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). Several 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 serum creatinine (Scr) or death [6], and 30% reduction in albuminuria. In 1513 patients with type 2 diabetes, hypertension and albuminuria between 11 and 999 μg/mL, treatment with irbesartan resulted in 20% reduction 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 > 0.5 g/day), treatment with enalapril and losartan 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. In the REIN study, including patients with protein excretion < 0.5 g/day they have no additional benefit compared to placebo [7]. Studies in non-diabetic proteinuric kidney disease also support the use of RAAS-blockade to preserve renal function. In the RENAL Study, including patients with mean Scr of 2.4 mg/dL and proteinuria > 3 g/day, ramipril was associated with significant reduction of 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, amlopidine or metoprolol. Patients treated with ramipril had a 36% reduction in the composite outcome of 50% decrease of GFR, ESRD or death compared to amlopidine, and 22% reduction compared to metoprolol [9]. In the advanced renal disease (SCr > 3.5 mg/dL and proteinuria 1.6 g/day) [10] treatment with 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 observed in patients with SCR < 1.0 mg/dL [13]. In post-hoc analyses on non-diabetic patients there were also no outcome data to support any difference in renoprotection between ACEEs 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/mL, showed that the two agents had similar effects on the CHARM trial, 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 prevalence of 10%, 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 showed no differences in GFR decline, proteinuria 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 need for renoprotection in early stages of CKD. A second challenge was to question 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 [19]. 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, with microalbuminuria and without overt nephropathy randomized to enalapril or metoprolol. The results of this trial were in strong contrast with the CHARM trial, which showed 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.

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].


