http://www.kidney-international.org

Microalbuminuria: target for renoprotective therapy PRO

Sara S. Roscioni[1,2], Hiddo J. Lambers Heerspink[1,2] and Dick de Zeeuw[1]

[1]*Department of Clinical Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*

Drug efficacy is ascertained using clinically meaningful outcomes that directly affect the well-being of patients. However, in studies of chronic kidney disease progression, clinically meaningful outcomes like end-stage renal disease take a long time to occur. The use of surrogate end points/markers as replacement for clinical outcomes is tempting as it may reduce sample size requirements, shorten follow-up time, facilitate trial conduct, and allow the performance of intervention trials in earlier stages of kidney disease to be carried out. We here reviewed recent data supporting the use of microalbuminuria as a valid surrogate end point in clinical trials of chronic kidney disease. We provide data that albuminuria is associated with worse renal prognosis and that pharmacological treatment aimed to reduce albuminuria levels delays the progression of renal disease and the occurrence of clinical outcomes. Furthermore, we review new studies showing that albumin is not only an inert molecule but also directly affects the function of several cell types in the kidney and may have a pathogenic role in renal disease. Accepting microalbuminuria as a surrogate marker for renal outcomes will lead to less resource-consuming hard outcome trials, will accelerate the development of drugs for chronic kidney disease, and enable earlier access of these drugs to individual patients.

Kidney International (2014) **86,** 40–49; doi:10.1038/ki.2013.490; published online 23 April 2014

KEYWORDS: diabetic nephropathy; diabetes mellitus; end-stage renal disease; microalbuminuria; randomized controlled trial

Correspondence: *Hiddo J. Lambers Heerspink, Department of Clinical Pharmacology, University Medical Centre Groningen, University of Groningen, Antonius Deusinglaan, 1, Groningen 9713 AV, The Netherlands. E-mail: h.j.lambers.heerspink@umcg.nl*

[2]These two authors contributed equally to this work.

Received 15 June 2013; revised 19 August 2013; accepted 22 August 2013; published online 23 April 2014

Despite the availability of effective treatments to delay the progression of renal function loss, the prevalence of end-stage renal disease (ESRD) continues to rise.[1] Novel strategies are needed to lessen the burden of this devastating condition. Health campaigns have focused on early detection of chronic kidney disease on the basis of the rationale that early intervention and appropriate treatment has a greater impact in delaying the progression of renal function loss compared with late intervention.

To study the efficacy of new drugs, clinically meaningful outcomes that directly affect the well-being of patients are needed. ESRD is a commonly used hard clinical end point in drug trials in nephrology. However, the progression of kidney disease to ESRD takes many years if not decades. Clinical trials enrolling patients at early stages of disease would therefore require a long follow-up and/or an impractical large sample size to establish drug efficacy toward ESRD. The use of a surrogate end point may be a solution to this problem.

A surrogate end point of a clinical trial is a laboratory measurement or a physical sign that measures the effect of a certain treatment and is intended to substitute for the clinical end point.[2] Although such a surrogate end point does not directly measure how a patient feels, functions, or survives, it is associated with clinically meaningful outcomes so that changes in the marker level are expected to predict benefit or harm. The use of surrogate end points in clinical trials is tempting as it may reduce sample size requirements, shorten the follow-up time of clinical trials, and allow the performance of early intervention trials to be carried out.

The presence of microalbuminuria is an early sign of renal damage and predicts an accelerated loss of renal function.[3] Clinicians currently use microalbuminuria to diagnose renal damage and establish the prognosis of an individual. Moreover, the change in albuminuria after treatment initiation with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is frequently used to monitor renal and/or cardiovascular -protective response to therapy. Microalbuminuria could therefore be used as target for treatment and as a surrogate end point in clinical trials. However, there is growing awareness that surrogate end points should be used in clinical trials only after they have been sufficiently validated and reflect a true clinical end point. In the past, a number of promising potentially valid surrogate end points (e.g., hemoglobin) have failed to reflect a true clinical end

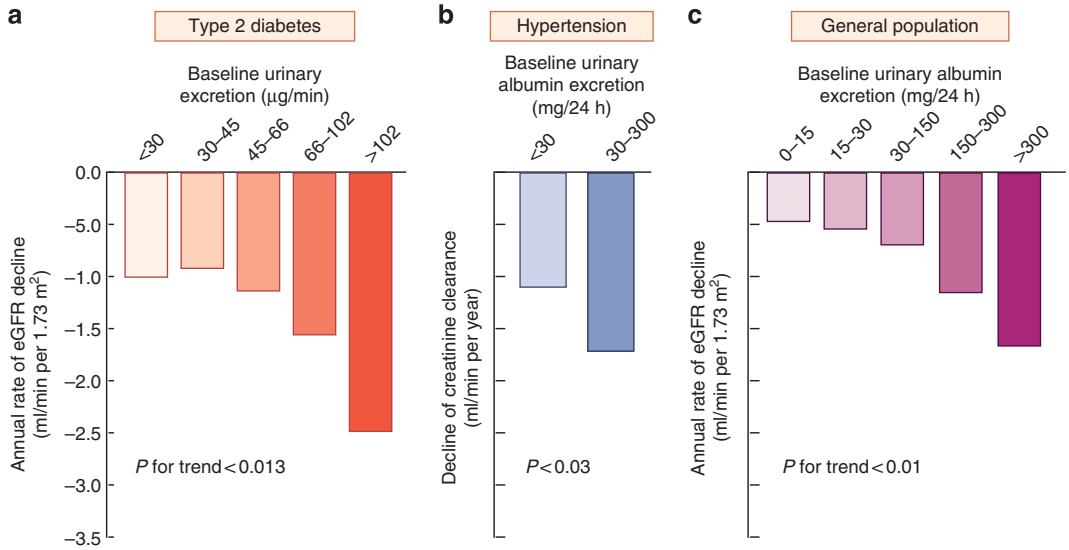

Figure 1 | Higher albuminuria associates with faster decline in renal function in different populations. The annual decline in glomerular filtration rate (GFR) relative to the levels of baseline albuminuria in patients with (**a**) type 2 diabetes, (**b**) hypertension, and in the (**c**) general population. Data on type 2 diabetes patients are from the Irbesartan Microalbuminuria-2 (IRMA-2) study,[90] data on hypertensive patients are from Bigazzi *et al*,[14] and data on the general population are from Prevention of Renal and Vascular End-stage Disease (PREVEND).[16] eGFR, estimated GFR.

point.[4,5] Therefore, rigorous validation of a surrogate end point is necessary before it can be implemented in clinical practice. The criteria for validation of surrogacy have been described in the 'statistical principles for clinical trials' of the International Conference on Harmonization.[6] First, prognostic evidence of the surrogate end point with patient outcome must be available. Second, a biologically plausible relationship between the surrogate and outcome should exist, and third, clinical trial data must demonstrate that the effect of interventions that change the surrogate end point is directly associated with the same change in clinical outcomes.

Herein, we provide new updates that support the concept that microalbuminuria is a valid surrogate renal end point and a target for treatment in renal disease.

MICROALBUMINURIA IS ASSOCIATED WITH RENAL OUTCOMES

Twenty-four-hour urine collection represents the gold standard method for determining the presence of microalbuminuria. However, as 24-hour urine collection is an inconvenient procedure for patients, more practical alternatives have been proposed, such as measurement of the albumin:creatinine ratio (UACR) derived from a first morning void or a spot urine sample. Of these, the measurement of UACR in a first morning void appears to be the most reliable alternative to the 24-hour urinary albumin excretion (UAE) in determining the presence of microalbuminuria and also in predicting the progression of disease.[7,8]

For practical purposes albuminuria is categorized into different classes—namely, normoalbuminuria (<30 mg albumin per day or per g creatinine), microalbuminuria (30–300 mg albumin per day or per g creatinine), and macroalbuminuria (>300 mg albumin/day or per g creatinine). The changes between these albuminuria states represent a hallmark of the progression or regression of disease.[9] Emerging evidence shows that individuals with high grades of albuminuria are at increased risk of accelerated loss of renal function.[10] Whereas the association between the severity of albuminuria and renal disease progression was initially described in individuals with high albuminuria (>1.0 g per day),[11] more recent studies show that an increase in albuminuria, even within the range that is currently considered normal, indicates higher renal risk.[10] This is a consistent finding that has been shown in different populations.

In patients with type 2 diabetes followed up for at least 5 years, higher UACR at baseline was associated with a faster decline in renal function. Importantly, although within the normal range, a UACR of ⩾10 mg/g in women or ⩾5 mg/g in men was associated with a significantly greater rate of renal function decline.[12] Similar data were found in patients with type 2 diabetes and microalbuminuria participating in the Irbesartan Microalbuminuria-2 (IRMA-2) trial. Subjects in the highest quintile of baseline albuminuria excretion (between 102 and 300 μg/min, which equals a UACR of ~150 and 450 mg/g) had approximately 2.5-fold greater rate of renal function decline compared with subjects with urinary albumin excretion between 20 and 30 μg/min[13] (which equals a UACR of ~30 and 45 mg/g) (Figure 1a). The association between the increases in albuminuria and hard renal outcomes in type 2 diabetes was established in the ADVANCE trial.[9] Although the majority of patients (69%) enrolled in this trial had albuminuria in the normal range, baseline albuminuria was an independent determinant of the progression to renal outcomes, and even subtle changes in albuminuria in the normal range were strongly associated with disease progression.