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RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM BLOCKADE IN HYPERTENSIVE PATIENTS WITH CHRONIC KIDNEY DISEASE

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Introduction

Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are recommended as first-line therapy for hypertension in patients with chronic kidney disease (CKD). The relevant evidence extends from background studies showing that blood pressure (BP) reduction with agents that block the renin–angiotensin–aldosterone system (RAAS) yielded greater structural and functional preservation of the kidney to major outcome trials showing that these agents slow CKD progression more effectively than other antihypertensive drugs [1]. However, studies in populations with less advanced nephropathy [2, 3] showed that RAAS-blockers confer no additional benefit compared to other agents and combined RAAS inhibition to increase the risk of acute renal failure [4]. In this report we discuss evidence from trials with hard renal end-points attempting to clarify the value of RAAS blockade for different types of hypertensive patients with CKD.

RAAS blockade in proteinuric kidney disease

The first major trial on the renoprotective effects of RAAS-blockers, that of the Collaborative Study Group, randomized 409 patients with type 1 diabetes and overt nephropathy (protein excretion > 0.5 g/day, serum creatinine [SCr] ≤ 2.5 mg/dL) to captopril or placebo [5]; captopril showed 43% reduction in the risk of doubling of SCr, 50% reduction in the combined end-point of death, need for dialysis or transplantation, and 30% reduction in albuminuria. In 1513 patients with type 2 diabetes, hypertension and macroalbuminuria (mean SCr 1.9 mg/dL, median albumin-to-creatinine ratio [ACR] 1.2 g/g), the RENAAL study showed that losartan reduced the primary endpoint of doubling of SCr, ESRD or death by 16%, and albuminuria by 35% [6], compared to placebo, with the two groups achieving similar levels of BP control. Similarly, in the IDNT study in 1715 type 2 diabetic hypertensive patients (mean SCr 1.7 mg/dl and proteinuria 2.9 g/day), treatment with irbesartan resulted in 20% reduction compared to placebo and 23% reduction compared to amlodipine in doubling of SCr, progression to ESRD or death; proteinuria decreased by 33% in the irbesartan group versus 6% in the amlodipine group and 10% in the placebo group [7].

Studies in non-diabetic proteinuric kidney disease also support the use of RAAS-blockade to preserve renal function. In the REIN study, including patients with mean SCr of 2.4 mg/dL and proteinuria > 3 g/day, ramipril was associated with significant reductions in proteinuria, GFR decline, and the risk of doubling of SCr or ESRD compared to placebo, even after adjustment for changes in systolic and diastolic BP [8]. In the AASK trial, 1094 African-Americans with hypertensive renal disease, mean SCr of 2.2 mg/dL and proteinuria of 0.6 g/day were randomized to ramipril, amlodipine or metoprolol. Patients treated with ramipril had a 36% reduction in the composite outcome of 50% decrease of GFR, ESRD or death compared to amlodipine, and 22% reduction compared to metoprolol [9]. In 224 patients with more advanced renal disease (SCr 3.1–5.0 mg/dl and proteinuria 1.6 g/day) [10] use of benazepril was associated with a 43% reduction in the risk of doubling of SCr, ESRD, or death, 23% decrease in the rate of renal function decline and 2.5 times greater reduction in proteinuria, compared to placebo; benefits that did not seem attributable to better BP control.

Secondary analyses of the above studies have exemplified the role of proteinuria for CKD progression, as well as the value of RAAS-blockade in proteinuric renal disease. On one-hand they showed a direct association between baseline proteinuria and the risk of the primary outcome; on the other, the renoprotective effect of RAAS blockers was proportionate to the degree of proteinuria reduction in the first months of follow-up [11, 12]. The stage of kidney disease seems also important in determining benefit from RAAS-blockade. In the Collaborative Study patients with baseline SCr > 2.0 mg/dL derived the greatest benefit from captopril, i.e. a 74% reduction in the risk of doubling of SCr compared with the placebo group, whereas only a 4% reduction in this endpoint was seen with captopril in patients with SCr < 1.0 mg/dL [5]. Meta-analytic data in non-diabetic patients also support that RAAS-blockers provide better renoprotection in individuals with heavier proteinuria whereas in those with protein excretion < 0.5 g/day they have no additional benefit compared with other antihypertensive classes [13]. There are also no outcome data to support any difference in renoprotection between ACEIs and ARBs. The DETAIL study, which compared the effects of enalapril and telmisartan in 250 patients with Type 2 diabetes, hypertension and albuminuria between 11 and 999 μg/min, showed the two agents to have had similar effects on the change in GFR, serum creatinine level, albuminuria and the rates of ESRD and mortality [14].

RAAS blockade in early or non-proteinuric kidney disease

Although the beneficial actions of RAAS blockers in patients with proteinuria or kidney diseases with established natural course (i.e. diabetic nephropathy) are based on solid background and clinical evidence, the effects of these agents on hypertensive subjects with early stages of CKD or those with reduced renal function in the absence of proteinuria have not been specifically investigated. This issue is of major clinical importance as, with the existing CKD definition, 40% of the adult population aged > 70 years have eGFR < 60 ml/min/1.73 m^2, but only 5% have macroalbuminuria; among hypertensive patients, around 15% have eGFR < 60 ml/min/1.73 m^2 (going up to 30% among those > 65 years) but again less than 5% have macroalbuminuria [15, 16].

The first challenge to the renoprotective action of ACEIs and ARBs came from a meta-analysis suggesting that any evidence of renoprotection from these drugs derived from placebo-controlled studies (where important BP differences favouring the active treatment were noted) whereas studies comparing active treatments showed no differences in patients with diabetic nephropathy and small BP-independent benefits in patients with non-diabetic nephropathy [17]. This meta-analysis faced severe criticism for several methodological issues, most importantly the obvious mix-up of populations at different ends of the CKD spectrum [1, 18]. Indeed, the results of this analysis were weak to controvert the clear findings of outcome studies of RAAS-blockade in proteinuric kidney disease; however, they helped to raise attention to the issue of renoprotection in early stages of CKD. A subsequent systematic review questioned the relevance of guidelines on the use of ACEIs and ARBs towards renoprotection to elderly patients with reduced eGFR, as three quarters of the studies on which the guidelines were based did not include patients > 70 years of age, and only one (the ALLHAT trial) included an important proportion of elderly subjects [16].

The ABCD trial [2] included a population of early CKD, i.e. 470 hypertensive subjects with type 2 diabetes with baseline creatinine clearance about 85 ml/min/1.73 m^2, of which only 18% had microalbuminuria. Participants were randomized to nisoldipine or enalapril and intensive or moderate BP control in a 2 × 2 design. There was no difference in creatinine clearance between the two drug groups over 5.3 years of follow-up although enalapril significantly lowered UAE. However, the most definite end-point of ESRD incidence was not recorded and it is not known whether a longer follow-up would have yielded different results.

In recent years, data on renoprotection in populations with low-risk for renal disease progression from secondary analyses of cardiovascular trials in hypertension have also been made available. The ALLHAT trial randomised more than 33,000 patients with hypertension and at least one more cardiovascular risk factor to chlorthalidone, amlodipine and lisinopril with a primary cardiovascular outcome. Following exclusion criteria of SCr > 2.0 mg/dL and treatment with an ACE-inhibitor for underlying kidney disease, the average eGFR was at 78 ml/min/1.73 m^2 and mean age was 67 years. Measurements of urine protein did not take place, but patients with proteinuria would have been a minority. At the end of the study, eGFR was significantly higher in amlodipine than chlorthalidone, and lisinopril groups (75 versus 70 and 71 ml/min/1.73 m^2, respectively). In addition, in post-hoc analyses there were no differences in the incidence of ESRD or a 50% or greater decrement in GFR between the 3 groups in the total cohort and in patients with mild (60–89 mL/min/1.73 m^2) or moderate-severe (< 60 mL/min/1.73 m^2) reduction of baseline GFR [3]. The authors of ALLHAT commented on the results suggesting that participants with decreased renal function were mostly patients with ischaemic renal disease, for whom an overwhelming renoprotective effect of ACE-inhibitors is generally not expected.

The renal outcomes of the ACCOMPLISH trial further support the above [19]. This study randomized 11,506 patients with hypertension and high cardiovascular risk to benazepril plus amlodipine or benazepril plus hydrochlorothiazide, and was terminated early due to evidence of benefit of the former in the primary cardiovascular outcome. Of the participants, 85% were > 65 years of age, 60% were diabetic, mean eGFR was at 79 mL/min/1.73 m^2 and baseline micro- and macroalbuminuria were at 19% and 5% of the population, respectively. The benazepril & amlodipine group had a slower eGFR decline (–0.88 versus –4.22 mL/min/1.73 m^2 per year) and a 48% reduction in the incidence of doubling of SCr, eGFR < 15 mL/min/1.73 m^2 and dialysis compared to benazepril & hydrochlorothiazide, although it reduced ACR less effectively [19]. The results of ALLHAT and ACCOMPLISH are in contrast with the aforementioned findings of the IDNT study, where amlodipine accelerated renal function decline [7]; it is easy to postulate, however, that this is directly related to the different populations under study. Better preservation of renal function with a dihydropiridine calcium antagonist than an RAS blocker or a thiazide is reasonable in study populations with mean age > 65 years, mean eGFR well above 60 ml/min/1.73 m^2 and low prevalence of macroalbuminuria.

Combined RAAS blockade

In the absence of specific therapies for advanced nephropathy, aggressive RAAS blockade was suggested to be even more beneficial towards renoprotection [1]. Short-term controlled studies in patients with proteinuric nephropathy showed that use of a single RAAS-blocker in ultra-high dose (i.e. 2–3 times the

Table 1. Preferred first-line agents for hypertensive patients with CKD based on available evidence from renal and cardiovascular trials

Type of kidney disease	Normoalbuminuria (< 30 mg/day or ACR < 30 mg/g)	Microalbuminuria (30–300 mg/day or ACR 30–300 mg/g)	Macroalbuminuria (> 300 mg/day or ACR > 300 mg/g) *or* clinical proteinuria (> 0.5 g/day)
Non-diabetic kidney disease	None preferred	None preferred	ACEI or ARB*
Diabetic kidney disease	ACEI or ARB**	ACEI or ARB**	ACEI or ARB*

*Based on short-term controlled trials with proteinuria as primary outcome, ultra-high doses of ACEIs or ARBs or dual blockade with conventional dosing of ACEIs, ARBs, aliskiren or spironolactone may be tried with caution by experienced physicians in selected individuals with high levels of proteinuria and low risk of complications from aggressive RAAS blockade (*see text*); **RAAS blockers have been shown to reduce progression of typical diabetic nephropathy from normo- to microalbuminuria and from micro- to macroalbuminuria. However, no specific agents are indicated in patients with diabetes, normoalbuminuria and other causes of reduced eGFR (especially in the elderly);

maximum dose recommended for hypertension) or combination treatment of two agents reduced proteinuria more than maximum single blockade [20, 21]. On this basis, the results of the COOPERATE trial in 2003, showing the important benefits of ACEI and ARB combination treatment on hard renal end-points in non-diabetic CKD, were considered expectable, only to be followed by embarrassment for the nephrology community when the whole trial was found to be a fraud. Other studies have shown significant reduction of proteinuria with the addition of an aldosterone receptor antagonist on background ACEI or ARB treatment; the rationale for this combination is that plasma aldosterone levels are high and may contribute to renal injury in patients with CKD, whereas use of ACEIs or ARBs does not necessarily result in a maintained decrease in aldosterone levels [1]. However, the benefits and risks (i.e. hyperkalaemia) of this approach in CKD patients need to be examined by controlled trials with hard renal outcomes before any recommendation can be made.

It was anticipated that the ONTARGET trial, which randomised 23,400 patients with a previous cardiovascular event to maximum doses of ramipril, telmisartan or the combination of both, would provide a definite answer on the value of double RAAS-blockade. With regards to renoprotection, the study provided useful information, but this was not relevant to proteinuric disease due to the population characteristics; mean age was 66.5 years, only 68% of participants had hypertension, 37% had diabetes, 23% had eGFR < 60 ml/ /min/1.73 m^2, but only 13% had microalbuminuria and 3% overt diabetic nephropathy. Along with higher incidence of hypotension and hyperkalaemia with combination treatment, the renal outcome of dialysis and doubling of SCr was 24% higher with combination treatment versus ramipril; however, this derived from significant differences only in dialysis for acute renal failure, which was included in the endpoint, whereas the risks of doubling of SCr and chronic dialysis were not different between groups [4]. In addition, urine albumin excretion rose continuously during follow-up in all three groups with combination treatment displaying the lowest rate, which was considered by some as evidence against the use of proteinuria as an intermediate renal outcome. Obviously such conclusions cannot be drawn from a cohort where the vast majority of participants had normoalbuminuria. In contrast, these findings represent another clear example of the risks of aggressive RAS blockade in susceptible individuals (in this case, elderly individuals with reduced eGFR and normal or well-controlled BP) [22, 23].

Introduction of the direct renin inhibitor aliskiren in clinical practice added another option for RAAS-blockade in kidney disease, with the theoretical advantage of preventing a rise in renin activity, resulting in more "complete" RAAS blockade. Addition of aliskiren on background treatment of losartan significantly reduced proteinuria, compared to placebo, in patients with type 2 diabetes, hypertension and macroalbuminuria in the AVOID trial [21]. Based on this, the ALTITUDE study was carefully designed to compare the effects of combination treatment of aliskiren on top of ACEI or ARB versus ACE or ARB alone on cardiovascular and renal outcomes in 8561 patients with type 2 diabetes. The premature termination of the trial at 69% of events due to renal complications, hyperkalaemia and hypotension in the aliskiren group received a lot of attention and was considered as the end of the era of double RAAS-blockade. However, a recently published report has clarified several issues [24], as no component of primary outcome differed between groups, with the exception of resuscitated cardiac arrest. Doubling of SCr was practically similar, and the end-point of ESRD, dialysis or death due to kidney failure also did not differ between groups. In the aliskiren group, BP was lower by 1.3/0.6 mm Hg, and ACR drop was greater by 14% than placebo. The main significant differences between groups was the higher proportion of patients with hyperkalaemia (11.2% vs. 7.2%), and with reported hypotension (12.1% vs. 8.3%) in the aliskiren group.[24] One must note that following the inclusion criteria (macroalbuminuria, or eGFR 30–60 ml/min/1.73 m^2 and microalbuminuria, or eGFR 30–60 ml/min/1.73 m^2 and history of cardiovascular disease), the mean age of the population was 65 years, 42% had cardiovascular disease, 67% had eGFR < 45 ml/min/1.73 m^2 and only 58% of participants had macroalbuminuria. Included patients also had baseline BP < 135/85, or BP between 135/85 and 170/110 if treated with at least three antihypertensives; thus mean baseline BP was 137/74 mm Hg and 69% of participants were receiving diuretics along with ACEI or ARB.

According to the above, a large proportion of ALTITUDE participants seemed susceptible to complications from BP lowering (indeed, hypotension was more frequent in the elderly and those receiving loop diuretics), much more from RAS blockade, and the important side-effects that led to premature termination can be directly attributed to "potent" RAS blockade in susceptible individuals [25], Furthermore, in subgroup analyses of ALTITUDE the risk of the primary outcome was significantly higher in patients with baseline potassium ≥ 6 mmol/L, a finding that could directly affect the outcome. In other words, the baseline population of ALTITUDE resembled more that of cardiovascular than that of renal outcome trials and was very different to the population of AVOID; in this sense, it is still not known whether dual RAAS blockade may be beneficial for renoprotection in selected patient groups, i.e. young patients with proteinuria, preserved eGFR, no vascular disease and high compliance to dietary potassium restrictions. The ongoing VA NEPHRON-D trial that randomised 1850 patients with diabetes and overt proteinuria to a combination of losartan and lisinopril versus losartan alone is expected to answer this important question.

Conclusions

Approaches of RAAS blockade for renoprotection in hypertensive patients should be based on the type and the severity of the underlying kidney disease. On one hand, major renal outcome trials have established beyond doubt that ACEI and ARBs protect against the progression of CKD to ESRD in patients with diabetic or non-diabetic proteinuric kidney disease, as well as against the progression from micro- to macroalbuminuria in kidney diseases with predictable natural course (i.e. diabetic nephropathy), as shown in Table 1 [1]. Currently, there is no hard evidence favoring combined RAAS-blockade in any type of CKD; the value of this approach in proteinuric nephropathy is still under investigation. On the other hand, sub-analyses of major cardiovascular trials suggest no specific benefit of RAAS-inhibition in hypertensive patients with normoalbuminuria and preserved eGFR, as well as possible harm (especially with combined blockade) in susceptible individuals (i.e. the elderly with a history of CVD and background ischaemic kidney injury) [23, 25]. Thus, use of RAAS-blockade in these patients should be balanced against the possible risks. In every patient, prescription of these agents should be coupled by follow-up of renal function at regular intervals according to the baseline eGFR to avoid acute deterioration of renal function and relevant complications in patients with undiagnosed ischaemic renal disease.

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