13).*

for ESRD (3). In patients with type 2 diabetes and early stages of nephropathy, the short-term reduction in albuminuria was also associated with a lower risk for renal disease progression (Fig. 3*A*) (6). Of note, these data extend to other populations, such as those with hypertension, as well (Fig. 3*A*).

Reductions in albuminuria are also linked to cardiovascular protection. Data from the Addenbrooke's hospital showed that patients with type 1 diabetes having a reduction or stable albuminuria during the first year of follow-up had a 48% reduction in their 5-year risk for cardiovascular disease compared with individuals with an increase >30% in the first year (16). A post hoc analysis of the diabetic individuals in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial showed that the more the angiotensin receptor blocker losartan reduced albuminuria, the better the long-term cardiovascular prognosis (17). Similarly, every halving of albuminuria during follow-up in the ADVANCE trial was associated with a 20% reduction in the risk for cardiovascular events. This relationship was independent of the level of systolic blood pressure during follow-up and was, interestingly, comparable to the 18% cardiovascular risk reduction for every halving of albuminuria reported in the RENAAL trial (Fig. 3*B*) (13,18). These studies enrolled a large proportion of individuals with hypertension, leaving the possibility that blood pressure reductions were the driving parameter for cardiovascular protection rather than albuminuria reduction (despite similar follow-up blood pressure levels in the treatment and control arm). An interesting small study in normotensive patients with type 2 diabetes and microalbuminuria showed that sustained reduction in albuminuria, with no changes or even rises in blood pressure, reflected reductions in the risk for cardiovascular complications (19). This study provides further evidence that albuminuria can be regarded as an independent treatment goal for renal and cardiovascular protection. It must be remembered of course that these studies are all post hoc analyses of randomized controlled trials. Evidence from prospective studies to demonstrate that albuminuria reductions in itself are associated with cardiovascular protection are only small and are performed in nondiabetic subjects (20). In diabetes, such large studies are needed to resolve the issue whether specific lowering of albuminuria results in cardiovascular protection.

Although RAAS intervention (RAASi) is clearly beneficial in reducing albuminuria and delaying the progression of renal and cardiovascular disease, the optimal renal/cardioprotective dose of ACE inhibitors and angiotensin receptor blockers with respect to albuminuria lowering needs to be established (21). Studies have shown that the use of high doses of angiotensin receptor blockers, beyond the maximal recommended doses for blood pressure reduction, further lower albuminuria and may provide greater renal and cardiovascular benefit (22,23). However, long-term renal/cardiovascular outcome studies are required to assess the long-term efficacy and safety of exposure to such high doses.

GFR

Upon start of treatment with RAASi, an acute rise in serum creatinine or drop in (e)GFR is noticed. This result has led to inappropriate safety concerns, particularly among cardiologists, and underutilization of RAASi despite its proven benefit in clinical trials. In fact, the acute fall in eGFR upon starting RAASi is not a sign of worsening renal function, but has been associated with long-term renoprotection and can be used as a marker of therapeutic response. How do we explain this relationship, which at first sight is perhaps counterintuitive? One should first realize that the acute fall in GFR upon RAASi initiation is of (reversible) hemodynamic origin owing to a reduction of intraglomerular pressure rather than a treatment-induced damage to functioning nephrons. Because of this reversible hemodynamic origin, treatment withdrawal leads to an increase in GFR of the same magnitude as the initial fall. A couple of studies demonstrated that after withdrawal of antihypertensive therapy, the GFR increased in the majority of patients and correlated with the initial GFR fall (24,25). Second, an increase in intraglomerular pressure was associated with progressive renal function decline (26). This result suggests that it may be

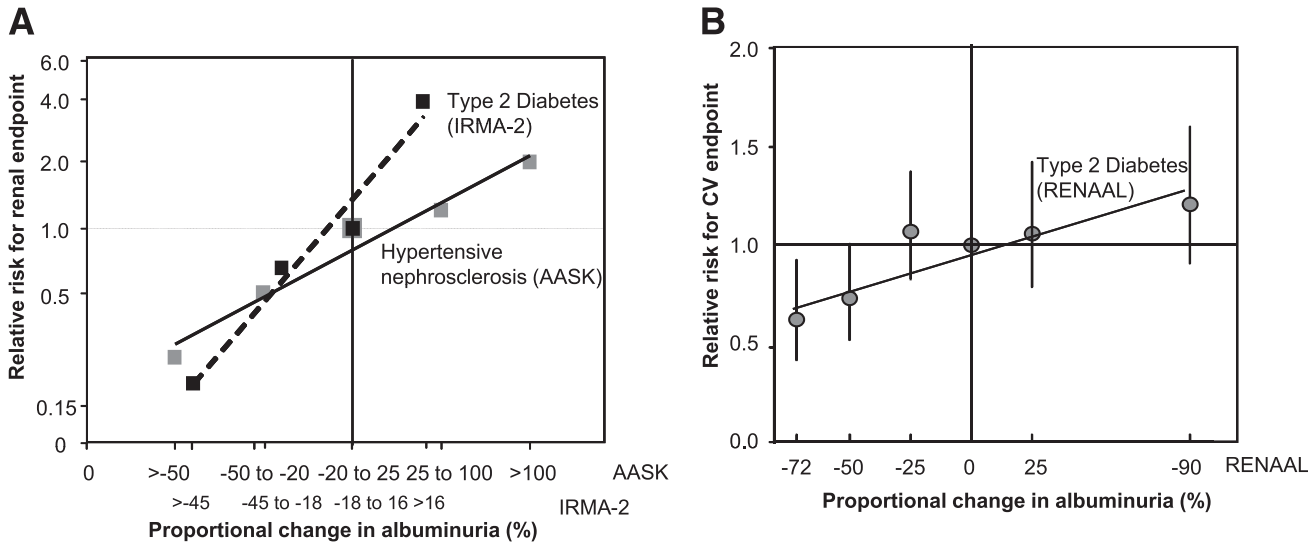

Figure 3—A*: Associations between the proportional change in albuminuria and the risk for renal outcomes. Renal end point in the Irbesartan in Patients with Type 2 Diabetes and MicroAlbuminuria Study (IRMA-2) trial is diabetic nephropathy. The renal end point in the African American Study of Kidney Disease and Hypertension (AASK) trial is ESRD. The two* x*-axes indicate the ranges of albuminuria reduction for the two different individual trials. Adapted with permission from Lambers Heerspink et al. (6).* B*: Associations between the proportional change in albuminuria and the risk for cardiovascular outcomes in the type 2 diabetic population (RENAAL). Adapted with permission from de Zeeuw et al. (18).*

possible that the degree of acute GFR fall (as a measure of reduction in intraglomerular pressure) is associated with renal and possibly cardiovascular protection. Indeed, Apperloo et al. demonstrated that the reversible reduction in GFR after the start of ACE inhibitor therapy was highly variable between patients. Interestingly, those patients with a greater initial fall in GFR had a significantly less steep GFR slope during long-term follow-up (Fig. 4). Similar associations between an ACE inhibitor–induced acute eGFR fall and long-term renal prognosis were observed in post–myocardial infarction patients (27). Treatment with captopril caused a distinct fall during the first 3 days after a myocardial infarction but remained stable during the 1-year follow-up. In contrast, the initial 3-day fall in GFR during placebo was less marked and continued to decline during the 1-year follow-up, resulting in an overall 1-year GFR decline of 5.5 mL/min versus only 0.5 mL/min in the captopril group. Bakris and Weir (28) reported a systematic review of 12 randomized trials (5 of them included solely patients with diabetes) and demonstrated that, while GFR may be reduced acutely during ACE inhibitor therapy, long-term renal function decline is markedly blunted compared with control treatment. Thus, a fall in eGFR after the start of RAASi can be interpreted as a marker of therapy responsiveness. This scenario should consequently be taken as encouragement to continue treatment, as long as other causes contributing to the fall in eGFR such as renal artery stenosis, diminished arterial blood volume, or safety issues such as hyperkalemia can be excluded.

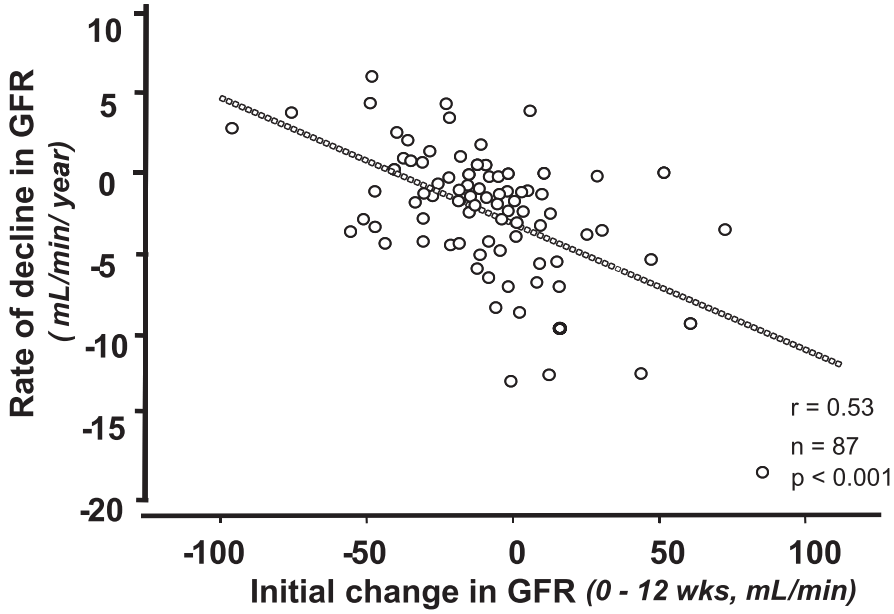

Figure 4—*Acute fall in eGFR associated with slower rate of long-term renal function decline.*

CONCLUSIONS—The renal biomarkers albuminuria and eGFR predict renal and cardiovascular complications in patients with diabetes beyond the set of traditional cardiovascular biomarkers. The short-term (treatment-induced) changes in albuminuria and eGFR indicate the long-term changes in renal and cardiovascular risk. This feature provides further clinical usefulness to these biomarkers.

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