Several large randomized, controlled trials have demonstrated that interruption of the renin-angiotensin-aldosterone system with angiotensin-converting enzyme inhibition (ACEi) or angiotensin receptor blockade (ARB) delays the progression of renal and cardiovascular disease.\(^1\)\(^-\)\(^6\) These beneficial effects of ACEis and ARBs are likely to be mediated through reductions in blood pressure and albuminuria: the more blood pressure or albuminuria is reduced in the initial months after start of therapy, the more reduction in renal or cardiovascular events is observed during the subsequent years.\(^7\)\(^-\)\(^9\) Although ACEi and ARB are effective protective agents, the residual risk in these populations for either renal or cardiovascular risk is still very high. This residual risk appears to be determined by the residual high blood pressure and albuminuria in these studied populations. Many studies and their recent meta-analyses have shown that one can further reduce blood pressure and albuminuria by combining ACEi and ARB therapies.\(^10\)\(^-\)\(^12\) Therefore, one would expect that such dual therapy would further offer renal and cardiovascular protection. The ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial) trial was designed to investigate this question, and it showed, surprisingly, in its primary analysis that dual therapy had no additional effect on either cardiovascular or renal outcomes.\(^13\)\(^,\)\(^14\)

How can we explain the lack of an enhanced effect of dual therapy in the ONTARGET trial? Angiotensin-converting enzyme inhibition or angiotensin receptor blockade combination therapy cannot truly afford additional renal or cardiovascular protection (and can even be harmful). Alternatively, the population enrolled in the ONTARGET trial or the design of the trial may not be suitable for detecting the true potentials of dual therapy, as has been discussed by others.\(^15\)\(^-\)\(^17\)

Could it be that the renal-protective effect of dual therapy with ACEi and ARB only comes to fruition in a special (renal) population? When one looks at individual ACEi or ARB studies, the populations studied are mostly patients with compromised renal function (reduced glomerular filtration rate [GFR]) and/or microalbuminuria or macroalbuminuria.\(^1\)\(^3\)\(^-\)\(^5\) Relative to the overall ONTARGET population (n=25 620), very few patients had reduced GFR and macroalbuminuria at entry into the trial (n=608; 2.4%). Indeed, the investigators involved in ONTARGET have reported previously from the Heart Outcomes Prevention Evaluation trial, with a similar trial population, that treatment with ACEi shows greater protection against all-cause death and cardiovascular death in a subgroup of patients with low GFR than in the overall population.\(^18\) In the current issue of Circulation, Tobe et al report on the TRANSCEND (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease) trial, in which the ARB telmisartan is compared to placebo in patients intolerant to ACEi.\(^19\) They demonstrate greater treatment effects on renal outcomes in patients with GFR below 60 mL/min and micro- or macroalbuminuria. Interestingly, in patients with normoalbuminuria, telmisartan had no beneficial effect, and it increased the risk of renal events compared with placebo. Other trials in patients with normoalbuminuria at low renal and cardiovascular risk have also failed to identify clear benefits for ARBs in the prevention of progression of nephropathy.\(^20\)\(^,\)\(^21\) If dual therapy were to have any renal benefits, one should preferably look at the patient population with reduced GFR and microalbuminuria or macroalbuminuria.

Tobe et al did an important analysis of the ONTARGET dataset to test whether dual therapy with ACEi and ARB was beneficial in the subgroup of patients with low estimated GFR and elevated albuminuria.\(^19\) Surprisingly, the authors did not find any protective effects of dual therapy on hard renal and cardiovascular outcomes. Important within this context is the question of what dual therapy did to blood pressure and albuminuria. A large set of previous studies and a meta-analysis show that ACEi/ARB combination therapy further reduces blood pressure and albuminuria in patients with decreased estimated GFR and/or microalbuminuria or macroalbuminuria. To our surprise, the data of ONTARGET show that dual therapy had no extra effect on blood pressure or albuminuria lowering compared to the individual ACEi or ARB therapy arms in patients with low estimated GFR and macroalbuminuria (Figure; albuminuria data derived from the main article, blood pressure data derived from the online-only Data Supplement). In fact, the reduction in albuminuria was approximately 67% during individual ACEi or ARB therapy, and it was even less during the combination. The lack of an effect of dual therapy on surrogate markers (blood pressure and albuminuria) may explain why there is no further renal protection observed in this renal-compromised subgroup. The cause of this discrepancy in surrogate marker effect between the ONTARGET patients and other populations previously studied remains as yet unclear. It could be that the infrequent measurement of risk markers, such as measurement of urinary albumin concentration and blood pressure in combination

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ONTARGET still OFF-TARGET?

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with the assessment of serum creatinine in local laboratories, as well as the lack of a confirmatory measurement of serum creatinine if it doubled from baseline, are flaws that may have biased the results.

Tobe et al also observe another important phenomenon in the current report on TRANSCEND: individual ACEi/ARB therapy may be harmful in low-risk populations (normal GFR and normal albuminuria). An explanation for this finding may be that ARB therapy not only affects blood pressure or albuminuria, but can also induce changes in hemoglobin and serum potassium. Each of these effects may influence the ultimate renal or cardiovascular outcome, either beneficially (the lowering of blood pressure and/or albuminuria) or harmfully (increasing potassium and/or lowering hemoglobin). In the case of ARB therapy, the balance between harm and benefit depends on the composite effects of all parameters. Theoretically, the balance may tilt to harm in those in whom the effect on albuminuria is less relevant, such as in the normoalbuminurics. Further (sub)analyses on this issue will have to clarify whether such mechanisms are indeed in play.

Finally, the interpretation of the ONTARGET trial has led to the suggestion that “albuminuria cannot be taken as a definitive marker for renal protection.”22 The current analysis of ONTARGET shows how careful one has to be with such interpretations. This article and the results in the online-only Data Supplement confirm what was known long before: if one is not able to reduce blood pressure or albuminuria in those with increased levels of albumin in the urine, one will fail to reduce the risk of renal or cardiovascular disease. Thus, ONTARGET actually shows that, next to blood pressure, effect on albuminuria is a good marker for renal protection. We need more on-target subanalyses of ONTARGET to fully understand why dual therapy had no additional effects on blood pressure and albuminuria in the patients at renal risk.

**Disclosures**

None.

**References**


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