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 dialysis 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 ml/min/1.73 m². The study drugs were discontinued in 16.5% (ramipril), in 16.7% (telmisartan) and in 16.3% (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
and all deaths was 13.5% (ramipril), 13.4% (telmisartan) and 14.5% (combined) in the three groups, respectively. Excluding the initial eGFR decline, which accounted for about 70% of the overall decline, the overall decrease in eGFR was $-1.17$ (ramipril), $-2.06$ (telmisartan) and $-2.49$ ml/min/1.73 m$^2$ (combined). The incidence of chronic dialysis ($n=98$) was similar among the groups, although acute dialysis was more frequent in the combined group (28% vs.13% in the ramipril and 13.4% in the telmisartan group).

**Observations and queries concerning ONTARGET**

Although the expectation that greater BP reductions should result in better GFR preservation would have been valid in a hypertensive trial, treatments in ONTARGET were not titrated to BP levels. The run-in period did not test tolerance to the double dosage given to the combined group. It is natural to expect higher intolerance in the form of inappropriate hypotension and GFR decline among those assigned randomly to receive the double tested dosage. How can we assume that the normotensive patients (31.5%) in this (combined) group would tolerate, with no side effects, such dose doubling of essentially an un-indicated antihypertensive therapy? Any potential effect on renal function is likely to be less tolerated when such hypotension is secondary to RAS blockade. As will be discussed, the excess mortality and the 29.4% dropout rate in the combined group were highly correlated with the occurrence of hypotension. It may be more accurate to conclude that ONTARGET has revealed worse renal outcomes with ‘inappropriate’ prescription of high-dose dual RAS blockade therapy!

While assessing RAS blockade, ONTARGET did not differentiate between the effects of higher potency vs. dual therapy. Ideally, the combined group should have remained on the run-in equipotent dosage of 5 mg ramipril plus 40 mg telmisartan. Only under these conditions would it be possible to weigh the theoretical merits of dual blockade versus the isolated blockade approach without introducing the confounding effect of inappropriate higher potency of the blockade itself. In two previous studies, the authors more appropriately halved the lisinopril and ramipril doses in the dual-blockade groups in both studies, respectively [3,4]. Despite limitations, neither study found any basic difference between single or dual RAS blockade therapy, as long as the therapy was equipotent. It should be pointed out that the COOPERATE study [5], as in ONTARGET, did not halve the dosages of the agents prescribed for the dual-blockade therapy group; however, COOPERATE was carried out in renal patients with significant renal dysfunction and proteinuria.

In ONTARGET, it appears that the potency of the 80 mg telmisartan dose was higher than that of the 10 mg ramipril dose. Compared to the ramipril group, the telmisartan group had greater BP reductions ($7.4/5.0$ vs. $6.4/4.3$ mmHg), higher initial eGFR declines ($-2.51$ vs. $-2.14$, $P=0.07$), higher rate of overall eGFR decline ($-2.06$ vs. $-1.17$ ml/min, $P=0.003$) and higher need for acute dialysis (20 vs. 13). Thus, there appears to be a continuum of side effects between the study groups which is more dependent on the potency of the blockade than on the number of RAS blockade agents. One may wonder whether a higher dosage of ramipril alone would have resulted in the same negative renal outcomes as seen in the combined group. While interpreting ONTARGET, should our colleagues now conclude that it was the potent RAS blockade, rather than the dual therapy, that caused poor patient outcomes? For the ONTARGET population, where treatment was not titrated against patient BP, I believe that the proper conclusion is that higher (not the dual therapy per se) RAS blockade is potentially harmful for renal function in the patients.

Occult uni- or bilateral renal artery stenosis is very common in the patient population examined in the ONTARGET study. For example, Przewlocki et al. [6] reported a renal artery stenosis prevalence (of >50%) of 35.4 and 60.2% among patients with single or multiple (>1) coronary artery disease or supra-aortic artery stenosis, respectively. It is very likely that many of the occult borderline renal artery stenosis and atherosclerotic renal disease lesions showed further progression during the 56 months of the study period. This is supported by the simultaneous development of other atherosclerotic complications related to cardiovascular death, MI or stroke in 14% of the study population during the study period. Such occult renal artery stenosis progression would obviously manifest itself with a greater rise in creatinine levels in the combined group and may adequately explain the reported eGFR differences.

The eGFR values utilized in the study were too crude to detect a change in the eGFR decline rate in the range of 0.01 ml/min/year! Because 81% of the study population had an eGFR >60 ml/min and because the usual practice is not to extract eGFR values using the Modification of Diet in Renal Disease (MDRD) study equation if eGFR is >60 ml/min, the bulk of the eGFR values utilized in the study were very crude. For example, Poggio et al. [7] reported an underestimation of eGFR in potential kidney donors by 9 to 29% when using the four-variable MDRD equation when compared to simultaneous GFR values derived from iohalatamide clearance.

An additional drawback of creatinine-based eGFR formulas is possible introduced errors caused by changes in muscle mass during the study period. The ONTARGET intervention appeared to interfere with age-related muscle wastage. Multiple studies [8–10] have suggested that ACE-I or ARB therapy may cause preservation of muscle strength and/or mass. For example, Di Bari et al. [8] reported larger lower extremity muscle mass in older persons using ACE-1 (16.5 ± 0.3 kg) than in users of other antihypertensive medications (15.3 ± 0.3 kg for β blockers, $P<0.001$) or on no medications (15.8 ± 0.1 kg, $P=0.01$); this difference, which correlated with the duration of ACE-I therapy, was maintained even after accounting for other covariates. Could higher dual RAS blockade have contributed to a better muscle mass preservation? The MDRD equation would interpret this as a greater decline in eGFR. Could evaluation of the creatinine index or alternative muscle mass index be of value in assessing this possible error in eGFR values?

Reversals from initial GFR declines after RAS blockade are well-known and have been well-documented [11,12]. Thus, it is important to exclude this initial GFR decline when calculating the overall ‘permanent’ decline in GFR. Unfortunately, ONTARGET used this initial eGFR decline,
which accounted for about ‘70%’ of the overall eGFR decline, in their final calculations and conclusions. These data were used even though the authors commented that the initial ‘decrease in GFR might even predict a long-term benefit’ [1]. This analysis is reminiscent of the MDRD study, where a later re-analysis of the GFR slopes suggested a beneficial effect of the low-protein diet in the subgroup with higher initial GFR decline [13]. The inclusion of this initial decline in the calculations for overall GFR decline in both the MDRD and ONTARGET studies, without an attempt to exclude reversible components of this decline, appears to be inappropriate. I suggest that the ONTARGET study could have been improved by measuring, or re-estimating eGFR, after a washout period from the study medications.

After excluding the initial GFR decline, the authors still reported GFR declines (± SD) of −1.17 ± 17.1 (ramipril), −2.06 ± 17.1 (telmisartan) and −2.49 ± 17.4 ml/min (combined). The average yearly eGFR decline would be 0.25, 0.44 and 0.53 ml/min/year in the three groups, respectively. Therefore, the acceleration of renal dysfunction in the combined group was only 0.09 or 0.28 ml/min/year compared to the telmisartan or ramipril groups, respectively. It is impossible to interpret ‘small’ differences in eGFR (i.e. of <0.1 ml/min/year) when the basic eGFR measurements were very crude (as discussed above). The reported SDs of these decline rates were ‘>17.0 ml/min’, and the dropout rate from the combined group was almost 30%. Such high SDs that had mean values near zero (i.e. −1.17 to −2.49) suggest that eGFR increments occurred in nearly half of the study population. How could this happen? What could have been the role of the stronger RAS blockade in limiting the hyperfiltration responses (average body mass index 28 ± 4.5 and diabetes in 38%)?

Overall, the statistical significance associated with these eGFR differences should not be translated into clinical significance, especially after considering the potential roles of co-factors such as those discussed in this paper.

The adverse effects attributed to the combined therapy in ONTARGET were limited to worsening renal outcomes. The primary CV outcome, as stated above, was similar in the three groups. Compared to ramipril, renal disadvantages of combined therapy were summarized as 83 excess cases of poor renal outcomes: 51 excess mortality occurrences (raising the mortality rate from about ‘0.13’ to 0.23%/year, according to the denominator) and 38 (note double counting!) excess cases of dialysis or a doubling of serum creatinine (raising that rate by ‘<0.1%/year’). The number of dialysis cases was higher by 15 (or ‘<0.04%/year’), and there was a doubling of serum creatinine in 26 cases (or by ‘<0.06%/year’; note further double counting!). These differences of ‘<0.04 and ‘<0.06%, however, have resulted in a hazard ratio (HR) for dialysis of 1.33 and for a doubling of creatinine of 1.33 to 1.20. Essentially all the excess dialysis cases were due to acute dialysis. This is a recognized risk of maximizing RAS blockade, which was prescribed blindly to an elderly group of patients, may not only have lacked survival benefit for the 81% with eGFR >60 ml/min but may also have been detrimental for the survival of this major subgroup. Hypotension has been associated with excess mortality in this type of elderly population with cardiovascular problems [15]. Collapsing the ONTARGET study groups into a single group and a comparison of primary composite outcomes to systolic blood pressure (SBP) revealed that CV mortality increased with each SBP reduction (P < 0.0001) in patients having a baseline SBP <130 mmHg. A previous study revealed a J-curve (nadir around 130 mmHg) in the relationship between in-treatment SBP and all outcomes except stroke [16]. Patients in the two highest tertiles of BP reductions had a 20% higher HR for the primary outcome. The diversion of HRs (combined vs. ramipril) for stroke (0.93) and MI (1.08) could have obviously been related to the changes in BP. Some non-CV mortalities could also have been initiated by hypotension.

How can we generalize the mortality risk associated with hypotension to encompass all indications and subjects, including young CKD and nephrotic patients, treated by well-titrated dual RAS therapy?

The ONTARGET patients were not the usual type of CKD subjects having underlying kidney diseases that can usually be treated with combined RAS therapy. It is reassuring for nephrologists that ONTARGET did not reveal any excess renal outcomes due to dual therapy in the subgroups with micro- or macroalbuminuria, eGFR <60 L/min/1.73 m2 or overt diabetic nephropathy. Because the ONTARGET population showed macroalbuminuria in only 4% of the patients and an eGFR decline rate of 0.25 to 0.53 ml/min/year, the findings almost completely excluded the possibility to show potential benefits of dual blockade. Since it consisted of mostly elderly, non-CKD and normoalbuminuric patients, the ONTARGET study population was less likely to benefit from RAS blockade than the average renal patient.

In summary, the ONTARGET-based arguments against dual RAS therapy are limited by the general absence of CV side effects, the limitation of any intrinsic renal hazard for the low-renal risk subgroups, the trivial absolute differences in the reported rates of non-fatal renal outcomes, the high dropout rate and several alternative valid explanations for the excess adverse outcomes. The ONTARGET conclusion regarding dual RAS therapy would still be valid if dual therapy was limited to cases where it is given for BP-dependent CV protection. Because RAS blockade in the ONTARGET study was not titrated against BP or proteinuria level, generalizing the study conclusions to other populations or to other indications for RAS blockade therapy is inappropriate. In clinical practice, we mostly prescribe RAS blockade for its antihypertensive or anti-proteinuric effects. In both situations, patients are monitored, and the progression to dual or higher dosed RAS monotherapy is dictated by clinical safety and patient gains.

Dual RAS therapy should remain a valid choice because of its additive antihypertensive, anti-proteinuric and anti-heart failure effects, but probably not for cardiovascular prophylaxis.

Conflict of interest statement. None declared.
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References

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