

Antihypertensive Therapy in Non-Diabetic Chronic Kidney Disease Associated with Proteinuria in Adults

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ABSTRACT

Controlling blood pressure and reducing proteinuria are common goals in Chronic Kidney Disease associated with hypertension and proteinuria and lead to fewer cardiovascular outcomes. This review summarizes the available literature.

Keywords: Hypertension; Proteinuria; Chronic Kidney Disease

1. Introduction

Proteinuria is a risk factor for progression of chronic kidney disease (CKD) and is associated with adverse cardiovascular outcomes. Controlling blood pressure particularly with strongly anti-proteinuric agents slows the progression of chronic kidney disease (CKD) and delays/prevents cardiovascular outcomes. Angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor antagonists (ARBs) have a blood pressure-independent antiproteinuric effect and are considered first line agents in this scenario [1]. This review will apprise the literature to date on antihypertensive agents studied in non-diabetic proteinuric kidney disease. **Table 1** summarizes these trials.

2. ACE Inhibitors

Captopril was the first ACE-I approved by Food and Drug Administration (FDA) in 1981 followed by enalapril which was marketed two years later. Since then at least twelve other ACE-I have been marketed. Multiple trials have identified a preferential benefit of ACE-I in reducing proteinuria when compared with other antihypertensive drugs. The basis of all these studies was the observation that protein excretion varies directly with the intra-glomerular pressure in animals with structural glomerular disease [2].

Apart from the reduction in intra-glomerular pressure, a variety of other mechanisms may contribute to ACE-I induced reduction in proteinuria. These include:

- The hemodynamic effects of ACE inhibition occur rapidly but then become stable, whereas protein excretion progressively decreases over weeks to several months [3].
- Acute administration of angiotensin II increases intraglomerular pressure by causing renal and systemic vasoconstriction but does not reverse the antiproteinuric effect of ACE-I [4].
- Nephritin is a major component of the podocyte slit pore membrane and an important contributor to the glomerular filtration barrier. Angiotensin II reduces the expression of nephritin [5]. In contrast, ACE-I increase expression of nephritin [6].
- ACE-I may contribute to slowing of renal disease by their possible anti fibrotic properties.
- ACE-I related reduction in proteinuria may be associated with a reduction in serum lipid level which may have a beneficial effect on progression of renal disease and systemic atherosclerosis.

Multiple clinical trials have demonstrated a beneficial effect of antihypertensive therapy with renin-angiotensin system (RAS) inhibitors, mostly ACE-I in patients with proteinuric non-diabetic chronic kidney disease (CKD).

Jafar *et al* studied 1860 patients with CKD in 11 randomized controlled trials (RCT) and the response to ACE-I versus other antihypertensives or placebo [7]. ACE-I use was associated with significant reductions in the rate of progression to end-stage renal disease (ESRD) (7.4% versus 11.6%, RR 0.69, 95% CI 0.51 - 0.94), while that for doubling of the baseline serum creatinine concentration or ESRD was 13.2 versus 20.5 percent (RR 0.70, 95% CI 0.55 - 0.88) independent of blood pressure

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Table 1. Studies of antihypertensive treatment in patients with chronic kidney disease.

Study	Design/Intervention	Effect on GFR	Effect on Proteinuria	Cardiovascular outcomes	Others
<i>Maione et al</i> ⁹	SR of 85 RCT. 21,708 patients. ACE-I, ARBs and combination therapy in patients with albuminuria and other cardiovascular risk factors.	ACE-I better than placebo. ARB better than placebo. Combination not better than monotherapy.	ACE-I better than placebo. ARB better than placebo. Combination not better than monotherapy	Better with ACE-I versus placebo only.	N/A
<i>Benazepril trial</i> ¹⁰	583 patients, 300 patients received benazepril and 283 received placebo. Primary end point: doubling of the baseline Cr or the need for HD.	Benazepril better than placebo for primary end point.	Benazepril therapy reduced protein excretion by 25 percent compared with placebo.	N/A	Outcomes better in patients with glomerular diseases, diabetic nephropathy and those with baseline urinary protein excretion >1 g/24 hr.
<i>REIN trial</i> ¹¹	Prospective double-blind trial, 352 patients were classified according to baseline proteinuria <ul style="list-style-type: none"> • 1 - 3 g/24 h • ≥ 3 g/24 h Randomly assigned to ramipril or placebo plus conventional antihypertensive therapy targeted at achieving diastolic blood pressure under 90 mm Hg. Primary end point: rate of GFR decline.	Significantly lower rate of GFR decline with ramipril.	In patients with baseline proteinuria of 3 g/24 h or higher, ramipril was more Reno protective than placebo	N/A	More benefits seen with higher proteinuria.
<i>REIN-2 trial</i> ¹³	Multicenter RCT, 338 patients on ramipril were randomized to intensified control with felodipine vs conventional blood pressure control. Primary outcome was progression to ESRD.	No benefit seen with intensified BP control with felodipine.	N/A	N/A	No Reno protection in patients with nondiabetic proteinuric renal disease with dihydropyridine calcium channel blockers.
<i>AASK trial</i> ¹⁴	1094 African American patients with hypertensive renal disease. Randomly assigned to ramipril, amlodipine or metoprolol. Primary outcome: rate of change in GFR. Secondary outcome: composite endpoint of reduction in GFR of more than 50% or more than 25 mL/min per 1.73 m ² ; ESRD; or death.	At 3 years, ramipril significantly reduced the relative risk of the composite endpoint but not primary outcome. Beneficial effect of ramipril was seen in patients with urine protein-to-Cr ratio >0.22 (300 mg protein/24 hr).	N/A	Ramipril showed benefit in patients with urine protein-to-Cr ratio >0.22.	N/A
<i>ONTARGET</i> ¹⁹	ACE-I and ARB combination versus monotherapy. 5623 patients with estimated GFR less than 60 mL/min per 1.73 m ² and/or proteinuria.	ACE + ARB resulted in a small but significant increase in the incidence of ESRD and a non significant increase in ESRD alone.	N/A	Combination therapy not better than monotherapy.	Higher potassium level with combination therapy.

Abbreviations: SR systematic review, RCT randomized controlled trial, ACE-I angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker, Cr creatinine, GFR glomerular filtration rate, HD hemodialysis

control. These benefits of ACE-I correlated with increasing baseline proteinuria but did not apply to those with proteinuria below 500 to 1000 mg/day [8].

Maione *et al.* conducted a systematic review of 85 RCTs (21,708 subjects) to look at ACE-I, ARBs and combination therapy in patients with microalbuminuria, macroalbuminuria and other cardiovascular risk factors [9]. Neither ACE I, ARB, nor the combination of the two was associated with a significant reduction in the risk of all-cause mortality or fatal cardiac-cerebrovascular events. ACE I, and not ARB, did however reduce the risk of nonfatal cardiovascular events. Development of ESRD disease and progression of microalbuminuria to macroalbuminuria were reduced significantly with ACE-I versus placebo, ARB versus placebo but not with combined therapy with ACE-I and ARB versus monotherapy. Authors concluded that ACE-I and ARB exert independent renal and nonfatal cardiovascular benefits while their effects on mortality and fatal cardiovascular disease are uncertain. Use of combination therapy was not supported by the evidence.

Maschio *et al.* performed a placebo-controlled RCT involving 583 patients with renal insufficiency (creatinine clearance 30 - 60 ml per minute) in which 300 patients received benazepril and 283 received placebo. The primary end point was a doubling of the baseline serum creatinine concentration or the need for dialysis. At three years the risk reduction attributed to benazepril was 53 percent overall (95% CI, 27% - 70%) and was particularly evident in milder kidney disease. The risk reduction was greatest among men; those with glomerular diseases, diabetic nephropathy, or miscellaneous or unknown causes of renal disease; and those with baseline urinary protein excretion above 1 g per 24 hours. Benazepril was not effective in patients with polycystic kidney disease [10].

The Ramipril Efficacy in Nephropathy (REIN) trial was a RCT in which patients (N = 352) with proteinuric non-diabetic CKD were randomized to ramipril or placebo plus other antihypertensive therapy to attain a diastolic pressure below 90 mmHg. It showed similar benefits as the Maschio trial [11]. Stratified by level of daily proteinuria, the primary endpoint was the rate of glomerular filtration rate (GFR) decline. The trial was terminated prematurely in patients excreting more than 3 grams of protein per day because of a significant benefit with ACE-I in ameliorating the rate of decline of renal function (0.53 versus 0.88 mL/min per month for placebo). Subsequently all patients with proteinuria of 3 g or more per 24 h either continued on ramipril or were shifted to ramipril.

A REIN follow-up study compared the rate of decline of renal function and the need for dialysis in patients who continued to receive ramipril (51 patients) and in those originally randomized to conventional antihypertensive

therapy plus placebo who were switched to ramipril at the beginning of the observational follow-up (46 patients). At 20 months (and at 44 months for the trial phase and observational follow-up combined), mean rate of GFR decline slowed significantly and end of trial GFRs were significantly higher in the ramipril group (36 vs 24 ml per minute, P = 0.01). Progression to ESRD was more common in those receiving placebo (35 versus 19, P = 0.027) [12]. The original and follow-up ramipril studies strongly suggest that patients who particularly benefit are those with prominent proteinuria, but significant benefit was also seen in patients with sub-nephrotic proteinuria (1.0 to 2.9 g/day).

REIN-2 evaluated lowering blood pressure beyond usual targets in patients with chronic nephropathies using ACE I. Patients receiving ACE I (Ramipril 2.5 - 5 mg/d) with non-diabetic proteinuric CKD (mean baseline GFR 35 mL/min and mean proteinuria 2.9 g/day, N = 338) were enrolled in this RCT [13]. Subjects were randomly assigned to either conventional (diastolic < 90 mm Hg; n = 169) or intensified (systolic/diastolic < 130/80 mm Hg; n = 169) blood-pressure control with Felodipine (5 - 10 mg/day) added as needed to achieve the intensified blood-pressure level. The primary outcome measure, time to ESRD over 36 months did not differ between the two groups (20% vs 23%, P = 0.99). Further blood pressure reduction with Felodipine therefore is not warranted to slow progression to ESRD in this population. These findings are consistent with previous observations showing that dihydropyridine calcium channel blockers fail to provide renoprotection in patients with non-diabetic proteinuric renal disease.

Hypertension and ESRD are more prevalent among African Americans than Caucasians. Monotherapy with a calcium channel blocker or a diuretic may be superior in this population than ACE-I. The African American Study of Kidney Disease and Hypertension (AASK trial) [14] included 1094 African American patients with hypertensive renal disease. Mean GFR was 46 ml/min (range 20-65 mL/min per 1.73 m²) and mean protein excretion was about 600 mg/day in men and 400 mg/day in women. Patients were randomly assigned to three different antihypertensive drugs and to two different blood pressure goals. The blood pressure target was a mean arterial pressure of 92 mm Hg or less in the intensive-control group (corresponds to lower than the traditional blood-pressure target of 130/80 mm Hg for CKD) and 102 to 107 mm Hg in the standard-control group (corresponds to the traditional blood-pressure target of 140/90 mm Hg). Patients were randomly assigned to treatment with an ACE inhibitor (ramipril, 2.5 - 10 mg/day), a calcium channel blocker (amlodipine, 5 - 10 mg/day), or a beta blocker (metoprolol, 50 - 200 mg day); other antihypertensive drugs were added to initial monotherapy to achieve the

blood pressure goals. The primary outcome was the rate of change in GFR; the main secondary outcome was a composite endpoint of: reduction in GFR of more than 50 percent or more than 25 mL/min per 1.73 m²; ESRD; or death.

Although the GFR decline with ramipril and amlodipine therapy were similar at 3 years, ramipril significantly reduced the relative risk of the composite endpoint by 38 percent. Additionally, ramipril was significantly better at slowing GFR decline among those with a urine protein-to-creatinine ratio >0.22 (approximately equivalent to 300 mg protein in 24 hours). It also showed that sustained-release metoprolol has antiproteinuric effects nearly equal to that of ramipril ($P = 0.06$ for the comparison of total change over 4 years) and better than that of amlodipine. Proteinuria increased by 58% for the amlodipine group and declined by 14% in the sustained-release metoprolol group between baseline and 6 months ($P < 0.001$) [14].

After completion of the AASK trial, all of the participants were invited to enroll in a cohort phase during which ramipril was prescribed to everyone. After an additional five years of follow-up progression of nephropathy was significantly slowed but not stopped [15].

2.1. Use of ACEI/ARB in Advanced CKD

The pitfalls of using an ACE-I or ARBs in advanced CKD include an initial GFR decline and hyperkalemia, prompting many practitioners to avoid their use. Fan Fan Hou *et al.* enrolled 422 patients with non-diabetic CKD and randomly assigned them to benazepril or placebo plus other antihypertensive therapy to attain a systolic and diastolic pressure below 130 and 80 mmHg, respectively [16]. Patients were divided into two groups based on renal function: Group 1 (N = 141, Serum Creatinine 1.5 - 3.0 mg/dL; mean GFR 37 ml/min/1.73 m², mean proteinuria 1.6 g/d) and Group 2 (N = 281, Serum Creatinine 3.1 - 5.0 mg/dL, mean GFR 26 ml/min/1.73m², mean proteinuria 1.6 g/d).

After an eight-week run-in period in which they received benazepril at 10 mg/day for four weeks 104 patients remained in Group 1 and 224 remained in Group 2. Group 1 subjects then received benazepril (at 10 mg twice daily, since it was deemed unethical to administer placebo), while Group 2 participants were randomly assigned to benazepril (10 mg twice daily) or placebo. Additional antihypertensive therapy was administered to attain blood pressure goals. The primary endpoint was the composite of doubling of the serum creatinine level, ESRD, or death, while secondary endpoints were change in proteinuria and rate of progression of the renal disease.

At a mean follow up of 3.4 years, significantly fewer Group 2 patients (mean GFR of 26 mL/min per 1.73 m²) treated with benazepril reached the primary endpoint (41

versus 60 percent with placebo), resulting in an overall risk reduction of 43 percent with active therapy. The primary endpoint was reached less often in group 1 patients (22 percent), who had less severe disease and were all treated with benazepril.

In group 2 doubling of the serum creatinine and reaching ESRD occurred in 51 and 40% fewer patients receiving Benazepril. Fall in proteinuria (52 versus 20 percent) and a slower rate of decline in GFR (6.8 versus 8.8 mL/min per 1.73 m² per year) were also noticed. The benefits with benazepril were independent of blood pressure. Benazepril conferred substantial renal benefits in highly selected patients without diabetes who had advanced renal insufficiency.

The REIN trial confirms the benefit from ACE-I in patients with advanced CKD. As previously mentioned, patients with an initial GFR within the lowest group (11 to 33 mL/min/1.73 m²) had a 20 percent decrease in the rate of decline in GFR and a 33 percent reduction in the incidence of end-stage renal disease.

2.2. Use of ACE I in Elderly Patients

The benefits from RAS inhibition in proteinuric CKD patients older than 70 years are largely unknown. Most of the above trials did not include such individuals since older patients with CKD are less likely to have proteinuria. This is confirmed by an analysis of 1190 National Health and Nutrition Examination Survey (NHANES) participants who were over age 70 and had CKD, which was defined as an estimated GFR < 60 mL/min per 1.73 m² or an albumin-to-creatinine ratio >200 mg/g of creatinine (approximately 300 mg/day) [17]. This level of proteinuria was present in only 13 percent. There is no evidence of benefit from RAS inhibition in patients with protein excretion below 500 mg/day. It suggests that the great majority of patients over age 70 with CKD would not benefit from RAS inhibition for renal protection and may have harm from a higher rate of side effects. However, this does not fully apply on patients excreting more than 1 g/day. Treatment of proteinuric individuals over the age of 70 with CKD remains an area for investigation.

2.3. Combination of ACE Inhibitors and ARBs

A number of small trials have shown that combination ACE-I and ARB therapy has a greater antiproteinuric effect than either agent alone. A meta-analysis of 14 trials in non-diabetic renal disease found that combination therapy produced a significant 18% - 25% greater reduction in proteinuria compared with monotherapy [18]. These trials did not attempt to identify a maximum antiproteinuric dose, did not compare combination therapy to high dose monotherapy, and did not assess renal out-

comes.

Combination therapy however may have adverse effects in proteinuric CKD. The *ONTARGET* trial evaluated combination therapy versus monotherapy in a subset of 5623 patients who, at baseline, had reduced renal function (defined as an estimated GFR less than 60 mL/min per 1.73 m²) and/or proteinuria [19]. Combination therapy resulted in a small but significant increase in the incidence of ESRD or doubling of the serum creatinine (0.79 versus 0.56 percent per year), but a nonsignificant increase in ESRD alone (0.34 versus 0.27 percent per year) and caused more hyperkalemia while failing to reduce the risk of cardiovascular disease or death [20].

3. Other Antihypertensive Drugs

3.1. Calcium Channel Blockers

Numerous studies suggest that the dihydropyridine calcium antagonists (DCAs) and non-dihydropyridine calcium antagonists (NDCAs) have differential antiproteinuric effects. The NDCAs, such as diltiazem and verapamil are generally considered to have significant antiproteinuric effects while DCAs, such as amlodipine and nifedipine either have no effect or cause a small rise in protein excretion [21].

Bakris *et al.* systematically reviewed 23 studies of NDCA versus DCA and found NDCAs decreased mean proteinuria by 30 percent and DCAs increased proteinuria by 2 percent (95% CI 10% - 54% for the differences between the two drug classes). Similar observations were noted when these agents were used in combination with ACE-I or ARBs: despite similar reductions in blood pressure, the mean change in proteinuria was minus 39 and plus 2 percent for NDCAs and DCAs, respectively. They concluded that NDCA and DCAs lower blood pressure equivalently, but that NDCAs are superior to DCAs in reducing proteinuria in both diabetic and non-diabetic kidney disease [21].

3.2. Aldosterone Antagonists

Addition of aldosterone antagonists may provide renal benefits to proteinuric CKD patients over and above the inhibition of RAS blockers by virtue of partially eliminating secondary hyperaldosteronism. Navaneethan *et al.* performed a meta-analysis of 11 trials in which patients were treated with an ACE-I and/or ARB plus either spironolactone (usually 25 mg/day) or placebo and found a significantly greater reduction in proteinuria in the spironolactone group (weighted mean difference 800 mg/day, 95% CI 330 - 1270 mg/day). Short-term changes in GFR (less than one year of follow-up) were similar with spironolactone and placebo. However, most of these studies did not first maximize the dose of the ACE-I or ARB,

and the aldosterone antagonist was associated with an increased risk of hyperkalemia (relative risk 3.1 in the meta-analysis) [22]. Longer-term data are lacking in this field.

3.3. Direct Renin Inhibitors

Aliskiren, being the first oral direct renin inhibitor (DRI) became available in the United States in March 2007. A number of studies have evaluated the blood pressure lowering effect of aliskiren in combination with other antihypertensive drugs [23-26]. Its novel mechanism of action, inhibition of catalytic activity of renin, the most proximal and rate-limiting step in RAS activation, makes it of particular interest. In the *AVOID trial*, aliskiren plus losartan was associated with a 20 percent greater reduction in proteinuria compared with losartan alone in patients with type-2 diabetes and nephropathy in the absence of a significantly greater effect on blood pressure [27]. However, this effect on proteinuria did not translate into a clinical benefit.

In the *ALTITUDE trial*, 8600 patients with type-2 diabetes and kidney disease already taking either an ACE-I or ARB were randomly assigned to additional therapy with aliskiren or placebo [28]. The trial was terminated early due to no benefit on the primary cardiovascular and renal outcomes and the preliminary analysis indicated that aliskiren therapy produced a higher rate of adverse events (i.e., non-fatal stroke, hypotension, hyperkalemia) [29]. Other studies also described an increased risk of hyperkalemia when aliskiren is combined with ACE-I or ARB [30]. Thus, aliskiren should not be combined with ACE-I or ARBs.

3.4. Drugs with Little or No Effect

Other antihypertensive drugs have little or no effect on protein excretion. As an example, beta blockers, diuretics, and the alpha-1-blockers (such as prazosin) typically have a lesser antiproteinuric effect than RAS inhibitors [31-33]. A meta-analysis showed that ACE-I lowered protein excretion by 40 percent compared with 16 percent for beta blockers and 14 percent for other non-calcium channel blocker antihypertensive drugs [31]. Methyldopa and Guanfacine, have little effect on protein excretion.

4. Conclusion

Proteinuria is associated with adverse renal and cardiovascular outcomes. Retarding proteinuria in CKD slows progression of CKD and can limit some cardiovascular outcomes. ACE-I and ARBs are the first line agents in this setting because they have a blood pressure-independent antiproteinuric effect and have shown to improve renal and cardiovascular outcomes. If proteinuria

is not controlled with ACE-I or ARB, combination therapy is generally discouraged. We recommend the addition of an NDCA such as diltiazem or verapamil, long acting metoprolol or a mineralocorticoid antagonist as the next line agent. Aggressive measures must be taken to improve blood pressure and reduce proteinuria for better renal and cardiovascular outcomes.

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