# May blockade of the renin-angiotensin system be optimised in proteinuric nephropathy?

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In multiple experimental models, angiotensin II has been shown to be the cornerstone of renal progression in proteinuric nephropathies due to its role on glomerular haemodynamics (increases resistance of the efferent arteriole), but also for its proinflammatory and profibrotic capacity by stimulating the synthesis of TNFa, Il-6, and cytokines such as MCP-1 and IP-10.[1] In recent years, this molecule has also been related to proteins forming the diaphragm junction between the feet of podocytes (nephrin, podocin, Zo-1, CD2AP, and Neph-1).[2]

In fact, drug treatments inhibiting its synthesis (angiotensin converting enzyme inhibitors, ACEIs) or blocking its action (angiotensin receptor blockers, ARBs) have been shown to slow progression of renal failure in both diabetic[3,4,5] and non-diabetic proteinuric nephropathies[6] beyond the effect to be expected from the decrease in systemic blood pressure. Despite this, dialysis continues to be a common endings for this group of patients.

Further knowledge of RAAS blockade has been achieved in recent years. In addition, new drug classes capable of acting in other limiting points of its cascade (renin inhibitors) and with an activity possibly synergistic to already known drugs will be marketed in the near future. This opens up new therapeutic doors that will allow us to optimise their use and achieve what has been called partial or complete remission of these conditions. While we are still far away from these ambitious objectives, some measures that may achieve objectives beyond those expected after the simple prescription of a drug blocking the renin-angiotensin system may currently be considered.

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## EFFICACY OF RAAS BLOCKADE IN ADVANCED RENAL FAILURE

Treatment with ACEIs and ARBs is underused in patients with proteinuric nephropathy when the glomerular filtration rate (GFR) is below 30-20 mL/min/1.73m$^2$ because it is thought to have little therapeutic benefit and potential associated side effects, mainly hyperkalemia.

The REIN study[7] showed a renoprotective effect of ramipril even in patients with the lowest GFRs (11-33 mL/min/1.73m$^2$). A clinical trial enrolling patients with advanced chronic proteinuric nephropathy (Cr 3.1-5 mg/dL; proteinuria > 0.3 g/24 hours) was recently reported.[8] In this study, use of benazepril reduced the risk of reaching the combined endpoint proposed (creatinine doubling, dialysis, or death) by 43% as compared to the group treated with antihypertensive drugs other than RAAS inhibitors (mean follow-up time, 3.4 years). Urinary protein excretion was also reduced (50% vs 20%, $p < 0.001$). Hyperkalemia (K > 6 mEq/l) occurred in 11 patients (11%), 8 of which were treated with dietary measures, potassium-losing diuretics, and improving acid-base balance. The remaining three patients discontinued the study for this reason. Mean potassium levels were higher in the benazepril-treated group as compared to the placebo group, but mean differences did not exceed 0.5 mEq/L. No differences were found in mean haemoglobin values or doses of human recombinant erythropoietin.

## OPTIMAL NEPHROPROTECTIVE DOSES

Most clinical trials assessing renal progression have used the ACEI and ARB doses recommended in the respective labels and representing the optimal doses for blood pressure control, though they are possibly below the optimal nephroprotective doses. Forclaz et al[9] noted that the usual dose of telmisartan (80 mg/day) achieved blockade of only 40% of AT1 receptors. The proportion increased to 57% when the dose was doubled.

In the IRMA[4] study, the renoprotective effect of irbesartan was dose-dependent, but no optimal dose was established. The same authors assessed whether supratherapeutic doses achieved a stronger reduction of albuminuria as compared to the standard dose.[10] Thus, 52 patients with type 2 diabetes mellitus and microalbuminuria were sequentially treated with irbesartan 300, 600, and 900 mg/day. All doses were able to reduce microalbuminuria. Mean reductions were 52% (95% CI 46% to 57%), 49% (95% CI 43% to 54%), and 59% (95% CI 54% to 63%) ($p < 0.01$) respectively. The greatest reduction in microalbuminuria with maximum irbesartan doses was achieved precisely in those patients showing the lowest decrease in albuminuria with the initial dose of 300 mg/day. In another clinical trial,[11] high telmisartan doses (80 mg every 12 hours) achieved a significantly stronger decrease in protei-

nuria as compared to standard doses and reduced loss of estimated GFR when compared to a 80 mg/24 hour regimen in patients with biopsied non-diabetic proteinuric nephropathy. There were no differences in blood pressure control during follow-up.

The ROAD study,[12] comparing standard doses of an ACEI (benazepril 10 mg/day) and an ARB (losartan 50 mg/day) to individualised optimal antiproteinuric doses, was recently published. Patients were treated with increasing doses of benazepril (10, 20, 40 mg/day) and losartan (50, 100, 200 mg/day). Optimal dose was defined as the dose that achieved a greater decrease in proteinuria without increasing serum creatinine by > 30% or SBP to < 120 mm Hg despite discontinuation of all other antihypertensive medication. Mean optimal dose was 20 mg/day for benazepril (range 10-40 mg/day) and 100 mg/day for losartan (range 50-200 mg/day). In both drug classes, optimal doses significantly decreased progression of renal disease as compared to conventional doses, even after adjusting for BP, proteinuria, and baseline GFR. No differences were seen between ACEIs and ARBs at standard or optimal doses.

These results show us of the significant predictive value of proteinuria and its response to treatment for evolution of these patients, but leave unresolved the question as to whether higher than antiproteinuric doses provide any additional nephroprotective benefit.

## COMBINED TREATMENT

There are alternative pathways not requiring the participation of renin and ACE for angiotensin II synthesis. Thus, synthesis of angiotensin II and aldosterone may occur even under treatment with ACEIs; this is the so-called «escape phenomenon». Approximately 40% of angiotensin synthesis in the kidney occurs through pathways independent from ACE.[13] Experimental studies suggest that chymase or cathepsin G may be related.

Blockade of angiotensin II binding to AT1 receptors inhibits most actions of this molecule, including aldosterone secretion, vasoconstriction, Na and water absorption, and profibrotic and proinflammatory effects, and on the other hand overstimulates expression of actions related to the AT2 receptor, such as vasodilation. However, recent studies attribute to AT2 receptors an active role in CKD progression. In a renal damage model (subtotal nephrectomy), AT2 blockade reduced proteinuria, nephrin and osteopontin expression, and monocyte-macrocellular infíltrate to a extent similar to valsartan.[14] Subsequent studies have confirmed that only blockade of both receptors or ACEIs effectively abort the inflammatory cascade triggered by angiotensin II.[15]

Combination of both drugs would therefore provide a more effective blockade of RAAS and would add the particular benefits of each of them. ACEIs reduce bradykinin degradation. Kinins are known to significantly contribute to the BP decrease attributed to ACEIs. Studies with the bradykinin B2 receptor antagonist in humans revealed that up to 30%-50% of the BP decrease seen after a single dose of ACEIs is mediated by these molecules.[16] Increased kinin levels also promote some of the undesirable effects of ACEIs, such as cough, angioneurotic oedema…

From the clinical viewpoint, the combination of both drugs has also shown more nephroprotective capacity than monotherapy. In the COOPERATE study[17] conducted in patients with non-diabetic proteinuric nephropathy (n = 263), only 11% of patients treated with losartan (100 mg/day) plus trandolapril (3 mg/day) doubled their creatinine levels or reached stage 5 CKD after three years of treatment, as compared to 23% of patients treated with monotherapy at the same doses. However, one may wonder whether the benefit seen resulted from the synergistic effect of the combination or use of a higher drug dose. In the Luño et al study,[18] monotherapy (lisinopril 40 mg/day, candesartan 32 mg/day) was compared to combined treatment at half the doses (lisinopril+candesartan 20 + 16 mg/day) in patients with glomerular nephropathies. At six months of follow-up, this latter option achieved a decrease in proteinuria significantly greater than any monotherapy.

There is less evidence available in diabetic nephropathies. The CALM study[19] included 199 patients with incipient nephropathy who were randomized to treatment with lisinopril (20 mg/day) or candersartan (16 mg/day) for 12 weeks. One third of patients were subsequently treated with the combination at the same dose for an additional 12 weeks, while the other two thirds remained on monotherapy. In the first treatment cycle, microalbuminuria reduction was 30% (95% CI 15% to 42%) and 46% (95% CI 35% to 56%) for candesartan and lisinopril respectively. After 24 weeks, the combination reduced microalbuminuria by 50% (95% CI 36% to 61%), i.e. an additional 34% (95% 3% to 55%) as compared to candesartan alone and an additional 18% (95% CI 20 to 44% ) as compared to lisinopril alone.

A systematic review showing that combination treatment is safe and achieves a greater reduction in urinary protein excretion than monotherapy has recently been published. A mean additional decrease of 440 mg/day (95% CI 289 to 591 mg/day) over monotherapy was estimated. In diabetic patients, the combination achieved a smaller decrease (210 mg/day, 95% CI 84 to 336 mg/day) than in patients with non-diabetic proteinuric nephropathies (582 mg/day, 95% CI 371 to 793 mg/day).[20] As regarding, the combination resulted in a statistically significant but clinically non-relevant increase in kalemia (mean increase 0.11 mEq/L, 95% CI 0.05 to 0.17 mEq/L).

In the ONTARGET study[21] (n = 25,620), conducted on a somewhat different population from the one considered here (patients at high vascular risk with preserved kidney function [mean creatinine levels 1.2 mg/dL] and only 13% with albuminuria), combination therapy achieved lower BP values than monotherapy (2.4/1.4 mm Hg), but did not reduce cardiovascular mortality, nor kidney disease progression. By contrast, higher rates of hyperkalemia ($p < 0.001$), symptomatic hypotension, and patient discontinuation for kidney function impairment (RR 1.58, $p < 0.001$) were reported in the study. It would be very interesting to have data from the substudy on patients with proteinuric renal disease.

## OTHER POSSIBLE COMBINATIONS OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

### Mineralocorticoid receptor antagonists

Diuretics had not been attributed any nephroprotective effect beyond that associated to blood pressure reduction. In recent years, the role of aldosterone in progression of kidney disease has started to be discussed.[22] Aldosterone has been shown to induce inflammation endothelial dysfunction, glomerular sclerosis, and tubular damage mediated by inhibition of expression of the plasminogen activator, TGb stimulation, and upregulation of angiotensin II receptors in different experimental models.[23]

In clinical trials, association of a mineralocorticoid inhibitor to an ACEI or ARB has achieved an additional reduction of proteinuria.[24] Thus, in a study, 268 patients with early type 2 diabetic nephropathy who were already being treated with enalapril were randomised to placebo, eplerenone 50 mg/day, or eplerenone 100 mg/day for 12 weeks.[25] Treatment with eplerenone, but not with placebo, reduced albuminuria as compared to baseline. At 12 weeks of treatment, reductions were 7.4% in the placebo group, 41% in the eplerenone 50 mg/day group, and 48% in the eplerenone 100 mg/day group. There was no increased incidence of moderate (K > 5.5 mEq/L) or severe (K > 6 mEq/L) hyperkalemia among the three groups, but all patients included had preserved kidney function (Cockcroft eGFR > 70 mL/min).

These results may be physiologically explained by the so-called «escape phenomenon» of aldosterone. Sato et al[26] found increased plasma aldosterone levels (< 40%) in type 2 diabetic patients with early nephropathy after 40 weeks of treatment with an ACEI. More recently, similar results have been confirmed in patients with type 1 diabetes treated with ARBs. The escape phenomenon of aldosterone occurred in > 40% of patients and was associated with a faster loss of glomerular filtration.[27]

Another, more controversial issue is whether inhibition of the mineralocorticoid receptor in monotherapy could be beneficial. Theoretically, the spironolactone antagonist may induce secondary elevation of renin and presumably also of angiotensin II, as other diuretics.[28] This reaction could exaggerate the harmful effect of this molecule.

Unfortunately, there are not yet long-term studies evaluating the role of these drugs and their possible combinations on renal evolution in patients with different grades of chronic kidney disease.

### Renin inhibitors

The possibilities of a new drug class that blocks another limiting step in the RAAS cascade, non-peptide renin inhibitors, have been studied in recent years. Aliskiren has an adequate pharmacological profile, and its administration achieves reductions in plasma renin activity and urinary aldosterone levels for at least 48 hours[29] with an antihypertensive potency similar to ARBs.[30]

Theoretically, these drugs would be an adequate adjunct for other drugs blocking the RAAS. Both ACEIs and ARBs stimulate reactive renin secretion because they break the feedback by which angiotensin II inhibits renin secretion in the kidney. It is known that renin may lead to increased angiotensin II levels by its generation through alternative pathways independent from ACE In fact, the combination of aliskiren and valsartan achieved a significantly greater blood pressure reduction than monotherapy with each of the drugs.[31]

In animal models of renal damage, renin inhibition combined with other ARBs has given encouraging results.[32,33] In a recent study, 599 hypertensive patients with established diabetic nephropathy were treated with losartan at the maximum recommended nephroprotective dose (100 mg/day) and subsequently randomised to aliskiren (300 mg/day) or placebo. In patients treated with the renin inhibitor, urinary albumin excretion was reduced by an additional 20% (95% CI 9-30, p < 0.0001).[34]

### Triple therapies

The RAAS may currently be blocked with drugs at four different sites. As discussed, pathophysiologically and clinically almost all possible combinations show synergism in at least the intermediate objectives (urinary protein excretion), and many of them may possibly show synergism in the final objectives (progression of kidney disease). We may wonder about the superiority of any of them, overall or in particular situations, such as diabetes, obesity…

A double-blind, controlled clinical trial compared treatment with ACEI monotherapy, ACEIs plus ARBs, ACEIs plus spironolactone, and the combination of all three in 41 patients with proteinuric nephropathy (> 60% diabetic patients). The combination of ACEIs plus spironolactone achieved a 41% greater reduction as compared to ACEI monotherapy, and a 26% greater reduction than that achieved with the combination of ACEIs plus ARBs after 3 months of treatment. Triple therapy did not achieve a greater decrease than seen with the combination of ACEIs plus spironolactone. Similar results were achieved at 6 months and were independent from blood pressure control.[35]

## CONCLUSIONS

The multiple clinical trials reported in recent years have allowed us to determine the clinical conditions where drugs blocking the RAAS have a renoprotective effect, proteinuric versus non-proteinuric nephropathies,[36] and to establish that a more complete blockade results in a greater slowing of renal progression. It is not clear, however, what therapeutic regimen achieves this objective. Several approaches have been suggested for this purpose, including high-dose monotherapy and different combinations, but there is still no adequate evidence to recommend any of them over the rest. It is highly possible that proteinuria is an early intermediate marker of an extraordinary prognostic value, so that the optimal dose is that achieving a maximum reduction in proteinuria, but we also do not know whether higher doses provide any additional benefit or only result in side effects.

Further clinical trials along these lines, but with more ambitious objectives and including patients with diffe-

rent grades of kidney disease that would help us select the adequate combination therapy in terms of efficacy, but also in terms of safety and tolerability in each condition, are undoubtedly required.

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