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Dual blockade of the renin–angiotensin system: are two better than one?

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The beneficial effects of blood pressure-lowering treatments on the risks of major cardiovascular events are well established [1]. Interruption of the renin–angiotensin system (RAS) with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) has been shown to be an effective strategy for lowering blood pressure. Randomized trials have shown that ACEi can lower blood pressure by an average of 5/2 mmHg and reduce the risks of cardiovascular events and cardiovascular mortality by ∼20% (and total mortality by 10%) [2–6]. ARBs produce similar reductions in blood pressure and vascular events (although fewer patients have received them in randomized trials) [7–9].

Further, RAS blockade has been reliably shown to reduce the risk of kidney disease progression [10–15]. A meta-analysis of ACEi and ARB monotherapy in diabetic nephropathy demonstrated reductions in end-stage renal disease (ESRD) of around one-quarter for both treatments [16]. Similarly, an individual patient data meta-analysis of ACEi in non-diabetic kidney disease showed a relative risk reduction of 31% (95% CI 5–49%). The major trials of ACEi or ARB monotherapy in various patient populations are summarized in Table 1. As shown in Table 1, among patients at a low risk of renal progression ESRD occurs rarely, and only after many years or even decades. This probably explains the lack of renal benefit reported in large general population trials and meta-analyses of such trials [17–19]. Furthermore, there is some evidence that even the relative benefit might depend on baseline risk, making it even less likely that any true benefit could be detected in existing trials [10].

Whether the observed benefits of RAS blockade are only mediated by their blood pressure-lowering effect or whether other effects also play a role remains controversial; there is some evidence that interruption of the RAS provides more benefit than would simply be expected by the degree of blood pressure reduction alone [5,7,20]. It has been suggested that incomplete blockade of the RAS with ACEi or ARB monotherapy can cause a phenomenon called 'aldosterone escape', in which the lack of negative feedback from end-products of the RAS causes a reactive increase in renin and consequent increases in angiotensin I and II concentrations which overwhelm the pharmacological blockade [21]. Dual blockade would therefore be attractive as ACEi and ARB inhibit the RAS at different steps. However, there is continuing uncertainty about the balance of benefits and harms of dual RAS blockade, both in terms of cardiovascular risk and progression of kidney disease. This question will be discussed here in the context of recent evidence from randomized controlled trials.

Dual renin–angiotensin system blockade and cardiovascular risk

The combination of ACEi and ARB has been studied in a number of clinical scenarios.

Hypertension

In patients with hypertension, a systematic review of 14 randomized trials showed that the combination can reduce blood pressure by 4.7/3.0 mmHg compared to ACEi monotherapy and by 3.8/2.9 mmHg compared to ARB monotherapy. Most studies used submaximal doses or once-daily doses of short-acting ACEi. In trials using maximal doses or longer-acting ACEi, there was no additional reduction in blood pressure with dual RAS blockade [22].

Left ventricular systolic dysfunction

A meta-analysis of seven trials of dual RAS blockade versus ACE inhibitor alone in patients with heart failure and reduced ejection fraction showed a 23% reduction (95% CI 13–31%) in admission for heart failure, but no effect on total mortality [23].

Table 1. Major trials of ACEi or ARB monotherapy in progression of kidney disease

Trial	Selection criteria (sample size)	RAS blockade agent and dose	Background renal risk[a]	Relative risk ratio[b] (95% CI)
ALLHAT [17]	Hypertension with ≥1 other coronary heart disease risk factor (31 897)	Lisinopril 40 mg	0.7% (chlorthalidone arm)	1.03 (0.89–1.20) versus chlorthalidone
TRANSCEND [18]	Known cardiovascular disease or diabetes (5926)	Telmisartan 80 mg	0.3%	1.29 (0.87–1.89)
Maschio *et al.* [41]	Serum creatinine 133–354 μmol/L and eGFR 30–60 mL/min (562)	Benazepril 10 mg	6.7%	0.44 (0.27–0.70)
AASK [15]	African American GFR 20–65 mL/min (1094)	Ramipril 10 mg	5.9% (amlodipine arm)	0.62 (0.44–0.87) versus amlodipine
REIN [14,42]	Non-diabetic; GFR 20–70 mL/min and ≥1 g/day proteinuria (323)	Ramipril 1.25–5 mg	4.1% (ESRD only)	0.47 (0.29 – 0.77)
ISDN [12]	Diabetic nephropathy (type 2 DM) (1715)	Irbesartan 300 mg	7.1% (ESRD only)	0.77 (0.57–1.03) (ESRD only)
RENAAL [11]	Diabetic nephropathy (type 2 DM) (1513)	Losartan 100 mg	13.2%	0.79 (0.66–0.95)
Lewis *et al.* [13]	Diabetic nephropathy (type 1 DM) with creatinine ≤221 μmol/L and proteinuria ≥0.5 g/day (409)	Captopril 25 mg tds	7.1% (doubling only)	0.52 (0.31–0.84) (doubling only)

[a]Annual risk of dialysis or doubling of serum creatinine (except where stated otherwise) in control arm.
[b] Relative risk ratio for dialysis or doubling of serum creatinine (except where stated otherwise) associated with single RAS blockade.

Atherosclerotic disease

Dual RAS blockade has been tested in patients with acute myocardial infarction (MI). The Valsartan in Acute Myocardial Infarction (VALIANT) study compared combination captopril and valsartan with either agent alone in patients within 10 days of acute MI [24]. Blood pressure was 2/1 mmHg lower in the combination group compared to the captopril group. However, after a median follow-up of 2 years, there were no significant differences between treatment groups with regard to the primary outcome measure of death from any cause [hazard ratio (HR) in the combination group as compared with the captopril group, 0.98; 97.5% confidence interval (CI) 0.89–1.09], or in multiple secondary outcomes involving various combinations of death from cardiovascular events. However, more patients receiving combination therapy reduced or discontinued their study treatment because of hypotension or an adverse renal effect (a broad definition that included rise in creatinine to acute renal failure).

Recently, dual RAS blockade has been tested in patients at a high risk of cardiovascular events [9]. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) compared the combination of ramipril (10 mg daily) and telmisartan (80 mg daily) with either agent alone. Despite a 2.4/1.4 mmHg lower blood pressure in the combination group (compared to ramipril), there was no reduction in the composite primary outcome of death from cardiovascular causes, MI, stroke or hospitalization for heart failure (relative risk 1.01; 95% CI 0.94–1.09). As in VALIANT, more patients stopped combination treatment due to hypotension and renal causes during ONTARGET. (Incidentally, more people in the combination therapy group also stopped treatment due to diarrhoea.)

The lack of significant reductions in vascular events observed in VALIANT and ONTARGET may not be as conclusive as first appears. From the other 'more-intensive versus less-intensive' blood pressure-lowering trials, one would expect that the modest blood pressure reduction achieved in these trials (∼2/1 mmHg) would have led to <10% reduction in the risk of cardiovascular events (which is consistent with the 95% confidence interval observed).

Therefore, in terms of cardiovascular protection, dual RAS inhibition may be of modest additional benefit, as compared to either drug alone. In patients at a high risk of cardiovascular disease the absolute benefit is greatest, but in lower risk settings (including secondary prevention of vascular disease) any benefits are much less certain and may not exceed the potential harm (see below).

Dual renin–angiotensin system blockade and progression of kidney disease

Proteinuria is a useful prognostic marker in renal disease and may be a target of therapy independent of blood pressure [25]. Dual RAS blockade reduces proteinuria more than ACEi or ARB monotherapy alone. A meta-analysis of 49 studies showed that dual RAS blockade reduced proteinuria by 25% (95% CI 8–39%) compared with ARB alone and by 22% (95% CI 16–28%) compared with ACEi alone [26]. It remains unclear whether proteinuria is a valid surrogate outcome in the progression of kidney disease [27]. One small and controversial trial of dual RAS blockade versus either monotherapy in patients with non-diabetic kidney disease suggested that there was a dramatic reduction in the risk of end-stage renal disease with dual RAS blockade [28]. The composite endpoint of death, dialysis or doubling of creatinine were reported to be reduced by 62% (95% CI 37–82%) in patients on dual RAS blockade compared to ACEi alone and by 60% (95% CI 31–83%) compared to ARB alone. However, not only was this trial

Table 2. Renal outcomes from the ONTARGET study [32]

	Ramipril ($n = 8576$)	Telmisartan ($n = 8542$)	Combination ($n = 8502$)	Combination versus ramipril HR (95% CI)	*P*-value
All dialysis, doubling of creatinine, death	1150 (13.4%)	1147 (13.4%)	1233 (14.5%)	1.09 (1.01–1.18)	0.04
All dialysis, doubling of creatinine	174 (2.03%)	189 (2.21%)	212 (2.49%)	1.24 (1.01–1.51)	0.04
Death	1014 (11.8%)	989 (11.6%)	1065 (12.5%)	1.07 (0.98–1.16)	0.14
Doubling of creatinine	140 (1.63%)	155 (1.81%)	166 (1.95%)	1.20 (0.96–1.50)	0.11
All dialysis	48 (0.56%)	51 (0.60%)	63 (0.74%)	1.33 (0.92–1.94)	0.13
Acute dialysis	13 (0.15%)	20 (0.23%)	28 (0.33%)	2.19 (1.33–4.22)	0.02
Chronic dialysis	33 (0.39%)	31 (0.36%)	34 (0.40%)	0.94 (0.58–1.54)	0.85
Doubling of creatinine or chronic dialysis	160 (1.87%)	172 (2.01%)	185 (2.18%)	Not stated	0.14

small (there were only 50 events), but it has since been criticized for an implausible balance in baseline characteristics casting substantial doubt over the reliability of the conclusions [29]. Therefore, whether the reduction in proteinuria (independent of any additional reduction in blood pressure) associated with dual RAS blockade retards the progression of kidney disease remains uncertain.

Diabetic nephropathy is the proteinuric nephropathy in which ACEi were first found to be reduce renal progression [13]. A meta-analysis of 10 small trials of dual RAS blockade found a modest reduction in proteinuria of 177 mg/day (95% CI 35–319 mg/day) [30], but there was no benefit observed in the trials which used maximal dose ACEi as the comparator. Similar results have been found in more recent larger trials [31]. However, no long-term studies with hard renal outcomes have been reported.

The ONTARGET investigators recently published the results of prespecified analyses of the effects of dual RAS blockade on renal outcomes (see Table 2) [32]. Notably, of the 3691 'renal' outcomes recorded, 3068 (87%) were due to death (from any cause), while only 162 (5%) were due to dialysis [of which 61 (38%) were due to acute dialysis] and 461 (13%) were due to doubling of creatinine. A high proportion (almost 60%) of deaths were due to cardiovascular disease.

The risk of acute dialysis was doubled in patients receiving dual RAS blockade (HR 2.19; 95% CI 1.33–4.22; $P = 0.02$). This is probably due to haemodynamic consequences of dual RAS blockade, especially in patients with known vascular disease who may have had clinically occult critical renal artery disease. It may also be that patients receiving dual blockade were more prone to hypotensive kidney injury (e.g. during sepsis or hypovolaemia) because of impaired autoregulation of intrarenal haemodynamics.

In contrast, doubling of creatinine and chronic dialysis probably reflect renal progression. There was no difference in the incidence of chronic dialysis, and the larger numbers of patients receiving combination therapy who doubled their serum creatinine (166 versus 140 patients) could be explained by chance alone (hazard ratio 1.20; 95% CI 0.96–1.50; $P = 0.11$). Within ONTARGET, 75% of participants had an eGFR >60 mL/min/1.73 m^2 and 83% had <30 mg/day albuminuria in the population. There was some evidence that dual RAS blockade in the group of patients at perhaps the lowest risk of renal progression (without diabetes or hypertension) tended to be harmful ($P = 0.019$ for interaction, but this is of questionable significance given the number of such tests performed). There was no evidence of benefit in patients with diabetic nephropathy ($P = 0.346$ for interaction) whose risk of progression was highest. Overall, the risk of renal progression was very low with an average decline in renal function of <1 mL/min/1.73 m^2/year observed during the study. ONTARGET was therefore underpowered to detect any long-term benefit or harms in terms of renal progression, because although a large number of patients were included, only very few progressed to end-stage renal disease.

In order for studies to detect a reduction in the risk of renal progression, participants must have conditions with a clinically significant rate of deteriorating renal function. This is especially important for trials of therapies such as ACEi or ARB which cause an acute decline in GFR when first introduced [33]. For a RAS inhibitor to retard long-term progression, it must slow progression sufficiently to compensate for this initial decline, as illustrated in Figure 1 [34]. In this figure, the low-risk patients are modelled on the ONTARGET population with the known rate of renal progression (∼0.5 mL/min/1.73 m^2/year) and initial decrement in GFR (∼3.5%). The virtually parallel curves illustrate that, in a low-risk population, even if dual RAS blockade were to reduce the risk of renal progression by 20% (e.g. from 0.5 mL/min/1.73 m^2/year to 0.4 mL/min/1.73 m^2/year), the hazards (acute deterioration in kidney function) may outweigh the benefits (long-term retardation of renal progression).

The high-risk curves are modelled on the participants observed in the RENAAL and IDNT studies [11,35]. In Figure 1, a 5% reduction in GFR following initial introduction of each RAS inhibitor is assumed. In RENAAL and IDNT, renal function declined at ∼5 mL/min/1.73 m^2/year in the control groups, and this rate was ∼20% slower (i.e. 4 mL/min/1.73 m^2/year vs. 5 mL/min/1.73 m^2/year) among those randomized to receive ARB. In such a population with more rapid renal progression, a similar early adverse effect on GFR with dual RAS blockade may be mitigated by a 20% reduction in the rate of renal progression, leading to an improved outcome in the dual RAS blockade group after ∼3 years. The ONTARGET study has demonstrated

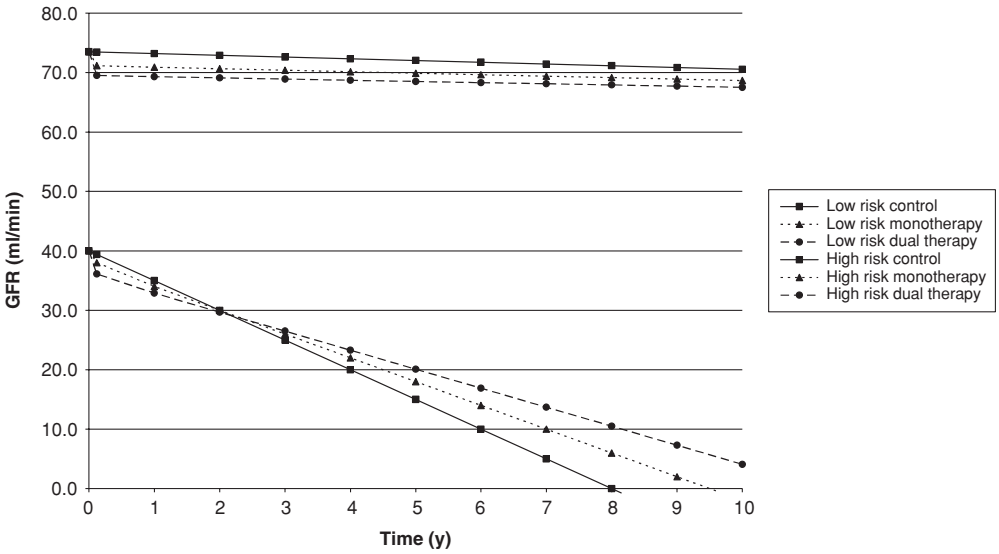

Fig. 1. Renal function over time for patients at low- and high-risk of renal progression treated with single or dual RAS blockade. In all patient groups, the introduction of dual RAS blockade produces an initial decrement in glomerular filtration rate (GFR). In populations at a low risk of renal progression (such as the ONTARGET population), the size of any subsequent reduction in the rate of renal progression is unlikely to be sufficient to compensate for the initial decrement in GFR. By contrast, in populations at a high risk of renal progression (such as in RENAAL or IDNT populations), dual RAS blockade may produce a more substantial impact on the rate of renal progession, so that after 3–4 years, those treated with dual RAS blockade are less likely to reach end-stage renal disease. This hypothesis has not been adequately tested in large-scale randomized clinical trials.

the hazards of dual RAS blockade among patients with cardiovascular disease, but without progressive CKD. It was not designed to examine any long-term benefits or harms in patients at a high risk of renal disease (as very few were included). A study of dual RAS blockade among patients with progressive CKD is required to examine this issue. However, such a study must be in a population at a high risk of renal progression and must be sufficiently large and sufficiently long to assess any impact on renal outcomes reliably.

Should nephrologists use dual RAS blockade?

After diagnosis, the priorities in the management of chronic kidney disease are to prevent cardiovascular events, retard progression, manage metabolic complications, and prepare patients for renal replacement therapy (if indicated). The current evidence suggests that dual RAS blockade may be a treatment with significant benefits and risks. Therefore, understanding the baseline risk of the patient for various outcomes (cardiovascular and renal events) is crucial. In terms of cardiovascular protection, dual RAS blockade might have modest benefit in patients at a high risk of cardiovascular disease (e.g. those with known impaired left ventricular systolic dysfunction), but this would need to be balanced against the risk of hyperkalaemia and acute-on-chronic renal failure. In terms of renal protection, dual RAS blockade is unlikely to be of benefit in patients at a low risk of renal progression, but it remains possible that dual RAS blockade might retard the progression of kidney disease in patients at higher risk. The efficacy and safety of this strategy remains unproven.

The decision about whether to initiate dual RAS blockade for an individual patient, therefore, requires careful assessment of their risks of renal progression, of cardiovascular events and of acute complications of dual RAS therapy. Until further results are available, it would seem prudent to reserve dual RAS blockade for patients who are at an increased risk of renal progression, such as those with significant proteinuria or with evidence of deteriorating renal function despite monotherapy. Additionally, as the cardiovascular risk increases, so does the potential for cardiovascular benefit that may lower the threshold for the introduction of dual RAS blockade. A possible schema for making such decisions is shown in Figure 2.

The initiation of dual blockade is likely to cause an acute reduction in GFR due to reduction in intraglomerular pressure just as starting ACEi or ARB monotherapy does [34]. Given the concerns raised by ONTARGET, it would be important to monitor such patients closely for potential hazards of such treatment (including acute-on-chronic renal failure and/or hyperkalaemia) [36]. If the reduction in GFR is not progressive, however, it would be reasonable to continue such treatment, especially if it reduces blood pressure or perhaps proteinuria. Close monitoring is also indicated if the patient is receiving other medications that may increase the risks of acute-on-chronic renal failure and/or hyperkalaemia (e.g. aldosterone antagonists, non-steroidal anti-inflammatory drugs or beta-blockers). Should a patient receiving dual RAS blockade be at a risk of hypovolaemia (e.g. following diarrhoea), then he or she should be advised to stop his or her dual RAS blockade until the intercurrent illness resolves.

Not for the first time, nephrologists are practising in the absence of evidence: two trials, each of which plan to recuit more than 1000 patients, are currently investigating dual

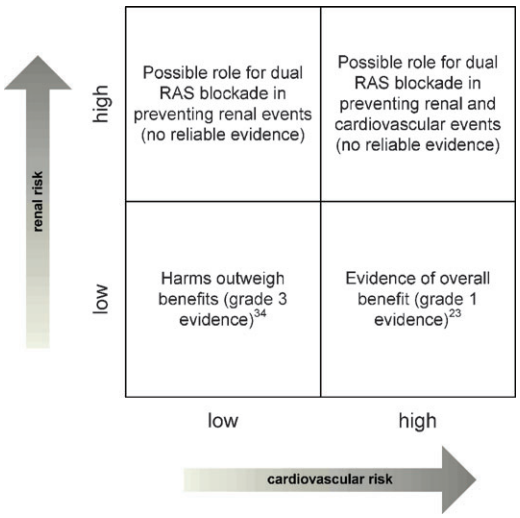

Fig. 2. Schema for decision making about the use of dual RAS blockade in various patient groups. Patients are categorized according to their cardiovascular and renal risk. Low cardiovascular risk refers to primary prevention and ONTARGET populations and high cardiovascular risk to heart failure with reduced ejection fraction populations. Renal risk can be determined from eGFR, urinary protein excretion and underlying renal disease. Evidence (where available) is graded according to Sackett's hierarchy of evidence [43].

RAS blockade in patients with diabetic nephropathy (VA NEPHRON-D [NCT00494815]) [37] and in patients with polycystic kidney disease (HALT PKD [NCT00283686]). Given the issues described above, it is not clear if these trials will be large enough to provide a reliable answer. Aldosterone antagonism [38] and direct renin inhibition [39] offer alternative strategies to block the RAS at more than one step and the latter approach is currently being tested in a large-scale randomized trial (NCT00549757) [40]. Further adequately sized trials in patients with progressive kidney disease with meaningful clinical endpoints are required to provide robust answers for clinicians and patients.

Conflict of interest statement. None declared.

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Role of podocytes in lupus nephritis

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Much attention has been focused on the complex pathology of lupus nephritis (LN) in an attempt to develop specific therapies targeted to this serious manifestation of systemic lupus erythematosus (SLE). The classification of LN depends on the findings at histology according to the International Society of Nephrology (INS) and Renal Pathology Section (RPS) classification criteria [1] and involves deposition of immunoglobulin in glomerular and tubular basement membrane-enhanced inflammatory response and renal fibrosis [2]. Clinically, proteinuria and haematuria are characteristic features in patients with LN and have traditionally been thought to be the result of immune complex deposition and endocapillary proliferation causing a disruption to the filtration barrier. However, in a subset of proteinuric lupus patients, there is no evidence of the typical immune complexes and instead there appears to be extensive podocyte effacement [3]. The effacement of the foot processes as result from podocyte injury has been associated with the development of proteinuria and the nephrotic syndrome. In addition, podocytes have been identified in the population of cells comprising crescentic forms of LN. This