The results of the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) study were unexpected, demonstrating no cardiovascular or renal benefit but substantial adverse effects of adding an angiotensin II receptor blocker (ARB), telmisartan 80 mg/day, to an angiotensin-converting enzyme (ACE) inhibitor, ramipril 10 mg/day (‘dual therapy’) vs ramipril alone [1,2]. Those results stirred up a number of commentaries especially from the nephrological community and in most major nephrological journals [3–11]. In this journal, Dr. Abutaleb [10] brings up a number of concerns related to the design and the renal results of ONTARGET, and we will reply to those concerns in the following. From the beginning, we would like to stress that ONTARGET is the only reliable outcome trial at present to build our judgment on dual therapy outside heart failure and one flawed renal study [13,14]. All other evidence comes from randomized controlled studies with only surrogate endpoints and from inferences of experimental studies. It is important to ponder strengths and weaknesses of that singular major trial.

ONTARGET did not test different levels of blood pressure but tested more or less complete blockade of the renin–angiotensin system. The hypothesis was that more complete blockade of the renin–angiotensin system with the increase in bradykinin from the ACE inhibitors would result in less cardiovascular and renal outcomes. Blood pressure was lower with dual therapy by 2.4/1.4 mmHg compared to monotherapy with ACE inhibitors in people with a mean blood pressure of 142/82 mmHg at inclusion. Current guidelines for people with renal disease propose that we should aim for target blood pressure <130/80 mmHg and <125/75 in those with substantial proteinuria. Therefore, we can safely state that antihypertensive treatment in ONTARGET was not inappropriate or un-indicated but in accordance with accepted strategies of patient management. The latter is underlined by the findings of the HOPE study, a placebo-controlled trial with lower baseline blood pressure than in ONTARGET and inclusion of 50% normotensive participants, where ramipril 10 mg/day demonstrated cardiovascular and renal benefits [15–17] and a lower blood pressure than placebo. In contrast to Dr. Abutaleb’s assumption, there was no difference in mortality between randomized groups in ONTARGET and very few dropouts (study discontinuation <0.5%). However, there were more people discontinuing randomized therapy, more in the dual therapy group (about 29% vs 23% with monotherapy), but of those 29%, 22% discontinued both drugs, and 7% discontinued only one drug. Discontinuation of study medication occurred at some time during the study, was in part intermittent and was in the range of other major trials.

There is no easy way to choose the right dose of drugs in clinical outcome trials. Ideally, one would like to do dose–response curves, as with experimental studies, but in the case of the ONTARGET study that would require five to 10 times the number of participants, this is an impossible undertaking. When asking whether more inhibition is better than less inhibition of the renin–angiotensin system, it is unreasonable to compare moderate doses of dual therapy with moderate doses of monotherapy. Thus, ONTARGET choose to compare the addition of a high dose of an ARB to the highest recommended dose of ramipril, namely 10 mg/day. There are other studies showing a dose–response for major outcomes of ramipril from 1.25 to 10 mg/day in patients [15,18,19].

Unknown renal artery stenosis in people with vascular disease is a problem in any outcome study that includes participants with vascular disease such as in ONTARGET. To our knowledge, there is no good clinical data that addition of an ARB to high dose ACE inhibitors increases renal risks associated with inhibition of the renin–angiotensin system in people with renal artery stenosis. Incidentally, observational data suggest that such inhibition plethora substantial cardiovascular benefits in people with renal artery stenosis at the cost of a lower glomerular filtration rate (GFR) and the risk of acute kidney injury. Estimated GFR values above 60 ml/min are often far from true GFR. However, unpublished data of ONTARGET show that the small but significantly greater decrease in eGFR with dual therapy than with ramipril was driven by...
participants with an eGFR <60 ml/min at inclusion (Tobe et al., manuscript in preparation) even after accounting for the expected initial change at 6 weeks. More than 6000 people had an eGFR <60 ml/min at baseline, not a small number by any standards of renal trials. We have no measure of muscle mass in ONTARGET and cannot exclude differential effects of randomized therapy on that parameter. However, the parallel changes of eGFR and of doubling of serum creatinine argue against that explanation for the differences in eGFR change. A washout period would have been helpful to fully evaluate the renal effects of randomized therapy, and we discuss that design aspect in a further paper [20].

The age-related decrease in eGFR, on the whole, was smaller in ONTARGET than in other observational studies, probably attesting to the high standard of care in ONTARGET. The main point is that eGFR fell with decreasing urinary albumin excretion in the dual therapy group as compared to ACE inhibitor monotherapy. In other words, a therapeutic reduction in albuminuria in people with little urinary albumin excretion at outset cannot be taken as an indicator of renal benefit or cardiovascular benefit for that matter. ONTARGET dismisses urinary albumin excretion or proteinuria as a ‘general’ surrogate marker, namely in people with low levels of proteinuria.

Dual therapy had no cardiovascular benefit, a major target of drug therapy in people with renal insufficiency or with proteinuria because they tend to succumb to cardiovascular events including death before reaching end-stage renal disease. Dual therapy had also no effect on preventing chronic dialysis but increased the risk for acute dialysis, even in subgroups with low eGFR or high-grade proteinuria (Tobe et al., manuscript in preparation). In contrast to the faulty description of others [5], dialysis and other renal outcomes were prospectively (and not retrospectively) monitored in ONTARGET. Thus, ONTARGET provides a solid foundation to show the potential for serious adverse events of dual therapy that will escape other often woefully underpowered studies. Several commentaries such as Dr. Abutaleb’s tried to explain acute kidney injury by the hypertensive effect of dual therapy, especially in people with normal baseline blood pressure. That explanation is unlikely because acute kidney injury was caused by the usual suspects, namely trauma, sepsis etc., as detailed before [2]. In those instances, the specific intrarenal hemodynamic action of a more complete blockade of the renin–angiotensin system is a reasonable culprit for the higher incidence of acute kidney injury.

Many commentaries of the ONTARGET study asked for data in subgroups with renal risk markers and with different blood pressure at baseline or follow-up and combinations thereof! We will publish data for subgroups with renal insufficiency and with different degrees of urinary albumin excretion (Tobe et al., manuscript in preparation). Those data, however, can only be hypothesis-generating, and we would like to issue a warning to do too many subanalyses of subgroups, inflating the chance finding of differences that are not real. In the end, subanalyses may also distract from the main thrust of the renal ONTARGET findings or lead to inappropriate interpretations.

Our conclusions of the ONTARGET findings are in stark contrast to some other comments [3,5,6] including Dr. Abutaleb [12] but in line with others [4,7,8]. ARB and ACE inhibitors have been shown to reduce cardiovascular and renal outcomes in people at high vascular or renal risk. Contrary to our hypothesis, dual therapy had no additional cardiovascular benefit, did not reduce chronic dialysis or doubling of serum creatinine but exhibited albeit infrequent but life-threatening adverse events, including acute kidney injury and hyperkalaemia as in heart failure trials [21]. These findings are solidly based on a population of about 26 000 people at high vascular risk including about 6000 with low eGFR and about 1000 with macroalbuminuria, substantial numbers by published evidence in nephrology and a benchmark for other studies.

There is objective evidence now to eliminate dual therapy as an antihypertensive regimen and as a means to blunt progression of renal disease in people with albuminuria below the macroalbuminuric threshold. Whether the antiproteinuric effects of dual therapy will translate into less end-stage renal disease in specific proteinuric populations has to be tested. ONTARGET does not contradict the latter, but it emphasizes the need to carefully monitor adverse events in future outcome studies with dual therapy. We caution, however, against the sole reliance on the surrogate marker proteinuria, also because small studies with surrogate endpoints tend to overlook (and under-report) adverse events and to over-interpret surrogate benefits. We may cautiously consider dual therapy in patients that are left with proteinuria above 1 g/g despite normotension, high-dose ARB or high-dose ACE inhibitor and negative sodium balance, but those patients have to be informed about and monitored for potential adverse events. Finally, the latter population is nowadays rather the exception than the rule for incident dialysis patients.

Conflict of interest statement. None declared.

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ONTARGET should not be over interpreted

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Introduction

Anti-proteinuric therapy has long been accepted as an essential component for the management of chronic kidney disease (CKD). Such therapy includes maximizing the dosages and number of antihypertensive agents having anti-proteinuric features. An excessive initial decline in glomerular filtration rate (GFR), often associated with relative hypotension, is the most common reason for withdrawal from maximal anti-proteinuric therapy. In practice, treatment is individualized and titrated against changes in blood pressure (BP) and GFR, in addition to its effects on proteinuria.

The ONTARGET study reported an accelerated decline in estimated GFR (eGFR) and higher diastolic and mortality rates in a combined angiotensin receptor blockers (ARB) and angiotensin-converting enzyme inhibitor (ACE-I) therapy group, despite greater reductions in BP and proteinuria [1,2]. To what degree are these findings truly significant, valid and suitable for generalization to clinical scenarios? To what degree is it legitimate to abandon the dual renin angiotensin system (RAS) blockade therapy? Here, I will try to highlight a few important observations and queries that may be helpful in attaining a more appropriate reading of the ONTARGET findings.

ONTARGET summarized [1,2]

After a run-in period to test tolerance to a combined dose of 5 mg ramipril plus 40 mg telmisartan, a total of 25 620 patients, aged 66.5 ± 7.2 years, were randomly assigned to receive telmisartan 80 mg/day, ramipril 10 mg/day or the two drugs combined. Participants had either atherosclerotic vascular disease (about 75%) or diabetes with end-organ damage (about 38%); 31% were normotensive, 13.1% had micro- and 4% macroalbuminuria, and 81% had an eGFR of 50 to 199 ml/min/1.73 m². The study drugs were discontinued in 23.7% (ramipril), 21.0% (telmisartan) and 29.4% (combined) of the patients, respectively. Symptomatic hypotension was documented more often in the combined group (406 vs. 149 in ramipril). The primary outcome of cardiovascular (CV) death, myocardial infarction (MI), stroke or hospitalization for heart failure occurred after 56 months in 16.5% (ramipril), in 16.7% (telmisartan) and in 16.3% (combined) in the three groups, respectively. The primary renal outcome of dialysis, a doubling of serum creatinine

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