ACE Inhibition versus Angiotensin Receptor Blockade: Which Is Better for Renal and Cardiovascular Protection?

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Abstract. Chronic renal disease is characterized by a gradual loss of renal function and an increased cardiovascular risk. Renin-angiotensin system blockade by angiotensin-converting enzyme inhibition or angiotensin receptor blockade has distinct renoprotective and cardiovascular protective effects, but which of the two drug classes confers more protection is still a matter of debate. This review highlights and compares the effects of the two drug-classes in nondiabetic renal disease and in overt or incipient nephropathy of type 1 and type 2 diabetes. Both renal and cardiovascular outcomes are considered. Regardless of their relative efficacy, both drug classes have a dose-response relationship for intermediate renal and cardiovascular parameters. Moreover, combined treatment with angiotensin-converting enzyme inhibition and angiotensin receptor blockade seems to provide better long-term renoprotection than monotherapy. Actually, in most patients, achieving maximal renal and cardiovascular protection requires a multidrug regimen, usually including several antihypertensives. Within this approach, full dose titration of either RAS blocker followed by add-on with the second drug is more important than the choice of the initial drug.

Chronic renal disease is characterized by a gradual loss of renal function and an increased cardiovascular risk (1). A disturbed renal function per se is a major predictor of cardiovascular complications (2). Particularly patients who have reached ESRD experience dramatically reduced life expectancy as a result of cardiovascular mortality. Thus, renoprotection (aimed to prevent ongoing renal function loss toward ESRD) and cardiovascular protection (to prevent cardiovascular events) are independent but related goals in patients with chronic nephropathies.

During the past decades, a tremendous body of research, both experimental and clinical, has unequivocally shown that pharmacologic blockade of the renin-angiotensin system (RAS) slows progressive renal function loss more effectively than other antihypertensive treatments (reviewed in 3). Two classes of antihypertensive drugs that block the RAS are in clinical use: the angiotensin-converting enzyme (ACE) inhibitors and the angiotensin receptor blockers (ARB). Both types of drugs limit the effects of angiotensin II (AngII), the former by inhibiting the AngI–II conversion and the latter by blocking the type 1 receptor of AngII. In addition to the antihypertensive effect, AngII inhibition exerts specific effects in the vasculature (4) and the kidney, i.e., decreased intraglomerular pressure, improved glomerular-barrier size selectivity, and reduction of proteinuria (5,6).

Renoprotection trials with ACE inhibition and ARB have invariably shown that the renoprotective benefit of these drugs is mainly explained by their specific antiproteinuric effect (7–9). This is consistent with the view that proteins, once leaked through the glomerular barrier, act as mediators of ongoing renal fibrosis (10).

Still, the mechanisms of action are not completely similar. Inhibition of ACE results also in decreased breakdown of the vasodilator bradykinin (11), whereas signaling through the AT2 receptor may be increased during ARB treatment. Thus, theoretically, there might be relevant differences between the drug classes, but the clinical importance for renal disease of these differences is not clear. In this review, we discuss the renal and cardiovascular effects of ACE inhibition and ARB in patients with chronic nephropathies, and we attempt to answer the question of which treatment is to be preferred in renal patients.

RAS Blockade: Renoprotective Effects in Chronic Nephropathies

Renoprotective Effects of ACE Inhibition

Nondiabetic Renal Disease. In nondiabetic renal disease, there is a clear renoprotective advantage of ACE inhibitors as compared with BP-lowering therapies not interfering with the RAS. The Ramipril Efficacy In Nephropathy (REIN) study included 352 patients with chronic nephropathies, primarily of nondiabetic origin, and these were randomized to treatment with the ACE inhibitor ramipril or placebo on top of other antihypertensive agents. The main finding was that ramipril treatment resulted in a slower decline in GFR compared with placebo, despite equivalent BP control (12). A later analysis

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indicated that a subset of patients on prolonged treatment with ramipril even had a rise in GFR (13). Recently, a large-scale trial demonstrated that the renoprotective effect of ACE inhibition is superior to that of conventional antihypertensive regimens (including β blockers and calcium channel blockers) also in black patients (14), a population so far considered to be poorly responsive to RAS blockade.

**Type 1 Diabetes.** The collaborative study found that in patients with overt nephropathy of type 1 diabetes, ACE inhibition with captopril induced a clear reduction in proteinuria, as compared with treatment not directly interfering in the RAS. The antiproteinuric benefit of captopril was associated with a slower decline in creatinine clearance and a reduction of the primary end point “doubling of serum-creatinine” of approximately 50% (8).

The European Microalbuminuria Captopril Study showed that in microalbuminuric patients with type 1 diabetes, ACE inhibition decreases the risk to develop overt nephropathy by approximately 75% (15), which proves that ACE inhibition has beneficial renal effects also at the earlier stage of incipient nephropathy. This is clinically important because microalbuminuria is a strong predictor of overt nephropathy and cardiovascular morbidity (16).

**Type 2 Diabetes.** Six small studies that included 352 patients altogether uniformly found that ACE inhibition reduces proteinuria more effectively than conventional therapy also in overt nephropathy of type 2 diabetes (17). However, as well as the *post hoc* analysis on the small subgroup of patients with diabetes (*n* = 27) enrolled in the REIN study (18), these studies did not have sufficient statistical power to detect a difference in renal function loss. Thus, a considerably larger clinical trial of approximately 1000 to 2000 patients would be required to test the hypothesis of a specific renoprotective effect of ACE inhibition in type 2 diabetic nephropathy. Unfortunately, such a trial has not been conducted so far.

At the stage of incipient nephropathy, a decrease in microalbuminuria has been observed with ramipril compared with placebo (19). The substudy in 3577 patients with diabetes (primarily type 2) of the Heart Outcomes Prevention Evaluation (HOPE) trial showed that, compared with placebo, treatment with the ACE inhibitor ramipril resulted in a 24% reduction of the risk to develop overt nephropathy in patients who were either normo- or microalbuminuric (20). In the same line, ACE inhibition with enalapril reduced in normoalbuminuric patients with type 2 diabetes the risk to develop microalbuminuria by 12.5% (21). The BErgamo NEphrology DIabetic Complications Trial (BENEDICT) is now in progress to test whether the ACE inhibitor trandolapril—alone or in combination with the calcium channel blocker verapamil—reduces the risk to develop microalbuminuria in hypertensive patients with type 2 diabetes and normoalbuminuria (22).

**Renoprotective effects of ARB**

**Nondiabetic Renal Disease and Type 1 Diabetes.** Large-scale trials on the long-term renoprotective effect of ARB in nondiabetic and type 1 diabetic renal disease are missing so far.

**Type 2 Diabetes.** Two rigorously powered trials that included >1500 patients, the Irbesartan in Diabetic Nephropathy Trial (IDNT) (23) and the Reduction of Endpoints in Type 2 Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial (24), compared ARB with conventional therapy in patients with type 2 diabetes and overt nephropathy. In these two studies, ARB treatment reduced the relative risk of reaching the primary composite end point (doubling of serum creatinine, ESRD, or death) by 20% and 16%, respectively. In addition, the IDNT showed a reduction of the risk to reach the primary end point by 23% also as compared with calcium channel blockade by amlodipine, the third treatment arm in this study.

Recently, the Microalbuminuria Reduction with Valsartan study (25) and the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria study (26) showed the beneficial effect of ARB also at the stage of incipient nephropathy. In the Microalbuminuria Reduction with Valsartan study, valsartan reduced albuminuria by 44%, compared with an 8% reduction in the control arm with amlodipine. Moreover, normoalbuminuria was restored in 30% of the patients who were treated with valsartan (*versus* 15% with amlodipine). The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria study showed, in addition to a clear-cut reduction of the primary end point “overt nephropathy” (*i.e.*, progression to macroalbuminuria), a 24% and 38% decrease in albuminuria with irbesartan 150 mg and 300 mg, respectively, whereas albuminuria remained almost unchanged (−2%) in the placebo arm.

**Renoprotective Effects of ACE Inhibition versus ARB**

In summary, there is ample evidence that blocking the RAS is advantageous for renoprotection over other antihypertensive drugs. At first sight, however, the trials with ACE inhibitors and ARB show some striking differences (Figure 1). If one considers only the renal end points in the trials in type 2 diabetic nephropathy, then ARB reduced the risk of ESRD by 28% in the RENAAL and by 23% in the IDNT. Although statistically significant and clinically important, these reductions look remarkably less impressive as compared with those observed with ACE inhibitor therapy in nondiabetic renal disease and type 1 diabetic nephropathy, which are close to 50% (Figure 1). Because the characteristics of the different study populations may of course contribute to the differences in outcomes with ACE inhibition and ARB treatment, these data clearly call for trials aimed to compare formally the renoprotective effects of the two classes in similar clinical settings.

In this respect, however, data from trials primarily designed to compare the effects of combined ACE inhibitor and ARB treatment to single therapy with each agent alone provide some useful information, albeit indirect. The recent Combination Treatment of Angiotensin Receptor Blocker and Angiotensin Converting Enzyme Inhibitor in Non-diabetic Renal Disease (COOPERATE) trial studied in 263 Japanese patients with nondiabetic nephropathies whether dual RAS blockade with trandolapril and losartan provided better renoprotection than either drug alone (9). Although not designed or powered to test
this, during 3 yr of follow-up, the investigators found that the effects of trandolapril and losartan seemed remarkably similar, with respect to both reduction of proteinuria and reaching the end point. On the same line, the Candesartan and Lisinopril Microalbuminuria study found that the ACE inhibitor lisinopril and the ARB candesartan, at comparable BP control, achieved a similar reduction in albuminuria in 197 patients with type 2 diabetes and incipient nephropathy (27).

Altogether, these data suggest that in nondiabetic renal disease and in type 2 diabetes with incipient nephropathy, ACE inhibition and ARB share a similar renoprotective effect. That this may apply also to type 1 diabetes and to overt nephropathy of type 2 diabetes is reasonable but still unproved.

**RAS Blockade: Cardiovascular Protective Effects in Chronic Nephropathies**

**Cardiovascular Protective Effects of ACE Inhibition**

ACE inhibitors decrease mortality and cardiovascular morbidity in a wide array of conditions, including type 2 diabetes (20), post-myocardial infarction (with/without left ventricular dysfunction) (28–33) and heart failure, and New York Heart Association (NYHA) II-IV (34–36). Recent studies found that this specific cardioprotective effect may also apply to patients with renal disease.

**Nondiabetic Renal Disease.** The HOPE study included 9541 high-risk patients, and the main finding was that ramipril—on top of other agents—was associated with a reduction of the cardiovascular risk (37). The outcomes of the 980 patients with impaired renal function at baseline (serum creatinine ≥1.4 mg/dl) were evaluated in a separate analysis and, first of all, this substudy highlighted the strikingly increased risk of cardiovascular mortality and morbidity associated with chronic renal failure (38). Of note, treatment with ramipril resulted in a clear-cut reduction of the cardiovascular risk in the patients with impaired renal failure, and this benefit seemed even larger than in patients with normal renal function (especially with respect to cardiovascular and total mortality and heart-failure related hospitalization).

The precise mechanisms of this specific cardioprotective effect are unclear. In addition to direct vascular effects of limiting AngII, the specific reduction in proteinuria by ACE inhibitors and the secondary amelioration of the lipid profile may contribute to exemplify the direct beneficial effects of RAS blockade on heart and vessels (39).

**Type 1 Diabetes.** In the Collaborative Study, captopril treatment reduced the combined end point, which included mortality, by 50% (8). Although the relatively small number of events did not allow the analysis to detect the effect on mortality as statistically significant, these findings suggest that ACE inhibitor therapy may be cardioprotective in overt nephropathy of type 1 diabetes.

**Type 2 Diabetes.** No data from large clinical trials are available showing the effects on cardiovascular outcomes of ACE inhibition in type 2 diabetic nephropathy. Nevertheless, the subgroup analysis of the HOPE study that focused on diabetic patients (micro-HOPE) showed a clear reduction in cardiovascular end points with ramipril also in this clinical setting (20). In addition, among the patients with impaired renal function included in HOPE, ramipril had the same benefits in diabetic as in nondiabetic patients (38). In summary, these HOPE findings support the use of ACE inhibition to prevent cardiovascular complications in patients with type 2 diabetes with or without concomitant renal disease.

**Cardiovascular Protective Effects of ARB**

ARB, on top of other antihypertensives, reduces mortality and morbidity in heart failure (40). Moreover, the Losartan Intervention for Endpoint Reduction in Hypertension study showed in 9222 patients with hypertension and left ventricular hypertrophy (based on ECG) that ARB by losartan resulted in
a clear reduction of the primary composite end point of death, myocardial infarction, and stroke as compared with the $\beta$ blocker atenolol, and this difference was found despite equivalent BP control (41). A substudy of the Losartan Intervention for Endpoint Reduction in Hypertension study showed that the reduction of the primary composite end point with losartan also applied to 1195 patients with diabetes and hypertension (42). Whether this beneficial effect applies also to patients with renal disease has not been proved so far.

**Nondiabetic Renal Disease and Type 1 Diabetes.** Data on cardiovascular outcomes with ARB in nondiabetic and type 1 diabetic renal disease are lacking so far.

**Type 2 diabetes.** The RENAAL and IDNT were designed to test the effects of ARB in patients with type 2 diabetic nephropathy, and both studies had formulated a secondary composite outcome of cardiovascular mortality and morbidity. Both studies showed a reduction in the rate of heart failure with ARB. Disappointingly, however, despite the large sample size, these trials failed to demonstrate any beneficial effect on cardiovascular events.

**Cardiovascular Protective Effects of ACE Inhibition versus ARB**

No direct comparative data are available on cardiovascular outcomes in chronic renal patients. Subgroup data from patients with diabetes and renal impairment in the HOPE study seem to suggest better cardiovascular protection with ACE inhibition than with ARB in RENAAL and IDNT. This comparison is hazardous, however, because the specific category of high-risk patients with dipstick-positive proteinuria were excluded from the HOPE study. The possibility of a superior cardioprotective effect of ACE inhibition as compared with ARB is suggested by the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan study. This randomized, controlled trial in patients at increased cardiovascular risk found less cardiovascular mortality in the captopril arm than in the losartan arm (43). However, whether this may apply also to patients with renal involvement is not established so far.

**Effect of Combination Therapy on Renal and Cardiovascular Outcomes**

**Nondiabetic Renal Disease**

In the COOPERATE trial, dual RAS blockade withtrandolapril and losartan reduced the risk to reach the primary composite end point of doubling of serum creatinine or ESRD by almost 50% as compared with the single agents. The advantage was explained by the superior 75% reduction of proteinuria in the combined group compared with 40 to 45% reduction with monotherapy (9).

**Types 1 and 2 Diabetes**

In patients with diabetes and overt nephropathy, no data are available so far on the long-term renoprotective effects of combined RAS blockade. The Candesartan and Lisinopril Microalbuminuria study demonstrated in patients with type 2 diabetes and microalbuminuria and hypertension that combined treatment with the ARB candesartan and the ACE inhibitor lisinopril resulted in stronger BP reduction than monotherapy (27).

In summary, these data show the added renoprotective benefit of combined RAS blockade, at least in nondiabetic renal disease and incident nephropathy of type 2 diabetes. Nevertheless, the cardiovascular effects of such a regimen remain to be established.

**How Should RAS Blockade Be Applied in Renal Patients for Optimal Renal and Cardiovascular Protection?**

Comparative data on the long-term renal and cardiovascular protective effects of ACE inhibition and ARB are so scarce that it is not possible to conclude which of the two drugs is better. All renoprotection trials have invariably shown that the strongest predictor of long-term renoprotective efficacy is the antiproteinuric effect. It is becoming increasingly clear that the ACE inhibitors (39,44,45) and ARB (46,47) have a dose–effect relationship for proteinuria, and substudies of HOPE also show a dose-response for the effect of ACE inhibition on the progression of atherosclerosis (48) and improvement of myocardial remodeling (49). With respect to the renal effects, it is also becoming clear that the dose–effect relationship is different between individual patients, and, as a general rule, patients with a poor response to ACE inhibition also respond poorly to ARB (reviewed in 50). Moreover, the differences between individual patients exceed those observed between classes of drugs (50). Therefore, these considerations implicate that it is important to titrate individually for the optimal antiproteinuric effect, the choice of the initial drug being less important.

A recent study found an additional antiproteinuric effect when the combination of halved doses of ACE inhibitor and ARB were used to reduce the BP to a level similar to that achieved by full dose of monotherapy (51), and this extends previous findings showing the additional antiproteinuric benefit of combination therapy (52,53). It also has been shown now that there is additional antiproteinuric benefit of combined ACE inhibition and RAS blockade, even if the combination is applied at the top of the dose-response for proteinuria of the individual agents (45). The COOPERATE trial has now provided evidence that also long-term renoprotection with dual RAS blockade is better than monotherapy, at least when fixed doses are used (9). It is tempting to speculate that even more end points could have been prevented if a strategy of individual dose titration had been applied (54). It would also be important to know whether such an approach affects the cardiovascular outcomes.

**Conclusions**

Notwithstanding differences in the mechanism of action between ACE inhibitors and ARB, no formal comparisons are available so far to conclude for a superiority of one drug class over the other one as for renal and cardiovascular protection. However, available data show impressive differences in re-
sponse to RAS blockade between subsets of patients, with outspoken high risks in patients with type 2 diabetes and nephropathy, even during treatment with RAS blockade.

For renoprotection, the first step is full titration of the ACE inhibitor or ARB aimed at optimal reduction of proteinuria, and this is probably much more important than the choice of the initial drug. To achieve maximal cardiovascular and renal protection in terms of BP control, dyslipidemia, and proteinuria will usually require a multidrug regimen (55), based on dual RAS blockade and combined therapy with diuretics and lipid-lowering agents.

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