Optimal nephroprotection: Use, misuse and misconceptions about blockade of the renin–angiotensin system. Lessons from the ONTARGET and other recent trials

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Abstract

Results from the ONTARGET trial remind us that acute haemodynamically mediated renal dysfunction, triggered by low arterial pressure or volume depletion, can occur in high-risk cardiovascular patients (who usually have some degree of diseased intrarenal vessels) treated with renin–angiotensin system (RAS) blockers (especially in combination). However, nephroprotection could not be properly assessed in the trial, as the population was at low renal risk. Although albuminuria remains a useful marker in many patients, it can neither predict acute renal dysfunction nor replace end-stage renal disease (ESRD) as the endpoint in clinical trials. Recent trials using surrogate endpoints suggest that some RAS blockers (ACE inhibitors, angiotensin receptor blockers, the renin inhibitor aliskiren) may be more nephroprotective than others, but proving this requires comparing them (alone or in combination) in populations with identified renal disease (mainly diabetic nephropathy) and the use of hard endpoints. RAS-blocker dosages are critical: as some patients need much larger doses to decrease proteinuria than do others, the efficacy of a high-dose RAS blocker needs to be assessed in patients with persistent proteinuria. In patients with massive proteinuria despite maximum RAS-blocker dosages, combination RAS blockade should be considered by nephrologists, but will require close monitoring of renal function; also, the treatment needs to be withdrawn (at least temporarily) as soon as volume depletion or excessively low arterial pressure arises. In recent trials, lowering blood pressure towards values recommended by the current guidelines (130/80 mmHg) has reduced microvascular (lower levels of urinary albumin excretion) and macrovascular events in diabetic patients.

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Résumé


Les résultats de l’essai ONTARGET nous rappellent que l’insuffisance rénale aiguë sous IEC et/ou ARA2 survient volontiers chez les patients à haut risque cardiovasculaire (ayant souvent une néphroangiosclérose) en hypoperfusion rénale par hypovolémie ou hypotension. Cet essai n’a pas permis de tester véritablement la néphroprotection des bloqueurs du système rénine-angiotensine (SRA), car le risque rénal des patients inclus était faible. L’albuminurie est un marqueur de risque chez de nombreux patients, mais est inutile pour prédire l’insuffisance rénale aiguë et ne remplace pas les événements durs (IRC terminale) dans les essais thérapeutiques. Des résultats d’essais thérapeutiques, fondés surtout sur des critères de substitution, suggèrent que certains bloqueurs du SRA (IEC, ARA2, inhibiteur de la rénine [aliskiren]) peuvent apporter une néphroprotection plus efficace que d’autres ; cependant, la preuve ne pourra être apportée que par l’utilisation de critères durs (dialyse chronique) chez des patients atteints d’une maladie rénale identifiée (néphropathie diabétique). La dose d’IEC ou d’ARA2 utilisée est un point critique : certains patients nécessitent une dose plus élevée que d’autres pour réduire la protéinurie : cela doit être testé pour chaque patient. L’association de bloqueurs du SRA doit
Ever since oral drugs that effectively inhibit the renin-angiotensin system (RAS) became available, it was suggested that escalating dosages would maximize RAS blockade and presumably result in optimal protection of target organs. More recently, several studies — mostly involving diabetic patients — indicated that the blockade of the RAS with combined angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) can reduce urinary albumin excretion (UAE), thereby supporting the idea that combined blockade provides better nephroprotection than either ACEI or ARB alone [1,2]. Indeed, Nakao et al. [3] later demonstrated that trandolapril (3 mg/day) combined with losartan (100 mg/day) reduced the occurrence of the usual renal composite endpoint, which may include doubling of serum creatinine, end-stage renal disease (ESRD) and even death, in Japanese patients with non-diabetic glomerulonephritis. In marked contrast, the results of the recent ONTARGET study suggested that the combination of telmisartan and ramipril was harmful for kidney function compared with either drug on its own, despite greater effects on proteinuria and arterial pressure [4,5]. For this reason, it is important to analyze the renal results of the ONTARGET and other trials to better understand the benefits and drawbacks of such a strategy in daily practice and, especially, in diabetic patients.

1. Renal effects in the ONTARGET trial

ONTARGET was a large, randomized, double-blind trial aimed at answering two questions:

- Is the ARB telmisartan inferior to the ACEI ramipril in terms of preventing cardiovascular events in high-risk patients?
- Does combined blockade result in better cardiovascular protection than ramipril on its own [4]?

A total of 25,620 patients were randomized to receive either ramipril (10 mg/day), telmisartan (80 mg/day), or both (combined blockade), for five years. These patients were all high-risk cardiovascular patients, aged 50 years or more, with a history of coronary artery disease, myocardial infarction, stroke or peripheral artery disease, or diabetes plus another cardiovascular risk. Overall, 38% had diabetes at baseline. Patients with serum creatinine levels more than 265 µmol/L were not included in the trial. Mean glomerular filtration rate estimated according to the Modification of Diet in Renal Disease (MDRD) study formula (eGFR) was 73.6 mL/min/1.73 m²; the eGFR was less than 60 mL/min/1.73 m² in 24% of patients and less than 30 mL/min/1.73 m² in 1%. Microalbuminuria — assessed when patients were still taking their usual pretrial treatment before the run-in period — was present in 3356 patients (13.2% of all patients, 29.7% of those with diabetes), and proteinuria in 1025 patients (4%).

Arterial blood pressure was, on average, 142/82 mmHg at baseline, and decreased by −6.4/4.3, −7.4/5.0 and −9.8/6.3 mmHg in the ramipril, telmisartan and combined blockade groups, respectively, compared with baseline. However, the exact arterial pressure values throughout the study were not provided by the authors. Also, it is noteworthy that the number of permanent discontinuations of the study treatment was significantly greater in the group taking the combined treatment, and that the primary reason for discontinuation was hypotension, which occurred three times more frequently with combined blockade than with ramipril alone.

Telmisartan was found to be not inferior to ramipril for cardiovascular death, stroke and myocardial infarction. However, surprisingly, the combination of telmisartan and ramipril was not superior to ramipril alone for cardiovascular protection, despite the lower blood pressure. In addition, the combined blockade brought about more renal safety issues than either ramipril or telmisartan alone [4]: serum potassium levels greater than 5.5 mmol/L were twice as frequent in the combination group than in the other two groups; “renal impairment” (no specific definition given in the report) and permanent discontinuation of study medication due to renal impairment were significantly more frequent (1148 vs 871 in the ramipril group and 94 vs 60 in the ramipril group, respectively); the number of patients who had doubling of creatinine did not differ across groups (166, 155 and 140 cases in the combined, telmisartan and ramipril groups, respectively); and dialysis was needed in only slightly more patients in the combined group (63 vs 51 and 48 in the telmisartan and ramipril groups, respectively).

It was assumed that the “dialysis” events reported in the study were the result of ESRD in all patients [4]. However, for the first time in a major clinical trial, acute and chronic dialysis (renal replacement therapy of less than or equal to two months vs more than two months) were presented separately. Yet, information as to whether the dialysis was acute or chronic could not be obtained from the investigators in three cases, and a further three patients who had originally been reported as having dialysis [4] were found to have had no dialysis after careful investigation [5]. The incidence of chronic dialysis was low, with no significant differences observed across the three groups (33, 31 and 34 cases in the combined, telmisartan and ramipril groups, respectively, out of more than 25,600 patients). However, acute dialysis was...
more frequent in the combined blockade group (28 patients) than in the ramipril (13 patients) and telmisartan (20 patients) groups [5].

2. Harmful renal effects: lack of nephroprotection or acute renal dysfunction?

The population included in the ONTARGET trial was at high cardiovascular risk and low renal risk: the rate of ESRD was ∼0.4% during the 4.5 years of follow-up, and the annual GFR decline was similar to that observed in the general population (∼1 mL/min/year); this meant that nephroprotection could not be properly assessed in the trial. In addition, the risks of death (30 times more frequent) and of permanent discontinuation of the study drugs (around eight times more frequent) were much greater than the risk of ESRD. However, it might have been more interesting to have used competing risk analyses in such a situation instead of the Kaplan–Meyer method [6]. Also, the authors did not separate the incidences of acute vs chronic doubling of serum creatinine, and no confirmatory measurement of serum creatinine was performed in the trial [5].

Despite these important caveats, there is no doubt that the ACEI–ARB combination was harmful to renal haemodynamics—albeit in some patients. The decline in GFR was significantly faster in the combined blockade group (−6.1 mL/min/1.73 m²) than in either the ramipril (−2.8 mL/min/1.73 m²) or telmisartan (−4.1 mL/min/1.73 m²) groups. Similar results were observed when the change in eGFR was calculated using measures taken at six weeks as a reference value rather than the baseline values [5].

The greater need for acute dialysis with the combination blockade was seen mostly in haemodynamically fragile patients (22 patients with severe infection, nine with volume depletion and seven after surgery), an observation consistent with a greater risk of acute, haemodynamically mediated, renal dysfunction. Thus, despite the huge sample size of the ONTARGET study, whether or not the ACEI–ARB combination is more nephroprotective than either drug on its own is still not known in patients at high renal risk (especially those with diabetic nephropathy).

3. What is the mechanism of acute renal dysfunction with combined blockade?

At this time, it is not known whether the renal effect of the drug combination was similar in patients with diabetes, hypertension, proteinuria or eGFR less than 60 mL/min/1.73 m² [5]. In fact, the relative risk of the primary renal outcome (death, ESRD, doubling of serum creatinine) in each subgroup was reported, but not the relative risk of developing one of the components of the composite endpoint [5].

Sodium balance may be a critical issue. So far, there is no information on sodium intake during the ONTARGET trial, as such a parameter was not collected for such a large cohort. Nevertheless, it should be noted that the patients included in the ONTARGET trial were older, and it has long been recognized that regulation of sodium homeostasis is less effective with advancing age [7]. In addition, the study medications were more often stopped because of diarrhoea in patients taking telmisartan and ramipril together compared with patients taking these agents separately [4]. Indeed, the higher incidence of diarrhoea may have been due to inhibition of the intestinal tract or colonic RAS [8]. Extracellular fluid volume depletion secondary to diarrhoea may have worsened the renal tolerability of the combined treatment. It is not known whether or not the patients were instructed to stop ACEI, ARB and/or diuretics in cases of hypovolaemia (including diarrhoea and vomiting). More important, both Jover et al. [9] and Menard et al. [10] have shown that ACEI–ARB combined blockade resulted in impaired growth, lower body weight, and reduced renal function and survival in normal rats with low sodium intakes. Such a detrimental outcome was prevented by a switch to high salt intakes, and was promptly reversed if treatment was stopped or if the rats were given extra sodium chloride [11]. In addition, it has been shown that dual blockade at suboptimal dosages can modify the blood pressure–natriuresis relationship through cumulative mechanisms in double transgenic (human renin and angiotensinogen) rats [12].

There were no data for arterial pressure in the subgroups of patients who required acute or chronic dialysis in the ONTARGET trial [5]. For this reason, it is not possible to assess whether or not low blood pressure played a significant role in the renal function impairment. Yet, this issue may be even more important than sodium intake: necropsy studies have demonstrated that systemic atherosclerosis is accompanied by severe nephrosclerosis [13]. Acute renal failure triggered by low arterial pressure could have developed in the high-risk cardiovascular patients in the ONTARGET trial as they probably had diseased intrarenal vessels (ischaemic renal disease) [5,14]. In fact, the degree of blockade of the RAS system may differ between systemic and renal levels. In Wistar rats on a low-salt diet, the combined administration of captopril and losartan reduced arterial pressure, GFR and plasma levels of angiotensin II (Ang II) similarly to captopril alone, whereas combining the ACEI and ARB reduced kidney Ang II more than higher doses of either agent alone [15]. Thus, the capacity for renal autoregulation may be severely altered in individuals receiving combined blockade.

These results remind us that renal function monitoring is essential in patients treated with ACEI, ARB or both, as well as in older patients receiving diuretics.

4. Nephroprotection: do ACEI and ARB have different properties?

The change in renal function was significantly faster in the telmisartan group (−4.1 mL/min/1.73 m²) than in the ramipril group (−2.8 mL/min/1.73 m²) in the ONTARGET trial. However, this finding did not translate into more chronic dialysis or doubling of serum creatinine with telmisartan vs ramipril. Again, there were few hard renal endpoints in the trial [5].

The apparent discrepancy between small changes in eGFR and the similar incidence of ESRD has already been noted in other trials in which hypertensive patients with normal or subnormal renal function were involved. In the ALLHAT study, eGFR was 3–6 mL/min/1.73 m² higher during the follow-up of patients
receiving amlodipine or lisinopril compared with chlorthalidone [16]. However, no significant differences were noted across the three groups of patients (including those with diabetes) in the development of ESRD, regardless of baseline eGFR [16]. Interestingly, there were more ESRD events in the ALLHAT study ([448/33,357 patients; 1.3%], including 268/12,063 diabetic patients [2.2%] during the 6-year follow-up) than in the ONTARGET trial [98/25,620 (0.4%) during the 4.5-year follow-up].

In the DETAIL study of diabetic patients with normal renal function (GFR: 91–94 mL/min/1.73 m²) who were taking either enalapril or telmisartan, there were no meaningful differences in GFR during the 4-year follow-up [17]. More recently, telmisartan (80 mg/day) was associated with a greater reduction in urinary albumin-to-creatinine ratio than was losartan (100 mg/day), despite a similar arterial pressure in diabetic patients followed-up for 52 weeks [18]. Finally, in the ROAD study, there was no difference in either doubling of serum creatinine or ESRD with either benazepril or losartan (using either conventional dosages or after up-titration) during follow-up (median: 3.7 years) in nondiabetic subjects [19].

These findings suggest that:

- small in-trial changes in eGFR observed with antihypertensive medications do not necessarily translate to meaningful differences in nephroprotection, especially when the risk of ESRD is considerably lower than either the risk of death or study–medication discontinuation;
- among and between the ACEI and ARB classes of medications, some may be more nephroprotective than others but, so far, this has not been proven as hard endpoints are lacking in published trials.

5. What is the optimal dosage for ACEI or ARB?

Recently, the concept of an ‘ultradose’ was presented in several reports. The results of IRMA2 indicated that a reduction in UAE was more effective with irbesartan at 300 mg/day than at 150 mg/day [20]. Later, when much higher doses of ARB were tested, it was found that candesartan and irbesartan at higher dosages were associated with greater UAE reductions in diabetic patients [21,22]. However, from a renal point of view, the optimal dose of ARB (or ACEI) may differ from one patient to another: some may need much higher dosages of ACEI or ARB to reduce proteinuria than do others. This idea was tested in the ROAD study in nondiabetic Chinese subjects, which found that doubling of serum creatinine or ESRD was 40% lower in those receiving benazepril or losartan after up-titration than in those receiving benazepril or losartan at conventional dosages [19].

Thus, it may be concluded that the dosage of the ACEI or ARB is a crucial parameter: using high-dose ARB or ACEI may be beneficial to some patients. However, this needs to be tested on an individual basis in diabetic patients with proteinuria.

6. Is urinary albumin excretion a surrogate marker of chronic renal failure?

In the ONTARGET trial, the increase in urinary albumin/creatinine ratio (UACR, 0.82 mg/mmol on average at baseline) appeared blunted in the telmisartan–ramipril group (ratio to baseline: 1.21) than in either the telmisartan (ratio to baseline: 1.24) or ramipril (ratio to baseline: 1.31) group — and yet, the combination blockade group had the poorest renal function outcome [5]. These results are in marked contrast to the findings reported in nondiabetic African-Americans with nephrosclerosis from the AASK study [23] and in type 2 diabetic patients from the RENAL study [24]: in both these studies, the reduction of albuminuria/proteinuria was associated with better renal outcomes (doubling of serum creatinine and ESRD) [23,24].

For this reason, it is important to assess the relationship between baseline proteinuria or albuminuria and subsequent ESRD or doubling of serum creatinine in the ONTARGET study [5]. It would also be of interest to assess whether or not baseline UAE was predictive of diabetes in the nondiabetics in the study, as this finding has been observed in the general population and in renal-transplant recipients [25,26].

Albuminuria is a widely accepted marker of cardiovascular risk and predictor of renal insufficiency in diabetes (more so in type 1 than in type 2) [27]. It also remains a useful surrogate marker for assessing the risk of subsequent renal degradation and for comparing the benefit of medications to renal protection [27]. However, albuminuria does not predict acute renal dysfunction triggered by hypovolaemia and/or excessively low arterial pressure.

Proteinuria has been suggested as a marker of, and factor in, the progression of chronic kidney disease [28]. However, a recent meeting of the US Food and Drug Administration was reluctant to accept both albuminuria and proteinuria as valid surrogates of renal disease [29].

7. What can we do in daily practice for diabetic patients?

Maintaining strict blood pressure control is still recommended in patients with diabetes: strict vs less strict arterial blood pressure (144/82 vs 154/87 mmHg) was associated with lower incidences of stroke, heart failure, diabetes-related death and retinal panphotocoagulation (but not with significantly reduced rates of micro- or macroalbuminuria, or significant differences in serum creatinine, after nine years of follow-up) in the UKPDS [30]. In the ADVANCE study, reduction of blood pressure from 140/73 mmHg (control group) to 136/73 mmHg (indapamide–perindopril group) was associated with reduced risks of a major macro- or microvascular (mostly new microalbuminuria) event, death from cardiovascular disease and death from any cause, after 4.3 years of follow-up, thus extending the early findings of the UKPDS to even lower levels of blood pressure [31]. Thus, reducing blood pressure to less than 130/80 mmHg appears to be reasonable in type 2 diabetics, although there is no compelling evidence to support further reduction to lower blood pressure values.

In patients with diabetes and excessive albuminuria, treatment of high blood pressure should include an RAS blocker, usually with a diuretic. In the absence of any compelling indication, the third medication should be a calcium-channel blocker,
which is mainly effective for reducing blood pressure (and much less effective for reducing albuminuria), whereas diuretics offer additional effects on UAE when used in combination with RAS blockers [32–34]. However, combination RAS blockade should not be used in diabetic patients with microalbuminuria (UAE < 300 mg/day), as its effect on UAE and blood pressure is weak compared with RAS monotherapy [35–37].

On the other hand, although the scientific credibility of the Nakao et al. [3] results has been seriously questioned [38], it does not necessarily follow that ACEI–ARB blockade should never be used in diabetic patients with massive proteinuria: in such patients, aggressive early management — usually including several antihypertensive medications, in addition to sodium intake reduction and weight reduction in obese patients — is warranted. ACEI or ARB should primarily be used and the dosage increased to obtain an optimal proteinuric response. Diuretics may also help to decrease arterial pressure and proteinuria. ACEI–ARB blockade should probably be decided upon by the nephrologist, and restricted to only those patients with massive proteinuria despite the use of maximum dosages of ACEI or ARB. In such patients, close monitoring of renal function is needed, and the treatment should be temporarily withdrawn in the event of volume depletion and/or low blood pressure.

The cardiovascular and renal benefits of intensive glucose control (and the correct way to achieve it) remain controversial. In the ADVANCE study, intensive therapy (HbA1c 6.5% vs 7.3% with standard therapy) resulted in a lower risk of microalbuminuria, but no change in the incidence of retinopathy [39]. However, the ACCORD trial ended its intensive therapy early — after 3.5 years — because of a significant increase in the rate of deaths in the intensive-therapy group (HbA1c 6.4% vs 7.5% in the standard-therapy group) [40], while the VADT study showed no significant effects on the rates of major cardiovascular events, deaths or microvascular complications with intensive glucose control (HbA1c 6.9% vs 8.4% with standard therapy) in patients with poorly controlled type 2 diabetes [41]; the effect on proteinuria was of borderline significance [41].

8. Perspectives for the future

The ONTARGET results cannot be extrapolated to other dual RAS–blockade combinations. The nephroprotective properties of ACEI, ARB and the renin inhibitor aliskiren [42,43] — used alone or in combinations — have to be compared in populations with identified renal disease, particularly those with proteinuric diabetic nephropathy. Such trials should also use hard renal endpoints (ESRD). Nevertheless, the proper use of UAE should not be abandoned, despite the fact that it does not help to predict haemodynamically mediated acute renal dysfunction.

Whether or not other agents, such as sulodexide (a glycosaminoglycan that may reduce proteinuria by acting on the glomerular basement membrane), calcitriol or vitamin D analogues such as paricalcitol, can provide additional nephroprotection is currently unknown, and needs to be tested in future studies [44–46].

Early reports support the idea that prorenin might be involved in diabetic complications [47]; however, a strong scientific basis is still lacking. Nevertheless, over the past five years, a number of new, fascinating and sometimes conflicting results have been published on the putative effects of prorenin and the (pro)renin receptor, and their involvement in the pathogenesis of diabetic nephropathy and retinopathy [48–50]. If this turns out to be true, it will drastically modify our current understanding and management of diabetes complications in the future [48–50].

9. Conflicts of interest

None.

References


