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COMMENTARY

Can two be better than one? Dual RAS blockade in patients with type 2 diabetes and overt nephropathy in the age of ONTARGET and ALTITUDE

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In the previous issue of *Hypertension Research*, Imai *et al.*[1] revisit the role of combination therapy with dual blockade of the renin–angiotensin system using angiotensin-converting enzyme (ACE) inhibition (ACEi) and angiotensin II receptor blockade (ARB) on primary renal outcomes or secondary cardiovascular and renal outcomes.[1] Their report is a *post-hoc* analysis of the prospective, randomized, placebo-controlled trial entitled, Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial (ORIENT). This study comprised a primarily male population of Japanese and Chinese patients (mean age 59 years) with hypertension (mean systolic blood pressure 141 mm Hg), type 2 diabetes (mean hemoglobin A1c 7.5%) and overt nephropathy (median albumin–creatinine ratio 1.7 g g^{-1}) at baseline and who were followed for 3.2 years for renal and cardiovascular end points. The participants in this study were randomized to receive either olmesartan or placebo, in addition to all pre-exiting pharmacotherapies, including ACEi. Among the 563 patients randomized to receive olmesartan ($n = 280$) or placebo ($n = 283$), ~74% received concomitant ACEi in each of the treatment groups. Owing to this similar distribution of ACEi in the two groups, the authors were able to compare the effect of combination ACEi plus olmesartan treatment to ACEi plus placebo treatment on renal and cardiovascular end points that were documented in ORIENT.

For the composite primary renal outcome for the study (time to first occurrence of doubling of serum creatinine, end-stage renal disease (ESRD) or death), the hazard ratio for olmesartan treatment was not significant, and combination therapy with ACEi did not provide additional benefit in that subgroup compared to placebo. For secondary renal outcomes, treatment with olmesartan did improve surrogate markers of renal protection, including a decline in urinary protein to creatinine ratio, and this effect was seen in ACEi and non-ACEi groups. Importantly, this anti-proteinuric effect was independent of blood pressure lowering. Perhaps not surprisingly, treatment with olmesartan slowed the decline in estimated glomerular filtration rate (eGFR) compared with placebo, and also significantly slowed the decline in eGFR when used in the absence of ACEi, but not when combined with ACEi. Taken together, olmesartan treatment as a monotherapy and as dual therapy reduced proteinuria independent of changes in blood pressure, while olmesartan monotherapy slowed the decline in eGFR. Unfortunately, these favorable effects on surrogate outcomes of renal function did not ultimately translate into clinically meaningful outcomes such as a reduced risk of ESRD or death in this patient population.

The underlying reason for the lack of benefit on the composite renal end point with combined ACEi therapy, despite a significant reduction in proteinuria, remains unclear, and is an ongoing conundrum in clinical nephrology. The dissociation between the favorable effects on proteinuria and the neutal impact on hard renal outcomes has several explanations. First, when combined with an ACEi, olmesartan did not cause a further lowering of blood pressure in this population. Accordingly, this suggests that the lack of effect of dual therapy on renal outcomes in this cohort may be partly attributable to a lack of improved blood pressure control. Second, the lack of benefit of dual therapy on renal outcomes may be due to the associated renal risks that have been appreciated in previous trials. In the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), for example, dual RAS blockade was used in a similar sample population, and was associated with an increased risk of adverse events including hypotension, acute kidney and hyperkalemia, despite reductions in proteinuria.[2] Similar beneficial effects on surrogate renal outcomes were observed in the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) trial, which demonstrated mild additional antihypertensive effects and significant anti-proteinuric effects with dual blockade.[3] ALTITUDE was, however, discontinued early due to an excess in serious adverse events, again highlighting the risk of using proteinuria as a marker of renal protection. The potential benefit of an anti-proteinuric effect with dual blockade is therefore greatly outweighed by the larger risk of organ hypoperfusion. Findings from ONTARGET, ALTITUDE and ORIENT therefore highlight a major limitation of the way renal protection trials are currently designed: the use of proteinuria as an surrogate outcome can often be misleading, as a

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variety of agents can provide powerful anti-proteinuric effects in the face of significant cardiovascular and renal harm.[4]

The observation that treatment with olmesartan in ORIENT was associated with a significant reduction in the time to developing secondary cardiovascular composite outcomes compared to treatment with placebo requires additional comment. It is important to appreciate that effects on the secondary cardiovascular composite outcome were not observed in the ACEi or non-ACEi subgroups. This suggests that combination ACEi/ARB does not confer additional cardiovascular protection, although the number of events in the subgroups was relatively small. Furthermore, a more detailed examination of the data shows that the overall statistical significance of this observation is largely derived from one factor, which was time to coronary, carotid or peripheral revascularization (hazard ratio 0.35, confidence interval (CI) 0.16–0.81, $P=0.013$). Moreover, this effect was based on 8 (2.9%) events in the olmesartan group and 21 (7.4%) in the placebo group. Although treatment with olmesartan may reduce the time to composite of cardiovascular outcomes, it had no effect on the time to cardiovascular death (hazard ratio 2.82, CI 0.76–10.43, $P=0.119$), or the time to nonfatal stroke (hazard ratio 0.73, CI 0.29–1.84, $P=0.506$) within the umbrella of the greater cardiovascular composite. Thus, the reader is left with some uncertainty around whether or not the potential cardiovascular benefit is actually clinically meaningful. From a mechanistic perspective, how might ARB therapy have exerted favorable cardiovascular effects that are independent of improvements in blood pressure lowering? While ORIENT cannot answer this question, blockade of angiotensin II can decrease vascular proliferation thereby reducing the need for revascularization procedures.[5] Dual blockade did not seem to enhance this vascular protective effect, and this area is unlikely to be investigated in future work, given the disappointing outcomes from ONTARGET and ALTITUDE.

In the article summary, the authors suggest that the possible cardiovascular benefit of olmesartan with and without ACEi requires further evaluation. However, given the findings from ONTARGET and ALTITUDE, and as olmesartan combined with ACEi did not reduce the composite cardiovascular outcome, further dual therapy trials are not likely to yield positive results. Of particular concern from a cardiovascular perspective from this and from other work is the knowledge that combination therapy increases the risk of potentially life-threatening hyperkalemia.[2,3,6,7] In the ORIENT cohort, treatment with olmesartan was associated with greater rates of discontinuation due to hyperkalemia compared with placebo (9.3 *vs.* 5.3%). Furthermore, as expected when combined with ACEi, the effect of olmesartan therapy on hyperkalemia was additive, leading to greater rates of discontinuation compared with placebo (24 *vs.* 15%). Although the authors do emphasize that within the first 6 months no participants required acute dialysis, only one patient in each group developed acute renal failure. It is therefore difficult to assess the magnitude of this adverse event compared to a non-study population. This is especially concerning as these relatively high discontinuation rates occurred within the confines of a highly controlled trial setting, where scheduled monitoring for acute electrolyte imbalances are highly regimented. The reader might question whether higher rates of hyperkalemia might occur in a less controlled setting with dual RAS blockade and therefore cause additional harm.

So what is the clinician to do with patients who have type 2 diabetes and overt nephropathy, especially when proteinuria is inadequately treated with an ACEi or an ARB or a direct renin inhibitor? The best level of evidence suggests that salt restriction and the addition of an appropriate diuretic can exert significant effects on blood pressure and proteinuria and can, most importantly, increase the renal protective effect of RAS blockers on important clinical outcomes.[8,9] In addition, researchers in this field have been tantalized by interesting preliminary findings using agents that lower uric acid, and by the activation of vitamin D-related pathways.[10,11] Both uric acid lowering and vitamin D agonists have been associated with positive effects on blood pressure and proteinuria in patients with nephropathy, in part through suppression of the RAS. Finally, the recently approved oral hypoglycemic drug class called 'sodium-glucose cotransport-2 (SGTL2) inhibitors' exert renal protective effects in animals, and also lower blood pressure in humans, which may be in part through diuretic effects.[12] Owing to their unique mechanism of action on tubuloglomerular feedback and sodium handling, SGLT2 inhibitors should also be studied as adjunctive therapies to RAS inhibitors in future work.[13] However, these agents will have to demonstrate protective effects on other relevant renal an cardiovascular end points before entering into widespread clinical use.

Is there any hope for dual RAS blockade in future studies? The VA NEPHRON-D study, which is not yet complete, will assess the effect of combination of losartan and lisinopril, compared with losartan monotherapy, on the progression of diabetic kidney disease in 1850 patients with overt proteinuria. The primary end points of the trial are time to (1) reduction in eGFR of $>50\%$; (2) reduction in eGFR of $30\,ml\,min^{-1}$ per $1.73\,m^2$; (3) progression to ESRD (need for dialysis, renal transplant or eGFR $<15\,ml\,min^{-1}$ per $1.73\,m^2$; or (4) death. The secondary end point is time to change in eGFR or ESRD. Tertiary end points are cardiovascular events, and slopes for eGFR and albuminuria at 1 year. Given existing trial data it seems increasingly unlikely that dual blockade in VA NEPHRON-D will demonstrate protective effects. Nevertheless, this study is needed to focus on important primary renal outcomes, and may help to settle some of the questions raised by Imai *et al.* around cardiovascular protective effects from dual blockade.

CONFLICT OF INTEREST

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