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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). However, recent 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 compared to placebo in the combination of death, need for dialysis or transplantation, and 30% reduction in albuminuria. In 1513 patients with type 2 diabetes, hypertension and microalbuminuria (mean SCr 1.9 mg/dL, ACR 10–19 mg/g creatinine ratio and 1.2 g/g), the RENAAL trial 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 1717 hypertensive patients with baseline SCr 1.7 mg/dL and proteinuria (150 g/24 h), treatment with irbesartan resulted in 20% reduction compared to placebo, 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 amlopidine 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 2.4 mg/dL and proteinuria > 3 g/day, ramipril was associated with 32% reduction in the risk of doubling of SCr or ESRD or death by 16%, and albuminuria by 35% [6], 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 2.2 mg/dL and proteinuria of 0.6 g/day were randomized to ramipril, amloidipine or metoprolol. Patients treated with ramipril had a 36% reduction in the composite outcome of 50% decrease of GFR, ESRD or death compared to amloidipine, and 22% reduction compared to metoprolol [9]. In the ADVANCE study patients with prevalent renal disease (SCr 3.1–5.5 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 noted with captopril in patients with SCr ≤ 1.0 mg/dL. Post-hoc 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 to placebo [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 population, 40% of the adult population aged > 70 years have eGFR < 60 mL/min/1.73 m², but only 5% have macroalbuminuria; among hypertensive patients, around 15% have eGFR < 60 mL/min/1.73 m² (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 revealed no differences showing that RAAS blockade was suggested to be even more beneficial towards renoprotection in nephropathies 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 importance of renoprotection in early stages of CKD.

A second challenge to the relevance of guidelines on the use of ACEs 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 old 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 m², which only 19% had microalbuminuria and 1% randomised 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 the nisoldipine 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, losartan 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 m² 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 amloidipine than chlorthalidone, and lisinopril groups (75 versus 70 and 71 mL/min/1.73 m², respectively). In addition, in post-hoc analyses there were no differences in the incidence of an event in a 50% or greater decrease in GFR between the 3 groups in the total cohort and in patients with mild (60–89 mL/min/1.73 m²) or moderate-severe (< 60 mL/min/1.73 m²) reduction of baseline GFR [3]. The authors of ALLHAT commented on the results: "Although there was no renoprotective effect, benefits that 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 amloidipine 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 m² and the baseline micro- and macroalbuminuria were at 19% and 5% of the population, respectively. The benazepril & amloidipine group had a slower eGFR decline (~0.88 versus ~2.22 ml/min/1.73 m² per year) and a 48% reduction in the incidence of doubling of SCr, eGFR < 15 mL/min/1.73 m², 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 amloidipine accelerated hypertension decline [7]; it is not easy to see, however, that this is directly related to the different populations under study. Better preservation of renal function with a dihydropiridine calcium antagonist than a RAS blocker or a thiazide is reasonable in study populations with mean age > 65 years, mean eGFR well above 60 mL/min/1.73 m² 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
maximum dose recommended for hypertension) or combination treatment of two agents reduced proteinuria more than maximum single blockade [20, 21]. On this basis, the ONTARGET trial in 2005, showing the important benefits of ACEI and ARB combination treatment on hard renal end-points in non-diabetic CKD, were considered acceptable, only to be followed by embarrassment for the nephrology community when the whole trial was found to be a fiasco. We have shown that the combination treatment 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 ARBs does not necessarily result in 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.

Diabetic kidney disease

ACEI or ARB**

None preferred

ACEI or ARB**

ACEI or ARB**

References


