The effect of RAAS blockade on the progression of diabetic nephropathy

Sara S. Roscioni, Hiddo J. Lambers Heerspink and Dick de Zeeuw

Abstract | The renin–angiotensin–aldosterone system (RAAS) has a key role in the regulation of blood pressure, sodium and water balance, and cardiovascular and renal homeostasis. In diabetic nephropathy, excessive activation of the RAAS results in progressive renal damage. RAAS blockade using angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers is the cornerstone of treatment of diabetic renal disease. Alternative RAAS-blockade strategies include renin inhibition and aldosterone blockade. Data from small initial studies of these agents are promising. However, single-agent interventions do not fully block the RAAS and patients treated with these therapies remain at high residual renal risk. Approaches to optimize drug responses include dietary changes and increasing dosages. The theoretically attractive option of combining different RAAS interventions has also been tested in clinical trials but long-term outcomes were disappointing. However, dual RAAS blockade might represent a good therapeutic option for specific patients. A better knowledge of the pathophysiology of the RAAS is crucial to fully understand the mechanisms of action of RAAS blockers and to exploit their renoprotective effects. Moreover, lifestyle interventions or diagnostic tools might be used to optimize RAAS blockade and identify those patients who are most likely to benefit from the therapy.

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Introduction

Diabetic nephropathy is a chronic progressive disorder that is characterized by microalbuminuria, followed by macroalbuminuria or overt proteinuria, increased blood pressure, and an irreversible decline in renal function, which ultimately leads to end-stage renal disease (ESRD). Diabetic nephropathy is the leading cause of chronic kidney disease (CKD) in developed countries and its prevalence has increased dramatically in the past few decades.[1] This increase is primarily the result of a pandemic increase in diabetes mellitus, because patients with long-standing diabetes are at increased risk of developing this complication.[2] Patients with diabetic nephropathy have a considerably higher risk of renal and cardiovascular morbidity and mortality than the general population.[3] Affected patients often show changes in renal haemodynamics, low-grade inflammation, endothelial dysfunction,[4] and structural alterations in the glomerulus, tubule and/or interstitium, which correlate with the severity of the disease.[5,6] Treatment of the mid-to-late stages of diabetic nephropathy is mainly focussed on the symptoms with the aim of slowing down the progressive loss of renal function. Efforts are also focused on diabetes prevention to avoid the dramatic consequences of diabetic nephropathy.

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Competing interests
H. J. Lambers Heerspink declares associations with the following companies: AbbVie, Astellas, Johnson & Johnson, Reata, Vitae. D. de Zeeuw declares associations with the following companies: AbbVie, Astellas, Chemocentryx, Johnson & Johnson, Novartis, Reata, Takeda, Vitea. See the article online for full details of the relationships. S. S. Roscioni declares no competing interests.

The renin–angiotensin–aldosterone system

Dysregulation of the renin–angiotensin–aldosterone system (RAAS) has a critical role in the pathogenesis of diabetic nephropathy. The classical RAAS cascade (Figure 1) starts with the production of prorenin, an aspartate protease that is secreted by renal juxtaglomerular cells in response to decreases in circulating blood volume.[7] Following conversion from prorenin, renin triggers the conversion of angiotensinogen to angiotensin I. The main effector hormone of the RAAS is angiotensin II, which is generated from angiotensin I in the circulation and in the tissues, mostly as a result of the action of angiotensin-converting enzyme (ACE). Angiotensin II is a pleiotropic hormone with several targets, including the kidneys, blood vessels, and nervous system.[8] Despite its physiological role, excessive activity of the RAAS has deleterious effects on the kidneys and contributes to a progressive loss of renal function.[8] Continued RAAS activation constricts renal arterioles leading to increased peripheral and renal resistance, increases glomerular capillary pressure leading to proteinuria, augments oxidative stress[9] (via the NADPH oxidase pathways) leading to endothelial dysfunction, promotes proliferation of mesangial cells (probably via mitogen-activated protein kinase or protein kinase C-dependent pathways), triggers pro-inflammatory pathways (including activation of nuclear

Key points

- Renin–angiotensin–aldosterone system (RAAS) blockade using angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers, which have antihypertensive and antialbuminuric properties, has become the cornerstone of treatment of diabetic renal disease
- As single-agent RAAS blockade does not completely block RAAS activation the residual renal risk of treated patients is high
- Data from clinical trials of dual RAAS blockade (including the use of aldosterone blockers or renin inhibitors) are contradictory and safety remains a concern
- Possible alternatives to dual RAAS blockade include restricting dietary sodium, increasing drug doses or using novel drugs to block the deleterious effects of RAAS activation whilst preserving its physiological role
- Novel omic techniques might enable the identification of patients who are most likely to benefit from RAAS blockade and the individual tailoring of interventions

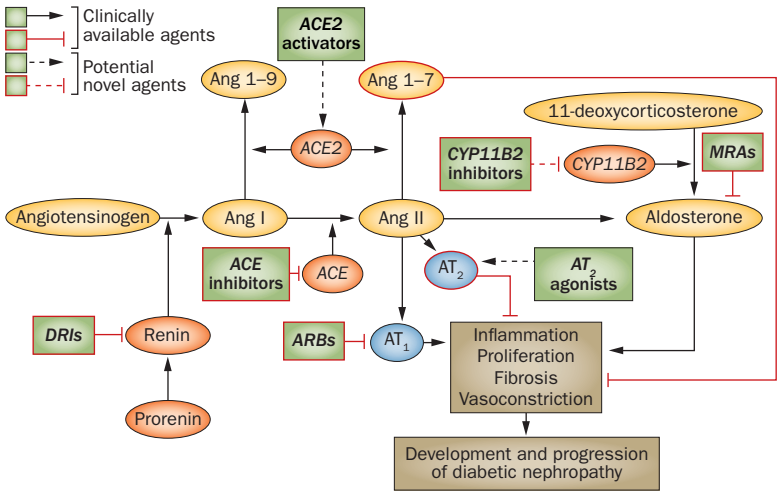

Figure 1 | Current and potential targets for therapeutic interventions in the RAAS cascade. Abbreviations: ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; ang I, angiotensin I; ang II, angiotensin II; ARB, angiotensin-receptor blocker; AT_1, type I angiotensin II receptor; AT_2, type 2 angiotensin II receptor; CYP11B2, aldosterone synthase; DRI, direct renin inhibitor; MRA, mineralocorticoid receptor antagonist.

factor-κB), and stimulates profibrotic processes.[10–12] These effects eventually result in the progression of diabetic nephropathy. The effects of RAAS activation on blood pressure seem to be mainly driven by systemically generated angiotensin II, whereas the specific effects on renal tissue seem to be caused by locally generated angiotensin II.[12] ACE inhibitors and angiotensin receptor blockers (ARBs) have been developed to block the formation and function of angiotensin II, with the ultimate aim of improving renal and cardiovascular outcomes. Use of these agents has indeed proven to be a good therapeutic strategy to halt the progression of renal dysfunction in patients with diabetic or nondiabetic nephropathy.[7]

ACE inhibitors and ARBs

Effects on disease progression

Diabetic nephropathy can occur in patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) and the development of microalbuminuria or macroalbuminuria is a hallmark of disease progression. From the time of diagnosis of T2DM, the annual rate of progression to microalbuminuria is 2%.[13] Approximately 3% of patients with microalbuminuria progress to macroalbuminuria, and 2.5% of patients with macroalbuminuria progress to renal replacement therapy or severely reduced renal function per year.[13] The effect of RAAS blockade at each stage of progression of diabetic nephropathy has been investigated in various trials (Figure 2).

Onset of T2DM

Patients with impaired glucose tolerance have an increased risk of T2DM and various strategies, including dietary modification and use of hypoglycaemic drugs, are effective in reducing this risk.[14] As insulin interacts with the RAAS,[15] *post hoc* analyses and meta-analyses of clinical trials have investigated whether RAAS blockade delays the onset of T2DM.[16,17] A meta-analysis of 12 randomized controlled trials involving 72,333 patients who did not have diabetes at baseline showed that use of ACE inhibitors or ARBs reduced the risk of T2DM by 27% and 23%, respectively.[18] Subsequent prospective randomized controlled trials were designed to test the effect of ACE inhibitors or ARBs on risk of T2DM in patients with impaired glucose tolerance. The DREAM trial, which enrolled 5,269 participants with impaired glucose tolerance and without cardiovascular disease, showed that treatment with the ACE inhibitor ramipril versus placebo resulted in a nonsignificant 9% (95% CI –3 to 19) reduction in the incidence of diabetes at 3 year follow-up.[19] By contrast, the NAVIGATOR trial, which included 9,603 patients with impaired glucose tolerance and either cardiovascular disease or at least one cardiovascular risk factor, demonstrated that the ARB valsartan versus placebo reduced the risk of T2DM by 14% (95% CI 8–20, $P<0.001$) at a median follow-up of 6.2 years.[20] These differing findings might be the result of the differing study populations (the DREAM trial participants did not have cardiovascular disease, whereas the NAVIGATOR trial participants had cardiovascular disease or a cardiovascular risk factor), the duration of follow-up (3 years in the DREAM trial and 6.2 years in the NAVIGATOR trial), drugs used, or sizes and durations of the trials and thus their statistical power.

Risk of microalbuminuria

ACE inhibitors and ARBs have also been shown to reduce the risk of microalbuminuria in patients with diabetes. In 1998, Ravid *et al.* reported that daily treatment with the ACE inhibitor enalapril compared with placebo decreased urinary albumin levels, reduced the risk of progression to microalbuminuria, and attenuated decline in renal function during 6 years of follow-up in 156 patients with T2DM.[21] This important study was followed by larger clinical trials that confirmed the benefits of early RAAS blockade for the prevention of progression of diabetic nephropathy. In the BENEDICT study, the ACE inhibitor trandolapril compared with placebo delayed the onset of microalbuminuria independently of blood pressure in 1,204 patients with T2DM and normoalbuminuria during a follow-up of 3.6 years.[22] The subsequent ROADMAP trial showed that the ARB olmesartan was also effective in

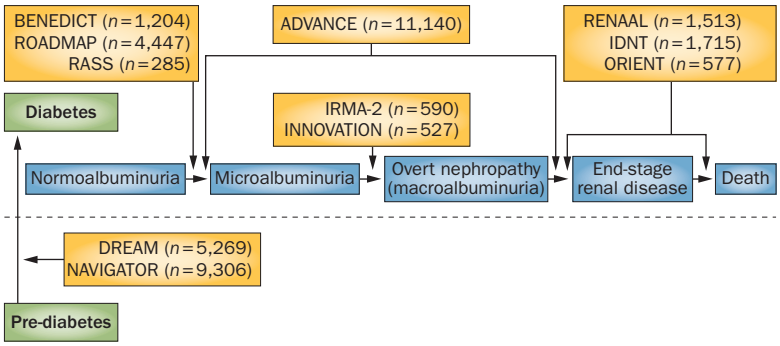

Figure 2 | Randomized controlled trials that have investigated the effects of RAAS blockade at the various stages of progression of diabetic nephropathy. Abbreviations: ADVANCE, The Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation;[26] BENEDICT, Bergamo Nephrologic Diabetes Complications Trial;[22] DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication;[19] IDNT, Irbesartan Diabetic Nephropathy Trial;[28] INNOVATION, Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy;[25] IRMA-2, The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Trial;[24] NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research;[20] ORIENT, Olmesartan Reducing Incidence of End-stage Renal Disease in Diabetic Nephropathy Trial;[31] RASS, Renin–Angiotensin System Study;[32] RENAAL, The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study;[29] ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention.[23]

delaying the onset of microalbuminuria independently of blood pressure, in 4,447 patients with T2DM.[23] However, an unexplained excess of cardiovascular mortality was observed in the olmesartan group.

Risk of macroalbuminuria

The IRMA-2[24] and INNOVATION[25] placebo-controlled trials, which enrolled patients with T2DM and microalbuminuria, were designed to determine whether RAAS blockade reduced the risk of progression of diabetic nephropathy, defined as the development of macroalbuminuria. The IRMA-2 study showed that treatment with the ARB irbesartan was associated with a dose-dependent reduction in risk of progression to macroalbuminuria, with an almost threefold risk reduction with the highest dose (300 mg per day) at 2 years of follow-up.[24] This effect was independent of the blood pressure-lowering properties of irbesartan. In the INNOVATION trial, the ARB telmisartan was associated with a lower transition rate to overt nephropathy than was placebo after 1 year of follow-up.[25] In this trial, telmisartan also significantly reduced blood pressure levels. However, after adjustment for the difference in blood pressure levels between the placebo and treatment groups, the beneficial effect of telmisartan in delaying progression to overt nephropathy persisted. Finally, the ADVANCE trial showed that the combination of an ACE inhibitor (perindopril) and a diuretic (indapamide) versus placebo significantly reduced blood pressure and the risk of albuminuria progression at a mean follow-up of 4.3 years in 11,140 patients with T2DM and either normoalbuminuira or microalbuminuria.[26] However, no clear effect of the therapy on decline in estimated glomerular filtration rate (eGFR) was observed.

Risk of end-stage renal disease

The beneficial effects of RAAS blockade extend to patients with moderate-to-severe kidney damage. As progression of diabetic nephropathy to ESRD takes many years, clinical trials designed to determine the effects of interventions on hard renal outcomes enrol these patients so that sufficient end points occur within a short time-frame. For example, the Collaborative Study Group showed that intensive blood pressure control with the ACE inhibitor captopril consistently reduced the risk of ESRD in patients with T1DM and diabetic nephropathy.[27] Subsequently, two landmark trials were conducted in patients with T2DM and nephropathy. In the IDNT trial, treatment with irbesartan compared with placebo resulted in a 33% decrease in the risk of doubling of serum creatinine concentration and was associated with a nonsignificant reduction in the incidence of ESRD.[28] This effect was independent of blood pressure. In the RENAAL trial, losartan significantly reduced the incidence of doubling of serum creatinine, ESRD or death by 16% compared with placebo in combination with 'conventional' antihypertensive treatment (that is, α-blockers, β-blockers, calcium channel blockers, diuretics and other centrally acting agents).[29] The renal protection conferred by losartan also exceeded the effect attributable to the small differences in blood pressure between the treatment groups.

A *post hoc* analysis of the RENAAL trial showed that the incidence of ESRD was higher in Hispanic and Asian patients than in white and black patients.[30] This finding led to the initiation of the ORIENT trial, which aimed to determine the effect of olmesartan therapy on renal outcomes in 577 Japanese and Chinese patients with T2DM and nephropathy.[31] In this trial, olmesartan treatment did not reduce the risk of the composite renal outcome (doubling of serum creatinine concentration, ESRD or death; hazard ratio [HR] 0.97, 95% CI 0.75–1.24) at a mean follow-up of 3.2 years. However, 77% of the ORIENT study population were receiving ACE inhibitor therapy at baseline and this therapy was continued throughout the trial period. Thus, in the majority of participants, the effect of olmesartan added to ACE inhibitor therapy was tested rather than the effect of the ARB alone. This difference might explain the lack of renoprotection observed in this trial as opposed to in previous trials that used ACE inhibitor or ARB monotherapy.[27–29] Moreover, an increased risk of cardiovascular events was observed in the olmesartan group. This finding, which is consistent with the results of the ROADMAP trial,[23] might suggest a drug-specific effect of olmesartan on cardiovascular risk.

Although the majority of data from clinical trials suggest a beneficial effect of ACE inhibitors or ARBs in the treatment of diabetic nephropathy, some negative findings exist. For example, in the RASS trial, which enrolled 285 patients with T1DM and normoalbuminuria, treatment with losartan or enalapril did not slow progression of nephropathy measured as change in glomerular mesangium volume in kidney biopsy samples.[32] However, a positive effect of these therapies on the progression of retinopathy (a clinically relevant complication of diabetes) was observed.

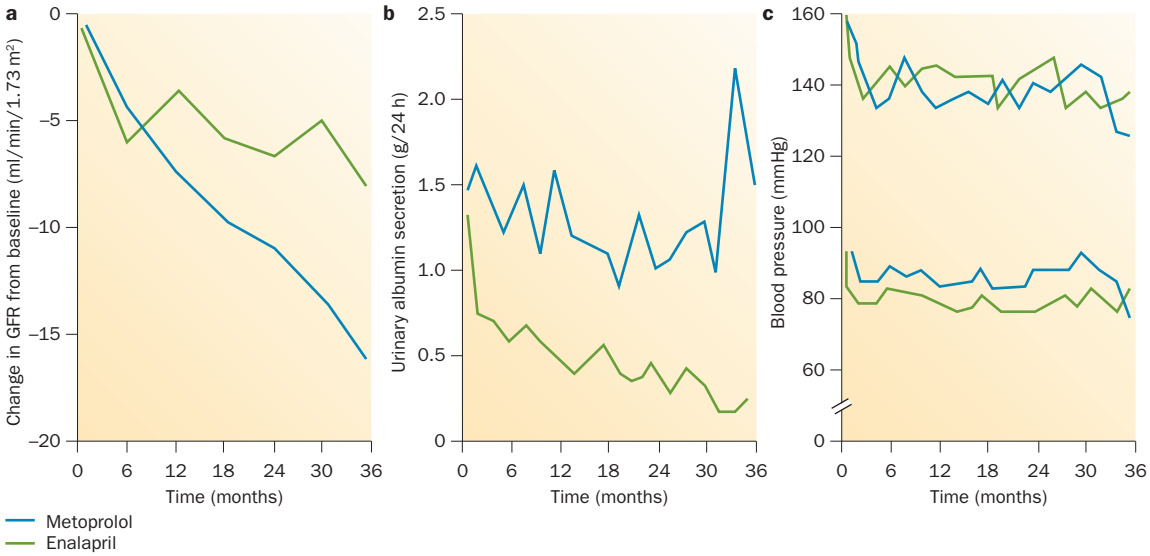

Figure 3 | The effect of enalapril versus metoprolol on surrogate outcomes in patients with type 1 diabetes ($n = 40$). Enalapril **a** | attenuated the decline in glomerular filtration rate and **b** | reduced urinary albumin excretion compared with metoprolol. **c** | Blood pressure control was similar between the treatment groups. Reproduced from © Björck *et al*. *BMJ* **304**, 339–343 (1992), with permission from BMJ Publishing Group Ltd.

In summary, the beneficial effects of treatment with ACE inhibitors and ARBs seem to be independent of the clinical stage of diabetic nephropathy. Whether early treatment (or even preventive treatment) with these medications is truly renoprotective (that is, associated with a significant reduction in risk of ESRD) still remains to be proven in a prospective trial. However, a very large sample size or long follow-up would be required and whether such a trial will ever be conducted is questionable.

ACE inhibitors versus ARBs

Only a few long-term head-to-head studies have been designed to compare the effects of ARBs and ACE inhibitors on the progression of diabetic renal disease.[33,34] One such study with a follow-up of 5 years found that treatment with ARBs and ACE inhibitors similarly decreased blood pressure and albuminuria and reduced the rate of GFR decline in 250 patients with T2DM and early-stage nephropathy.[33] In view of the existing evidence showing that RAAS blockade slows the progression of renal disease, ACE inhibitors or ARBs are currently recommended for the treatment of early and late-stage diabetic nephropathy.[35]

Renoprotective mechanisms

Blood pressure lowering

Blood pressure reduction and glycaemic control are the cornerstones of renoprotective treatment. Three decades ago, an observational study showed that aggressive blood pressure control attenuates the rate of decline in renal function in patients with T1DM.[36] The relevance of blood pressure control was further highlighted by a meta-analysis of clinical trials conducted in patients with and without T1DM or T2DM, which showed that patients with the lowest blood pressure levels experienced the least decline in renal function during follow-up.[37] Thus, blood pressure lowering is an important strategy to slow the progression of renal disease. Nevertheless, interesting differences are observed between various antihypertensive treatment regimens and their renoprotective potency.

An important clinical question is whether blood pressure reduction *per se* as a result of RAAS blockade provides renoprotection or whether pharmacological RAAS blockade exerts additional benefits. In the 1990s it became clear that RAAS blockade confers additional renal protection beyond what could be expected from blood pressure lowering alone. A study of 40 patients with T1DM, showed that at equal levels of blood pressure control, enalapril therapy resulted in a 60% reduction in albuminuria compared with the β-blocker metoprolol, and also attenuated decline in renal function to a larger extent than did metoprolol (GFR decline 2.0 ± 3.2 ml/min per year versus 5.6 ± 5.9 ml/min per year, $P = 0.021$; Figure 3).[38] Similarly, in a larger study of patients with T1DM ($n = 129$), captopril treatment versus placebo reduced the risk of the combined end point of death, dialysis, and transplantation by 50%, an effect that was independent of blood pressure.[27] These findings are consistent with those of the IDNT trial, which showed that despite identical blood pressure control, irbesartan therapy significantly reduced the risks of proteinuria, doubling in serum creatinine levels or ESRD compared with the calcium channel blocker amlodipine.[28]

Not all trials have demonstrated that RAAS blockade confers additional renoprotection beyond conventional antihypertensive therapy. In the UKPDS trial, which enrolled 1,148 patients with hypertension and T2DM, captopril therapy decreased blood pressure levels to the same extent as did the β-blocker atenolol but did not provide additional renoprotection.[39] Moreover, a small study that compared enalapril with atenolol in

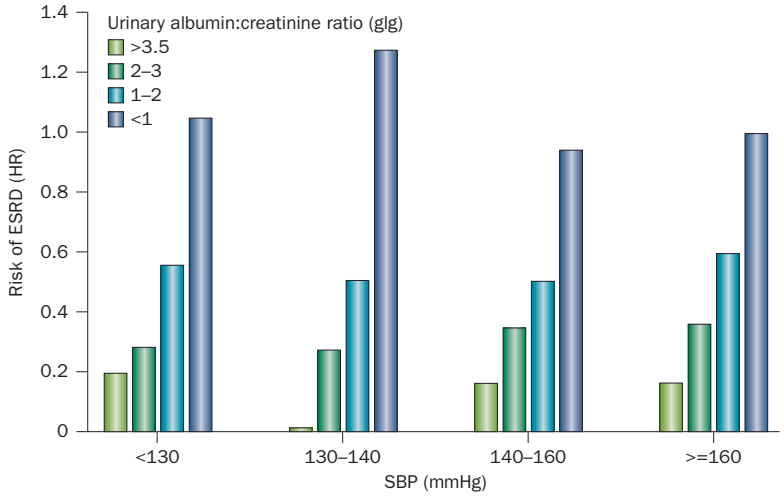

Figure 4 | Residual risk of ESRD in patients with hypertension and diabetic nephropathy receiving angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker therapy (n=1,428). Abbreviations: ESRD, end stage renal disease; HR, hazard ratio; SBP, systolic blood pressure. Permission obtained from the American Society of Nephrology © Eijkelkamp *et al*. *J. Am. Soc. Nephrol.* **18**, 1540–1546 (2007).

patients with T2DM and hypertension did not show additional renoprotection with enalapril.[40] These conflicting findings might be related to the specific trial designs and patient populations, or could be the consequence of distinct effects of different drug classes. For example, β-blockers inhibit renin release thereby blocking the RAAS through mechanisms independent of ACE inhibition or angiotensin receptor blockade.[41]

Reduction in albuminuria

Although the reported effects of RAAS blockade on albuminuria vary considerably between trials (as a result of individual, biological and measurement variability related to patient and study characteristics), collectively these trials indicate that reduction in albuminuria is a critical step in renoprotection. This finding is further illustrated by *post hoc* analyses of clinical studies that showed a consistent association between reduction in albuminuria during the first few months of RAAS treatment and a long-term reduction in the risk of ESRD.[42–44] Importantly, the association between short-term changes in albuminuria and subsequent long-term changes in renal function is not confined to patients with diabetes and macroalbuminuria but extends to patients at earlier stages of disease. A *post hoc* analysis of the IRMA-2 trial showed that changes in albuminuria are an independent predictor of the rate of decline in renal function: the larger the reduction in albuminuria the slower the decline.[44] Given the consistent albuminuria-lowering effects of RAAS blockade and the strong independent association between reduction in albuminuria level and renoprotection, the assumption that the specific anti-albuminuric effects of RAAS blockade exert additional renoprotective effects on top of the blood pressure lowering effects is reasonable. However, diabetic nephropathy can progress in the absence of albuminuria, suggesting that other tissue destructive pathways might also have a role in the decline in renal function.[45]

Effect on glomerular filtration rate

Despite the beneficial effects shown in many long-term randomized controlled trials, some clinicians are reluctant to start RAAS blockade in patients with diabetic nephropathy. This reluctance occurs because the initiation of RAAS blockade is often followed by an acute fall in GFR.[46,47] Although this acute decline in renal function might be a concern, drug withdrawal or dose lowering should only be considered if hyperkalaemia develops or GFR continues to decline. Importantly, studies with long-term follow-up have shown that the initial fall in GFR in response to initiation of RAAS blockade is inversely correlated with the long-term decline in renal function; patients whose GFR declined shortly after starting RAAS blockade had a slower rate of decline in renal function during follow-up than did those whose GFR did not initially decrease.[47,48] Given these findings, and in line with clinical practice guidelines,[35] we recommend that all patients with diabetic nephropathy should be started on RAAS blockers.

Residual risk of ESRD

Although ACE inhibitor or ARB therapy slows the progression of diabetic nephropathy to ESRD, the residual risk of ESRD remains high and correlates with the residual level of albuminuria in patients receiving this therapy (Figure 4).[49] The residual risk of ESRD could be the result of insufficient RAAS blockade attributable to insufficient dosing or compensatory feedback responses, or alternatively to the involvement of pathways that are not affected by RAAS blockade, such as endothelin pathways and specific inflammatory profibrotic pathways. Several strategies aimed at enhancing RAAS blockade and optimizing renoprotection that have been investigated in human and animal studies are discussed below.

Supra-maximal doses

Effects on surrogate outcomes

To enhance the efficacy of RAAS blockade and optimize control of blood pressure and albuminuria the optimal dose of ACE inhibitor or ARB must be used. As these agents are registered as antihypertensive drugs, the doses that are frequently used in clinical practice (and in clinical studies) are the maximum recommended for blood-pressure reduction. However, studies have shown that use of supra-maximal doses of ACE inhibitors or ARBs result in further lowering of albuminuria, in the presence or absence of additional changes in blood pressure. For example, in 52 patients with T2DM and microalbuminuria, treatment with supra-maximal doses of irbesartan (up to 900 mg per day) resulted in a 15% greater reduction in albuminuria at 2 months than did treatment with the maximum recommended blood pressure lowering dose (300 mg per day).[50]

Effects on hard outcomes

Unfortunately, the initial studies that assessed the effects of supra-maximal doses of ACE inhibitors or ARBs were too small with too short follow-up duration to determine whether this strategy eventually results in better

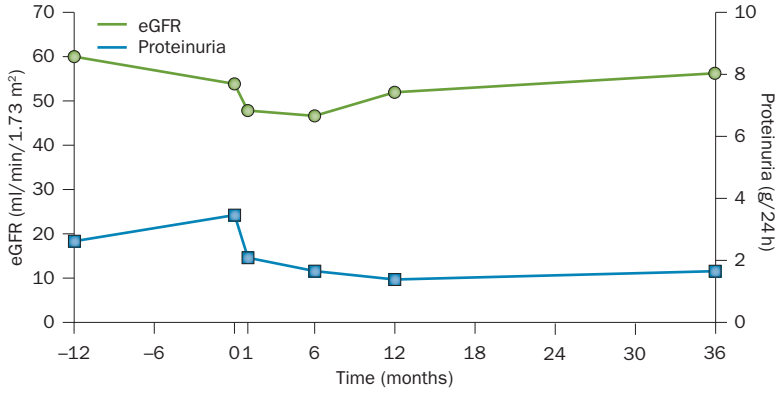

Figure 5 | The addition of spironolactone (25 mg per day) to renin–angiotensin–aldosterone system blockade in diabetic patients with proteinuria ($n = 87$) resulted in an initial acute fall in eGFR and a sustained reduction in proteinuria.[64] Abbreviation: eGFR, estimated glomerular filtration rate.

renal outcomes. Only one study, albeit in a nondiabetic population, followed patients long enough to determine whether increasing the doses of these agents beyond the maximum recommended level conferred additional renoprotection. In this study, the optimal antialbuminuric and tolerable doses of an ACE inhibitor (benazepril; mean 21 mg per day) or ARB (losartan; mean 118 mg per day) were compared with the conventional doses of these agents (10 mg benazepril, 50 mg losartan) in 360 Chinese patients with proteinuria and chronic renal insufficiency.[51] Up-titration of the doses resulted in an additional reduction in albuminuria and a 50% reduction in the risk of ESRD during 3.7 years of follow-up. Additional studies that target albuminuria and focus on safety issues are required to confirm these findings and to determine whether increasing doses of ACE inhibitors and ARBs to supra-maximal levels will have similar beneficial effects in patients with diabetic nephropathy.

Dual RAAS-blockade

ACE inhibitor plus ARB

As ACE inhibitors and ARBs have complementary effects on angiotensin II inhibition and distinct pharmacological properties, combining these agents has been regarded as an optimal way of improving the renoprotection conferred by the monotherapies. On the one hand, during long-term ACE inhibitor treatment, addition of an ARB could counteract the effects of the residual angiotensin II that is produced as a result of ACE-independent pathways. On the other hand, during chronic ARB therapy, increased compensatory production of angiotensin II occurs via renin stimulation, which may be blocked by adding an ACE inhibitor.[52]

A number of studies have investigated the effects of dual ACE inhibitor and ARB therapy on surrogate outcomes.[53] Meta-analyses of these mostly short-term studies have shown an additional reduction in blood pressure and albuminuria with dual RAAS blockade compared with monotherapy.[53] However, these enhanced therapeutic effects occurred at the expense of an increase in adverse effects, including an acute reduction in eGFR and an increase in serum potassium levels.

The ONTARGET trial, which enrolled 25,620 patients with established cardiovascular disease (including 9,603 patients with T2DM), was the first to report on the long-term efficacy and safety of dual RAAS blockade.[54] The study showed that in these patients, dual blockade with the ACE inhibitor ramipril (10 mg per day) and the ARB telmisartan (40 mg per day) compared with monotherapy did not enhance cardiovascular protection and increased the risk of renal events despite better blood pressure and albuminuria control.[54] Notably, most of the ONTARGET trial participants had urinary albumin levels in the normal range (indicating a low renal risk) making the interpretation of the effect of dual RAAS blockade on renal end points difficult.

MRA plus ACE inhibitor or ARB

The high renal risk that remains during ACE inhibitor or ARB treatment might be the consequence of the 'aldosterone breakthrough' phenomenon, which is defined as a compensatory elevation in plasma aldosterone levels during chronic ACE inhibitor or ARB therapy.[55] Although aldosterone is generally considered to be an antidiuretic hormone, it also has proinflammatory and profibrotic effects, which are mostly mediated by the upregulation of growth factors and inflammatory cytokines, and eventually culminate in glomerulosclerosis, vascular injury, endothelial dysfunction and fibrosis.[56–58] It is unsurprising, therefore, that aldosterone breakthrough attenuates the clinical benefits of angiotensin II blockade and is associated with progressive loss of renal function.[55,59]

Blockade of aldosterone using mineralocorticoid receptor antagonists (MRAs) might be an effective strategy to enhance the efficacy of RAAS blockade. Indeed, various studies in patients with and without T2DM have shown that adding MRAs to ACE inhibitors or ARBs results in a substantial reduction in albuminuria,[60,61] suggesting a potential long-term renoprotective effect. However, enthusiasm has been dampened by the finding that the two currently available MRAs, spironolactone and eplerenone, cause hyperkalaemia as a result of their potassium-sparing properties.[62] The high risk of hyperkalaemia, particularly in patients with advanced kidney dysfunction,[63] has severely limited the use of these agents for the treatment of diabetic nephropathy, and might also have contributed to the paucity of long-term randomized clinical trials evaluating the benefits and risks of MRAs as an adjunct to RAAS blockade. Interestingly, the only long-term study of add-on spironolactone therapy in diabetic and non-diabetic patients with proteinuria performed to date showed that the agent induced an initial acute fall in eGFR that predicted a later beneficial effect on decline in renal function and a remarkable and sustained reduction in proteinuria (Figure 5).[64] In another study in patients with T1DM or T2DM ($n = 81$), addition of spironolactone to the maximal ACE inhibitor regimen afforded greater renoprotection than did the addition of losartan, despite a similar effect on blood pressure and serum potassium levels at 48 weeks of follow-up.[65]

Prevention of hyperkalaemia

Novel approaches to mitigate the risk of hyperkalaemia in patients treated with a MRA in combination with an ACE inhibitor or an ARB are currently in development. Firstly, a new potassium binder RLY5016 has gained scientific interest. In a clinical trial of patients with chronic heart failure ($n = 105$), RLY5016 or placebo was administered together with spironolactone for 4 weeks.[66] RLY5016 therapy significantly reduced the incidence of hyperkalaemia and was associated with minimal adverse effects (mild gastrointestinal symptoms and a few cases of hypokalaemia).[66] This agent might, therefore, be a valuable tool for the management of hyperkalaemia resulting from RAAS blockade. Moreover, the novel highly selective and strongly potent nonsteroidal aldosterone blocker BAY 94-8862 has been tested in a phase II clinical trial in patients with chronic heart failure and mild-to-moderate kidney disease.[67] This agent was as effective as spironolactone in reducing the levels of biomarkers of haemodynamic stress and of albuminuria, but was associated with fewer episodes of hyperkalaemia and a slower decline in renal function at 4 weeks of follow-up.[67] In addition, evidence from rat studies suggests that the novel, nonsteroidal aldosterone blocker SM-368229 has favourable pharmacokinetic properties and somewhat stronger antihypertensive and antialbuminuric effects with less effect on serum potassium levels than spironolactone.[68,69] However, data from the studies described above, although encouraging, cannot be considered ultimate proof of the beneficial effects of these compounds and larger studies with longer follow-up are required.

Inhibition of the aldosterone synthesis cascade might be another approach to prevent the multiple renal and extra-renal deleterious effects of aldosterone. Aldosterone is synthesized from 11-deoxycorticosterone via the action of the aldosterone synthase CYP11B2.[70] Two inhibitors of aldosterone synthase (FAD286 and LCI699) are currently being evaluated in animal and clinical studies.[71,72] FAD286 and LCI699 have been shown to significantly reduce plasma aldosterone levels in animals[72] and in humans,[71] respectively. Moreover, FAD286 reduced hypertrophy and interstitial fibrosis in the kidneys of rats treated with angiotensin II and a high salt diet.[72] In 14 patients with primary aldosteronism,[71] and in 524 patients with primary hypertension,[73] LCI699 reduced aldosterone levels after 4 weeks of treatment and blood pressure levels after 8 weeks of treatment, respectively. However, the safety profile of this agent and the associated risk of hyperkalaemia have not yet been determined.

DRI plus ACE inhibitor or ARB

An increase in plasma renin activity during ACE inhibitor or ARB treatment as a result of compensatory mechanisms can limit the efficacy of these therapies.[7] Renin exerts its effects via the prorenin receptor, which binds both renin and its inactive precursor prorenin.[74] As renin has an upstream role in the RAAS cascade, blockade of renin might inhibit the detrimental effects of both angiotensin II and aldosterone, resulting in additive beneficial haemodynamic and structural effects on the kidney. Based on this hypothesis, several renin inhibitors have been developed.

Early studies using the direct renin inhibitor (DRI) remikiren showed the potency of this drug class in reducing RAAS activity in the tissues, lowering blood pressure and reducing proteinuria in hypertensive patients with normal or impaired renal function.[75] Subsequently, aliskiren became available for clinical use and has been tested in many experimental and clinical studies. In a transgenic rodent model of diabetic nephropathy, aliskiren reduced blood pressure, albuminuria and structural injury, measured by the severity of glomerulosclerosis and interstitial fibrosis.[76] Initial exploratory studies in patients with diabetic nephropathy showed that aliskiren reduces proteinuria and blood pressure, independently of each other.[77] Moreover, the combination of aliskiren with an ARB led to a further reduction in albumin excretion compared to aliskiren or ARB alone.[78,79]

The beneficial effects of aliskiren on albuminuria prompted investigators to initiate the AVOID trial.[80] This randomized, double-blind placebo controlled study in 599 patients with T2DM and macroalbuminuria, demonstrated that aliskiren, when given in combination with losartan, reduced albuminuria by 20% compared with placebo at 24 weeks of follow-up.[80] Aliskiren therapy was well tolerated but use of the agent was associated with a significant increase in the risk of hyperkalemia.

Outcomes in patients with established nephropathy

Enthusiasm regarding the promising effects of dual RAAS blockade on surrogate outcomes in small, short-term studies has been tempered by the disappointing results of large trials with hard outcomes, such as ONTARGET.[54] As previous trials had shown beneficial effects of RAAS monotherapy in patients with diabetic nephropathy, it was speculated that dual RAAS blockade could improve renal outcomes in patients with established nephropathy.[81,82] However, in subsequent trials, dual RAAS blockade failed to confer additional renal protection in these patients. First, in the ALTITUDE trial, the cardiovascular and renal protective effect of the combination of ACE inhibitors or ARBs with a DRI (aliskiren) was tested in 8,561 patients with T2DM who were selected based on their high renal and cardiovascular risk profile.[83] However, the safety monitoring board recommended early termination of the trial because an interim analysis showed more cases of worsening of renal function, hyperkalaemia, and increased risk of stroke in the combination therapy group versus the ACE or ARB plus placebo group. The final efficacy results confirmed an excess of adverse effects in the combination therapy group and provided definitive evidence of a lack of cardiorenal protection with aliskiren added to single RAAS blockade in patients with T2DM and high cardiovascular and renal risk.[83]

Second, the VA-NEPHERON-D trial assessed the effect of combination therapy with an ACE inhibitor and an ARB on hard renal end points in patients with

T2DM, macroalbuminuria and moderate-to-severe renal impairment (eGFR 30–90 ml/min/1.73m^2).[84] This trial was also discontinued prematurely because of severe hyperkalaemia and an acute loss of renal function in patients allocated to dual RAAS blockade.

Finally, an interesting subgroup analysis of the ORIENT trial showed that olmesartan therapy provided renoprotection in the absence of background ACE inhibitor therapy.[76] The 16% relative reduction in renal risk with olmesartan reported in this analysis was similar to the effect size reported for losartan versus placebo in the RENAAL trial.[27] However, olmesartan therapy did not improve renal outcomes when given in combination with an ACE inhibitor (2% relative increase in renal risk).[85] These data from large, independent clinical trials demonstrate that even in patients with established nephropathy, dual RAAS blockade fails to afford renoprotection. The authors of the Kidney Disease: Improving Global Outcomes clinical practice guidelines, therefore, discourage the use of dual RAAS blockade for the prevention and treatment of diabetic nephropathy.[35] However, this therapeutic strategy might be effective in other diseases, such as CKD.[86]

Mechanisms underlying adverse outcomes

The mechanisms that underlie the adverse outcomes of dual RAAS blockade are not fully understood. Pharmacological properties of RAAS blockers are important to consider and could explain some of the unexpected findings. In all of the trials with hard outcomes described above, dual RAAS blockade improved control of blood pressure and albuminuria. However, blockade of the RAAS has a broad range of additional effects, including effects on the levels of potassium,[87] haemoglobin,[88,89] uric acid,[90] and inflammatory factors.[91] As each of these factors influence renal and/or cardiovascular risk, drug-induced changes can positively or negatively influence renal and/or cardiovascular outcomes, and thus the ultimate efficacy of the agent. It might be useful, therefore, to take changes in multiple risk markers into account when interpreting the effects of drugs on hard outcomes, rather than simply focusing on changes in blood pressure or albuminuria. This approach implies that the development of hyperkalaemia, hypotension, and acute renal impairment consequent to dual RAAS therapy should not only be analysed as safety parameters (which are separated from the efficacy evaluation of a drug), but also as parameters that influence the ultimate efficacy of the drug.

In certain clinical circumstances, interventions in the RAAS can be harmful.[35] The RAAS has a major role in the homeostatic preservation of blood pressure and GFR during volume depletion. Consequently, in settings of diminished circulating blood volume, for example as a result of gastrointestinal losses, RAAS blockade can facilitate the development of hypotension and acute kidney injury.[35] Clinical circumstances under which kidney injury can develop during RAAS blockade, include hypotension, dehydration, renal artery stenosis,[92] exposure to contrast agents, and hospitalization.[93] These states of kidney injury might exacerbate CKD resulting in ESRD.[94,95] The National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines, therefore, recommend temporary discontinuation of RAAS blockers in patients with GFR <60 ml/min/1.73 m^2 who have serious intercurrent illness (particularly in a setting of dehydration such as diarrhoea and vomiting) that increases the risk of acute kidney failure.[35] Moreover, animal studies have shown that dual RAAS blockade in combination with volume depletion as a result of a low sodium diet causes hypotension and renal failure accompanied by massive increases in renin levels.[96] These effects do not occur in animals that are fed a high sodium diet.[96] Deleterious effects of dual RAAS blockade in combination with volume depletion (as a result of a low sodium diet or concomitant diuretic therapy) might partly explain the disappointing results of dual RAAS blockade in large trials. However, avoiding these deleterious effects is difficult because, as we discuss below, the beneficial effects of RAAS blockade, such as lowering of proteinuria, are enhanced by dietary sodium restriction or use of diuretics.[97]

A trend towards a higher risk of stroke with dual RAAS blockade was observed in the ALTITUDE trial.[83] It has been postulated that the recurring episodes of hypotension and stroke that have been observed in patients treated with RAAS blockade (especially in the case of dual therapy) might be the result of sensitisation of the Bezold–Jarisch reflex, a physiological mechanism that has important hypotensive and vagal components.[98] As this reflex is normally attenuated by angiotensin II, RAAS inhibition might lead to overstimulation, profound vasodilation and bradycardia.[99] Intriguingly, in the ONTARGET trial, dual RAAS blockade did not increase the risk of stroke.[54] Whether the differing findings of the ONTARGET and ALTITUDE trials relate to the different study populations or drug combinations used is unclear.

Dietary sodium restriction

Several studies have shown that restricting dietary sodium chloride to the WHO recommended target level of 5–6 g per day enhances the efficacy of single RAAS blockade.[100] In a short-term study of 52 nondiabetic patients with CKD, moderate sodium restriction (6 g per day) was significantly more effective in enhancing the antihypertensive and antiproteinuric effects of an ACE inhibitor than was adding an ARB.[101] In another study, a low sodium diet seemed to be as effective as the addition of diuretics in enhancing the antiproteinuric effect of losartan, and even seemed to be beneficial in patients who were resistant to RAAS blockade.[102] Moreover, moderation of dietary sodium intake has been shown to improve the long-term renal and cardioprotective efficacy of single RAAS blockade in patients with diabetic nephropathy.[97] In a *post hoc* analysis of the RENAAL and IDNT trials, treatment effects on renal and cardiovascular outcomes were compared in subgroups based on dietary sodium intake during treatment.[97] Importantly, ARB provided the best renoprotective effects in patients

who had the lowest tertile of sodium intake. The risk of renal events was reduced by 43% or increased by 37% in patients with the lowest and highest tertile of sodium intake, respectively. However, too aggressive sodium restriction (that is, restriction to levels well below the WHO recommended target) on top of single or dual RAAS blockade might elicit adverse renal and cardiovascular events, and titration to an optimal sodium status is warranted to avoid adverse effects.[100]

Novel strategies

Our understanding of the RAAS cascade has increased with the discovery of additional components that might have a role in the pathophysiology of diabetes and diabetic nephropathy (Figure 1). For example, ACE2 has been shown to convert angiotensin I to the inactive angiotensin 1–9 and, more importantly, to convert angiotensin II to the vasodilatory and antiproliferative angiotensin 1–7.[103] The first animal studies of ACE2 antagonists have shown that this enzyme seems to counterbalance the effect of angiotensin II on albuminuria.[104] The mechanism probably involves the production of angiotensin 1–7, which inhibits angiotensin II-dependent phosphorylation of proliferative and inflammatory stimuli, such as the ERK pathway, and enhances vasodilation.[105] These findings, together with the characterization of the type 2 angiotensin II receptor, which opposes the deleterious effects of angiotensin II binding to the type 1 angiotensin II receptor,[106] have led to new enthusiasm for the development of drugs that block the detrimental signals of the RAAS cascade whilst preserving its beneficial effects.

Conclusions

The importance of the RAAS in the development and progression of diabetic nephropathy has fueled the marketing of a therapeutic armamentarium to target every step in the RAAS cascade. Blockade of angiotensin II by mean of ACE inhibitors or ARBs is currently the best option to treat diabetic nephropathy because of the well-established renoprotective capacities of these agents. Alternative strategies encompass ACE inhibitor–ARB combination therapy, and the use of add-on aldosterone blockers and renin inhibitors, which have been tested in preclinical studies and in clinical trials in patients with diabetic nephropathy. Although data from the initial small studies suggest beneficial effects of dual RAAS blockade on blood pressure levels and albuminuria, the disappointing results of trials with hard outcomes, including ONTARGET,[54] ALTITUDE[83] and VA-NEPHRON-D,[84] underscore the need to go beyond the use of single biomarkers and develop better strategies to determine drug efficacy, for example by incorporating drug effects on multiple risk markers. In addition, these results highlight the importance of long-term trials to definitively prove drug efficacy and safety.

Our knowledge of the RAAS has improved considerably in the past decades. However, the morbidity and mortality of patients with diabetic nephropathy receiving RAAS blockade remains high. The existence of the systemic and local RAAS cascades, the genetic diversity in the RAAS, and the complex interconnectivity of the RAAS components represent causes of interindividual and intraindividual variation in the therapeutic effects of RAAS blockade. For this reason, research is now focused on tailoring interventions to ensure that each individual patient is treated with the best possible medication. The remaining questions are how to identify those patients who will benefit most from each intervention and whether patient-tailored strategies will eventually be cost effective. Novel genomic, proteomic or metabolomic techniques might be valuable tools to identify specific biomarkers that could help to identify those patients who are more likely to benefit from therapy. For example, the currently ongoing European PRIORITY project aims to use a proteomic score to promptly identify patients at risk of diabetic complications for subsequent preventive therapy.[107] Alternatively, new pharmacological targets that block the deleterious effects of the RAAS, whilst preserving its physiological modulatory role, might represent a better option for future therapeutic intervention to eventually halt the progression of kidney disease.

Review criteria

The PubMed database was searched for English-language, full-text papers on renin–angiotensin–aldosterone system (RAAS) blockade in patients with diabetic renal disease. Articles published between 1983 and 2013 were identified using the following search terms alone or in combination: "RAAS blockade", "diabetic nephropathy", "diabetes", "ACE inhibitors", "angiotensin receptor blockers", mineralocorticoid receptor antagonists", "direct renin inhibitors", "dietary sodium restrictions". This Review primarily focuses on articles published after 2000 although some large studies published before 2000 that we considered to be relevant because of their clear impact on clinical practice were also included.

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Author contributions

S. S. Roscioni and H. J. Lambers Heerspink contributed equally to researching the data for the article and writing the manuscript. D. de Zeeuw reviewed and/or edited the manuscript before submission. All authors made a substantial contribution to discussions of the content.