

Dual blockade of the renin–angiotensin–aldosterone system in renal disease: what is the future?

To the Editor In their recently published paper, Lizakowski et al.,¹ a renowned research group that focuses on the renin–angiotensin–aldosterone system (RAAS) in renal disease, demonstrated that the dual blockade of the RAAS with different combinations of drugs had a similar effect on several clinical and laboratory parameters in patients with nondiabetic proteinuric chronic kidney disease (CKD) to that observed for angiotensin II receptor blocker monotherapy. A combination of telmisartan with aliskiren led to a marked elevation of plasma renin levels (as compared with telmisartan with perindopril, telmisartan with eplerenone, or telmisartan in monotherapy), but the increase did not translate into worsening of renal function, aggravation of proteinuria, or urinary loss of transforming growth factor β (TGF- β), the key mediator and biomarker of renal fibrosis. We agree with the authors that these data may suggest lack of direct nephrotoxicity of renin. The authors pointed to the safety of telmisartan with aliskiren in patients with nondiabetic proteinuric renal disease and made it the key message of the paper, although they were cautious to limit their conclusions to early stages of CKD and patients with low cardiovascular morbidity.

This study¹ adds new data to our current knowledge on therapeutic interventions on the RAAS. An extremely attractive, from the conceptual point of view, dual (or even triple) blockade of the RAAS in renal disease did not, however, translate into patient benefit in large-scale prospective clinical trials. The authors cited some of those “unsuccessful” studies in their paper (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints [ALTITUDE] and Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial [ONTARGET]).^{2,3}

The renal community has often argued that, indeed, trials concerning dual RAAS blockade performed to date did not show benefits of this therapeutic approach, but in fact they were not designed to show renal benefit in carefully selected patients with well-defined renal disease. Hence, nephrologists were waiting for the results

of the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) study.⁴ In brief, the trial was performed exclusively in proteinuric patients with diabetic nephropathy (glomerular filtration rate [GFR] ranging from 30 to 89.9 ml/min/1.73 m², with patients equally distributed within the CKD stages: 2, 3a, and 3b). Patients were randomized to treatment with losartan (50–100 mg) plus placebo vs. losartan combined with escalated doses of lisinopril (10–20–40 mg). It should be emphasized that the trial incorporated detailed guidelines for investigators on how to proceed with subjects with any risk of hyperkalemia (the main “acute” threat of using dual RAAS blockade). Despite a precisely defined study group, careful methodology, and appropriate safety measures, the VA NEPHRON-D trial also failed to demonstrate any significant benefit from dual blockade of the RAAS in terms of nephroprotection and cardiovascular endpoints. As in many previous studies in the field, patients treated with dual RAAS blockade more frequently developed acute kidney injury and significant hyperkalemia.⁴

We think that a word of caution is needed before concluding on the safety of dual RAAS blockade because short-term safety of a carefully supervised small-size study group may not be reflected by large-scale, long-term clinical trials, or—particularly—everyday clinical practice.

The overall sound of the paper of Lizakowski et al.¹ is still in favor of dual RAAS blockade (although they acknowledged limitations of this approach). However, we wonder whether the studies by Lizakowski et al.¹ and Fried et al.⁴ herald the end of the “dual-blockade” era and we can now put the nail in the coffin or whether there is still place for additional concepts, projects, and trials in this interesting research field. The question of whether the results obtained in proteinuric diabetic patients with quite advanced CKD (the VA NEPHRON-D study population) would be the same in proteinuric nondiabetic patients with early CKD (as in the study by Lizakowski et al.)¹ still remains open.

For many years, it has been argued that pleiotropic effects of the RAAS blockade are at least

as important as blood pressure lowering in protecting the kidneys. Recent studies have brought somewhat opposite conclusions: blood pressure control (independent of the drug class) seems to be critical for renal outcome, and—even more importantly—for the overall outcome of patients with renal disease (although RAAS-blocking agents still remain the first-choice antihypertensive drugs in this population).^{5,6}

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Authors' reply The results of the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) study¹ cited by Stompór and Undas² were unavailable at the time of paper³ submission for publication in the *Polish Archives of Internal Medicine*. Hence, we would like to provide a few additional comments to the study by Frieda et al.,¹ thus playing the “devil’s advocate”.

The VA NEPHRON-D study,¹ similar to the previously published Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE)⁴ and Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET),⁵ noted the high risk of hyperkalemia, hypotension, and acute renal failure in patients receiving combination renin-angiotensin-aldosterone system (RAAS) blockade. These

results are not surprising considering the mechanism of action of these drugs and the fact that all those studies were conducted in patients with high cardiovascular risk or fairly advanced chronic kidney disease as it was in the case of the VA NEPHRON-D study,¹ and that the groups receiving combination therapy had lower blood pressure than those using monotherapy. It is hard to fully agree with the opinion of Stompór and Undas² that VA NEPHRON-D excluded the advantage of combination therapy over monotherapy in terms of nephroprotection. Similar to the findings of ALTITUDE and ONTARGET (analysis of the subpopulation with albuminuria), dual RAAS blockade in VA NEPHRON-D reduced albuminuria more effectively than monotherapy. Moreover, the analysis of the results obtained before the premature closing of the trial revealed a trend towards a lower risk in the combination-therapy group than in the monotherapy group for the secondary endpoint, namely, a decrease in the estimated glomerular filtration rate or incidence of end-stage renal disease. This trend was observed despite a higher incidence of hypotension and acute renal failure in the study group, which may have an adverse effect on renal function over a longer period of time. Because the study was stopped prematurely with a fraction of the planned accrued events, a potential benefit of combined therapy cannot be entirely excluded.

Given the high risk of serious complications confirmed by those studies, dual RAAS blockade cannot be treated now as the therapy of choice in patients with proteinuria. Furthermore, it appears to be contraindicated in most patients, especially in those with type 2 diabetes who were the target population in the above studies. In our opinion, however, the various forms of dual RAAS blockade may be an interesting alternative in a population of patients with nondiabetic kidney disease, high blood pressure, proteinuria, and good renal function, while maintaining low potassium intake and rigorous control of serum potassium levels. In such a population of patients, dual RAAS blockade may be safe as evidenced by many years of our clinical practice and results of our study.² To confirm the protective effect of the dual RAAS blockade on the kidneys, studies in a well-defined population of patients should be designed. This task, however, may be a challenge too difficult to implement.

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