

# Renin angiotensin aldosterone system (RAAS) inhibitors in the prevention of early renal disease in diabetes

Luigi Gnudi<sup>1\*</sup> and David Goldsmith<sup>2</sup>

Addresses: <sup>1</sup>Unit for Metabolic Medicine, Cardiovascular Division, King's College, 3rd Floor, Franklin-Wilkins Building, Waterloo Campus, Stamford Street, London SE1 9NH, UK; <sup>2</sup>Renal Department, 6th Floor Borough Wing, Guy's Hospital Campus, King's Health Partners, London SE1 9RT, UK

\* Corresponding author: Luigi Gnudi (luigi.gnudi@kcl.ac.uk)

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## Abstract

Diabetic nephropathy (diabetic kidney disease) is defined as a rise in urinary albumin excretion rate, often associated with an increase in blood pressure, and typically with concomitant retinopathy but without evidence of other causes of renal disease. It is characterized first by albuminuria and then by a progressive decline in glomerular filtration rate, eventually resulting in end-stage renal disease (ESRD). Diabetic nephropathy occurs in approximately 30-35% of type 1 and type 2 patients and tends to cluster in families. Diabetic kidney disease is associated with a very marked increase in cardiovascular disease and, even from the earliest stages, with microalbuminuria. A diabetic milieu is required for the diabetic glomerular lesion to develop, and the renin angiotensin aldosterone system (RAAS) has been implicated in the development and progression of diabetic nephropathy. Most patients with diabetes and renal impairment die from a cardiovascular disease event before they progress to ESRD. From the studies described in this review, we think that clear evidence of RAAS inhibition in the prevention of diabetic nephropathy is lacking and more studies are warranted. Nevertheless, tight blood pressure control with inhibitor of RAAS and multifactorial intervention (glycaemic, lipid control and so on) are warranted for secondary prevention and treatment of chronic kidney disease in diabetes.

## Introduction and context

Diabetic nephropathy (diabetic kidney disease) is defined as a rise in urinary albumin excretion rate, often associated with an increase in blood pressure, and typically with concomitant retinopathy but without evidence of other causes of renal disease [1,2]. It is characterized first by albuminuria and then by a progressive decline in glomerular filtration rate, eventually resulting in end-stage renal disease (ESRD). It is usually accompanied by hypertension and, in the later stages of diabetic kidney disease, by anaemia. Diabetic nephropathy occurs in approximately 30-35% of type 1 and type 2 patients and tends to cluster in families. Diabetic kidney disease is associated with a very marked increase in cardiovascular disease and, even from the earliest stages, with microalbuminuria [3].

A diabetic milieu is required for the diabetic glomerular lesion to develop, and the renin angiotensin aldosterone system (RAAS) has been implicated in the development and progression of diabetic nephropathy. The all-cause mortality in patients with diabetic nephropathy is nearly 20-40 times higher than that in patients without nephropathy and is 2-5 times higher than with other forms of chronic kidney disease [3]. Most patients with diabetes and renal impairment die from a cardiovascular disease event before they progress to ESRD.

Diabetic nephropathy is the most common cause of ESRD worldwide and represents about 30-40% of all patients receiving renal replacement therapy in the Western world [4]. Early intervention is therefore key to

contain the burden of this most feared diabetic chronic vascular complication.

### Recent advances

Multifactorial treatment approaches (e.g., hypoglycaemic, antihypertensive, and cholesterol-reducing) are now widely recommended in guidelines to be implemented in the treatment of renal disease in diabetes at the earliest stages, and inhibitors of RAAS appear particularly effective in delaying progression toward end-stage renal failure. What is not so clear, however, despite the realization that 'metabolically harmful' drugs like thiazide diuretics and beta blockers are associated in middle-aged hypertensive patients with a higher incidence of *de novo* diabetes, is whether targeted introduction of RAAS inhibitors can prevent the development of diabetic nephropathy. In a recent study, Mauer and colleagues [5] tested whether blockade of the RAAS system (using either angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]) before the onset of albuminuria in patients with type 1 diabetes could slow progression of the early histological lesions of diabetic nephropathy.

The findings on the prevention of diabetic nephropathy were discouraging; the changes in the fraction of glomerular volume occupied by mesangium did not differ from those of the placebo, enalapril or losartan groups, and worryingly, Mauer and colleagues observed that albuminuria was more common in the losartan group than in the placebo group, and more patients in the losartan group progressed to microalbuminuria than was the case in the enalapril or placebo groups [6]. The interpretation of these data is difficult, but we can speculate that a degree of RAAS activation is important and might be 'protective' in the kidney. Excessive RAAS inhibition in conditions in which it might not be significantly activated (e.g., normotensive normoalbuminuric patients) could be detrimental. Often in experimental and clinical research, we observe that a balanced activation of any biological pathway is crucial and that excessive inhibition or activation is to be avoided.

Similar results were observed in the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes (EUCLID) study. In that study, the effect of the ACE inhibitor lisinopril on the progression of renal disease in normotensive type 1 diabetic patients with normoalbuminuria or microalbuminuria was investigated; no clear nephroprotective effect was observed in type 1 diabetic patients with normoalbuminuria, but a clear antiproteinuric effect of lisinopril was seen in microalbuminuric patients [6]. Similarly, the Diabetic Retinopathy Candesartan Trial (DIRECT) failed to

demonstrate, in a *post hoc* analysis, any effect of the ARB candesartan on the development of microalbuminuria in type 1 diabetic patients [7].

In summary, it appears that there is no evidence of a benefit on structural/functional parameters from the blockade of RAAS with an ACE inhibitor or an ARB in normotensive patients with type 1 diabetes and normoalbuminuria. So, at the moment, the blanket prescription of an ACE inhibitor or an ARB to patients with diabetes, but without any cardiovascular or renal disease, cannot yet be recommended, and blood pressure should be treated along the lines indicated by the Joint British Societies guidelines (JBS-2) [8].

The observed changes in albuminuria are not always associated with a commensurate alteration/decline in renal function, especially in early diabetic nephropathy, and we should be aware of a potential uncoupling of albuminuria and renal function, especially in the early phase of renal disease in diabetes [9].

If we focus on type 2 diabetes, specifically in the United Kingdom Prospective Diabetes Study (UKPDS), better control of blood pressure (achieved mean blood pressure of 144/82 mm Hg) as compared with ordinary control (mean blood pressure of 154/87 mm Hg) translated into a 29% risk reduction of developing microalbuminuria over the course of a 6-year period. Treatments with an ACE inhibitor (captopril) and a beta blocker (atenolol) were equally effective but the study was not powered to detect between-drug differences [10]. Continued good blood pressure control is critical because, unlike glycaemic control, there was no legacy effect in the UKPDS follow-up on microvascular complications as blood pressure control worsened [11,12].

The Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) found that the risk of developing microalbuminuria was reduced by about 50% by the use of the ACE inhibitor trandolapril but not by verapamil for equivalent blood pressure reduction in hypertensive patients with type 2 diabetes and normoalbuminuria [13].

The Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) blood pressure trial showed that, in patients with type 2 diabetes, treatment with perindopril and indapamide (a thiazide diuretic) reduced renal events (predominantly new-onset microalbuminuria) by nearly 21% compared with conventional antihypertensive treatment. Achieved blood pressure was lower in the perindopril/indapamide group [14].

Along the same lines are the more recent data from the Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study, recently presented at an American Society of Nephrology meeting [15]. In that study, a significant effect of the angiotensin-receptor blocker olmesartan medoxomil (against placebo) on the development of microalbuminuria was observed in normoalbuminuric mildly hypertensive patients with type 2 diabetes on no treatment with inhibitors of the RAAS. From this preliminary information, it appears that the reduced incidence in new microalbuminuria observed in the olmesartan group can be attributed only partly to blood pressure control and that a significant effect is to be attributed to the direct action (presumably on renal vasculature) of olmesartan.

At variance with these studies, DIRECT failed to demonstrate, in a *post hoc* analysis, any effect of the ARB candesartan on the development of microalbuminuria in type 2 diabetic patients (similarly to type 1 diabetic patients as noted above) with preserved renal function (creatinine of less than 133 mmol/L) [7]. This was despite lower blood pressure levels in the candesartan-treated group.

Similarly, the Microalbuminuria, Cardiovascular, and Renal Outcomes-Heart Outcomes Prevention Evaluation (MICRO-HOPE) study [16], conducted in type 2 diabetic patients, studied the effect of the ACE inhibitor ramipril on myocardial infarction, stroke, or cardiovascular death. Ramipril had a significant reduction on the primary cardiovascular endpoint, but a significant role of ramipril on diabetic nephropathy was seen in microalbuminuric patients only, whereas no clear effect was observed between the intervention and placebo groups on the development of new microalbuminuria in patients not presenting this condition at baseline.

It would appear that a potential positive effect of RAAS inhibition is seen mainly in significantly hypertensive populations (UKPDS, BENEDICT, ADVANCE, and ROADMAP) and less in studies conducted in more normotensive and less 'at risk' normoalbuminuric diabetic patients (EUCLID, MICRO-HOPE, DIRECT), again possibly highlighting the importance of a balanced RAAS activation/ inhibition.

### Implications for clinical practice

From the studies described above, we think that clear evidence of RAAS inhibition in the prevention of diabetic nephropathy is lacking and more studies are warranted. Nevertheless, tight blood pressure control with inhibitor of RAAS and multifactorial intervention (glycaemic, lipid control and so on) are warranted for

secondary prevention and treatment of chronic kidney disease in diabetes.

### Abbreviations

ACE, angiotensin-converting enzyme; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamiron MR Controlled Evaluation; ARB, angiotensin receptor blocker; BENEDICT, Bergamo Nephrologic Diabetes Complications Trial; DIRECT, Diabetic Retinopathy Candesartan Trial; ESRD, end-stage renal disease; EUCLID, EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes; MICRO-HOPE, Microalbuminuria, Cardiovascular, and Renal Outcomes-Heart Outcomes Prevention Evaluation; RAAS, renin angiotensin aldosterone system; ROADMAP, Randomised Olmesartan and Diabetes Microalbuminuria Prevention; UKPDS, United Kingdom Prospective Diabetes Study.

### Competing interests

LG declares that he has no competing interests on the topic covered. DG has received speaking and consultancy honoraria from Merck (Darmstadt, Germany), sanofi-aventis (Paris, France), Pfizer Inc. (New York, NY, USA) and Bristol-Myers Squibb Company (Princeton, NJ, USA).

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