Renoprotection: A Matter of Blood Pressure Reduction or Agent-Characteristics?

LIFFERT VOGT,* GERJAN NAVIS,* and DICK DE ZEEUW†
*Department of Internal Medicine, Division of Nephrology and †Department of Clinical Pharmacology, University Hospital, Groningen, the Netherlands.

Abstract. Data from recent clinical trials show that lowering of BP reduces the rate of renal function loss in chronic renal disease. There is evidence supporting the assertion that BP lowering obtained by intervention in the renin-angiotensin-aldosterone system (RAAS) has an additive renoprotective effect in both diabetic and nondiabetic renal diseases. However, to dissociate BP-dependent and non–BP-dependent action of RAAS blockade, the relevant trials are in many cases flawed by design, resulting in BP differences between the comparative antihypertensive strategies. This review discusses whether the relevant literature allows for the conclusion that RAAS intervention has renoprotective effects in addition to its effects on BP. In particular, the main evidence for a specific renoprotective action of RAAS blockade is provided by its consistent antiproteinuric action, which cannot completely be attributed to the reduction in BP. Indeed, other strategies that lower proteinuria without having an antihypertensive effect, such as lowering dietary protein intake or the use of nonsteroidal antiinflammatory drugs, appear to have a renoprotective effect as well. Interestingly, a consistent finding across different intervention studies is that the more proteinuria is reduced the better the kidney appears to be protected. Therefore, it is concluded that agent-characteristics of RAAS intervention (i.e., antiproteinuric properties) independently influence renal function loss in addition to its BP-lowering effect. Future studies should further explore the renoprotective benefit of non-antihypertensive intervention measures, alone and in combination with antihypertensive strategies.

Antihypertensive therapy has always been the cornerstone of renoprotective intervention. Recent large trials particularly indicate that intervention in the renin-angiotensin-aldosterone system (RAAS) appears to be effective in retarding the decline of renal function loss in both diabetic and nondiabetic renal diseases. In nondiabetic patients, the AIPRI (1) and REIN (2) studies showed that angiotensin-converting enzyme (ACE) inhibitors delay the progression of renal function loss. Lewis et al. (3) showed a renoprotective effect of ACE inhibitors in type 1 diabetic patients. Moreover, two recent studies, RENAA (4) and IDNT (5), demonstrated angiotensin-II (AngII)-receptor (type 1) antagonists to be renoprotective in type 2 diabetics.

The above-mentioned trials, comprising thousands of patients, can be taken as impressive evidence for RAAS intervention to be superior to other treatment strategies. However, whether the effects of RAAS intervention are due to the specific pharmacologic properties of the agent (specific renoprotective properties) independently influence renal function loss or due to their antihypertensive potency is a crucial question. This issue is still open, because in many of the above trials, the obtained BP levels were lower in the patients treated with an agent that intervenes in the RAAS compared with the control groups. The current review focuses on this particular question, that is, is renoprotection obtained by a lower BP per se, or do the specific pharmacologic properties of the agent exert an independent renoprotective effect?

Reduction of BP

BP is an important risk factor for renal function loss. In the MFRIT study (6), BP was a strong predictor for the development of end-stage renal failure during 16-yr follow-up in middle-aged men. The study identified a strong graded relation between both systolic and diastolic BP and end-stage renal disease. Several other studies pointed out that a more aggressive BP control is beneficial on the course of renal function loss in renal patients.

In patients with diabetic nephropathy, the importance of aggressive BP reduction for renal function preservation has been demonstrated (7,8). Early on, Parving et al. (7) demonstrated in an observational study that the long-term, aggressive antihypertensive treatment retards the rate of renal function loss in type 1 diabetic patients.

Type 2 diabetic patients with nephropathy were studied in the ABCD study (9). In this study of 950 patients, the presence of hypertension was associated with nephropathy. Patients with hypertension were randomized to an intensive BP target (diastolic BP, 75 mmHg) versus a moderate BP target (diastolic BP, 80 to 89 mmHg). After 5-yr follow-up, an equally stabilizing effect on GFR decline was reported in both intervention groups (10). Also, in the nonhypertensive patients in this study, a more aggressive BP control did not influence GFR, although
a lower percentage of patients progressed from normoalbuminuria to overt albuminuria (11).

In nondiabetic patients, several studies showed that BP level was an important contributor to progression of chronic renal failure (12–14). Within the MDRD study, (non-IDDM) patients with a diverse array of renal disease were randomly assigned to either a usual or a low BP goal. In this (sub)study, a higher mean arterial BP over 3 yr was associated with a faster decline in GFR. Remarkably, these relations were even stronger for patients with a greater baseline proteinuria.

Bakris et al. (15) performed a meta-analysis of long-term clinical trials of BP lowering in both diabetic and nondiabetic patients. This analysis showed a linear relationship between the obtained BP and the rate of decline of renal function across the different studies. Thus, the available evidence indicates that BP reduction exerts a beneficial effect on the decline of renal function. Nevertheless, interesting differences in renoprotective potency between different regimens have also been observed.

**Antihypertensive Treatment Modality Differs in Renoprotection**

Over the last decade, several studies found additional renoprotective benefits of RAAS blockade in comparison with conventional antihypertensive treatment. These observations were made both in diabetes (type 1 and type 2) as well as in a variety of nondiabetic renal diseases.

Early studies on the effect of the ACE inhibitor captopril in small groups of both hypertensive (16) and nonhypertensive type 1 diabetic patients (17) demonstrated that the rate of renal function loss was effectively inhibited by RAAS intervention. In particular, in type 1 diabetic patients with nephropathy, Bjorck et al. showed that RAAS intervention with enalapril does reduce the rate of renal function decline more than antihypertensive treatment with metoprolol, both reaching a similar BP (18,19). Interestingly, in the patients of the enalapril group, a significant reduction in proteinuria was observed. A large randomized controlled trial (Collaborative trial) performed by Lewis et al. (3) compared captopril with placebo in type 1 diabetic patients with mild proteinuria. For both groups, additive conventional drugs were used to titrate the BP to a similar level. This study showed a better renal outcome in the RAAS intervention group that was still apparent after adjustment for small but nonsignificant differences in BP.

In type 2 diabetic patients, a beneficial effect of intervention in the RAAS was found as well. In normotensive type 2 diabetic patients, RAAS intervention by enalapril has been reported to attenuate progression of renal function loss (20). During 7-yr follow-up treatment with enalapril, a risk reduction of 42% (95% CI, 15 to 69%) for developing nephropathy was found. Recently, two extensive randomized double-blind placebo controlled studies investigated the renoprotective effect of RAAS intervention by AngII antagonists. In the RENAAL trial (4), fewer patients in the losartan treatment group in comparison with the placebo group reached the primary endpoint, defined as a composite of doubling of the baseline serum creatinine, end-stage renal disease, or death. In both groups, additional conventional antihypertensive drugs were used to lower BP to the target level. Although there were again small differences in BP observed between the two arms in favor of the losartan arm, the benefit exceeded that attributable to BP reduction after statistical adjustment. In accord with earlier findings, treatment with losartan was associated with a reduction in proteinuria. Also in the IDNT trial (5), treatment with irbesartan was associated with a lower risk of reaching the primary composite endpoint compared with the placebo group and compared with a calcium channel antagonist group. The changes or differences in BP that were achieved could not explain these differences. Again, after treatment with irbesartan proteinuria was reduced. In contrast, the type 2 diabetic patients in the UKPDS did not show that RAAS intervention is superior to conventional antihypertensive treatment, although the study did show the long-term benefit of a lower than usual BP goal (21). However, an additional benefit of the ACE inhibitor captopril against conventional treatment with the β-blocker atenolol could not be confirmed in reaching the end point of renal failure (22). Also, a small randomized double-blind parallel study comparing lisinopril and atenolol in hypertensive type 2 diabetic patients reported an identical BP reduction and GFR decline after a follow-up of almost 3 yr (23). In addition, the ABCD study did not show a larger benefit of ACE inhibition on renal function loss in either hypertensive or nonhypertensive type 2 diabetic patients (10,11). These contrasting findings may be due to the design of the studies comparing two single drugs, whereas the IDNT and RENAAL studies were designed to compare the AngII antagonist with placebo in addition to conventional antihypertensive therapy. Furthermore, β-blockers may not be the suited comparator drug, because it is reported that β-blockade effectively inhibits RAAS by another mechanism than ACE inhibitors and AngII antagonists (24).

In nondiabetic patients, the benefits of RAAS intervention have also been established. In the AIPRI study, Maschio et al. (1) conducted a randomized double-blind placebo-controlled trial comparing benazepril with placebo. Additive conventional antihypertensive medication was used to titrate to the BP goal in this study. After 3-yr follow-up, an overall risk reduction of 53 (95% CI, 27 to 50%) was found in the treatment group for reaching the primary endpoint, i.e., doubling baseline serum creatinine concentration or the need for dialysis. Again, a significant BP difference was observed in favor of the RAAS intervention arm. After adjustment for the lower BP in the benazepril group, the overall risk reduction prevailed. Again, benazepril induced a significant proteinuria reduction compared with placebo. Finally, the REIN trial (2) in patients with overt proteinuria demonstrated a clear-cut beneficial effect of ramipril. In this prospective randomized double-blind trial, a prestratification recognized two levels in proteinuria in patients assigned to ramipril or placebo plus conventional antihypertensive therapy. In patients with proteinuria of 3 g or more, ramipril safely reduced the rate of GFR decline and halved the combined risk of doubling serum creatinine or end-stage renal disease. These effects were accompanied by a substantial lowering of the urinary protein excretion rate. The reported reno-
protected effect appeared to exceed what could be expected from the degree of BP reduction. In a recent meta-analysis of 11 randomized trials in nondiabetic renal disease, the antihypertensive strategy with ACE inhibition was compared with placebo or conventional antihypertensive medication (25). In most reviewed studies, a better BP control was reached during treatment with an ACE inhibitor. After adjustment for BP, this meta-analysis showed also a significant beneficial effect in favor of ACE inhibition.

In conclusion, the available data strongly suggest that RAAS intervention has a renoprotective effect that goes beyond its antihypertensive effect in different renal diseases. However, in most studies, BP was not similar in the tested arms and was notably lower in the RAAS intervention arm. One could therefore still state that BP is the sole determinant of renoprotection and that no extra benefit is to be expected from RAAS intervention giving similar BP control. Of note, all of the studies showed that intervention in the RAAS led to a reduction of urinary protein excretion. This antiproteinuric effect was significantly higher than all the other treatment strategies.

**Proteinuria: Marker for Progression**

The above findings, adding to earlier data, have drawn attention to the role of proteinuria as a predictor of progressive renal function loss. Proteinuria is nowadays looked upon as a marker, or maybe even a causal factor, of progressive renal function loss, and not merely a consequence of renal disease. In different renal conditions, both in man and experimental renal diseases, proteinuria consistently determines the rate of progression of renal function loss (26,27). This may indeed point to the pathogenic role of proteinuria in progressive renal damage. The MDRD study (14) showed that baseline proteinuria was an important determinant of the renoprotective benefit in the follow-up after reduction of BP. The additional benefit of a lower BP goal was clearly more pronounced in patients with a higher baseline proteinuria.

In patients with diabetes, it was demonstrated that the amount of reduction in proteinuria achieved during treatment with captopril was associated with a better long-term effect on the decline of renal function loss (28). Also unpublished data of the RENAAL study show that the more one reduces proteinuria the better the renoprotection is achieved, defined as risk reduction for reaching end-stage renal disease (author presentation DdZ, ASN2001).

Similar effects are found in non-diabetic patients. Two studies (29,30) reported that the short-term antiproteinuric response to antihypertensive treatment predicted the GFR decline during follow-up. These correlations were independent of baseline proteinuria. From a therapeutic perspective, it is important to note that the residual proteinuria was correlated with the subsequent progression of renal function loss (30). Moreover, the REIN trial, with hard endpoint data, showed baseline proteinuria to be an independent and accurate predictor of disease progression and end-stage renal disease (31). In response to ramipril treatment, a stronger short-term antiproteinuric effect is a predictor of more effective protection against end-stage renal disease in the long term (32).

Thus, the large clinical trials comparing RAAS intervention with conventional antihypertensive strategies or placebo show that the renoprotective effect related to RAAS intervention is associated with a better antiproteinuric effect during RAAS intervention. Considering the predictive value of antiproteinuric potency for long-term renoprotection, and the consistent antiproteinuric efficacy of RAAS blockade, it would be logical to assume, that these specific antiproteinuric effects are involved in a renoprotective action exceeding the reduction of BP.

**Antiproteinuric Properties Count: Another Strategy?**

The importance of proteinuria reduction for renoprotection is supported by the renoprotective action of several BP-neutral interventions. As to nonpharmacologic intervention, data indicate that a low-protein diet lowers proteinuria and reduces the rate of renal function loss (33). In an interesting parallel to pharmacologic intervention, the amount of initial proteinuria reduction induced by the diet is correlated with the degree of subsequent renal function loss.

The effect of non-antihypertensive pharmacologic intervention on proteinuria is of interest as well. Immunosuppressive treatment was already reported to reduce proteinuria, and with that to influence the renal prognosis (34). Before the era of RAAS blockade, several groups focused on the effect of intervention in the synthesis of prostaglandins on proteinuria. Prostaglandins are modulators of vascular tone, glomerular hemodynamics, salt and water homeostasis, and renin-secretion in the kidney. The prostaglandin cascade is activated in several renal conditions. As such, prostaglandins may be involved in the pathophysiology of progressive renal function loss.

In nondiabetic renal disease, inhibition of prostaglandins by non-steroidal antiinflammatory drugs (NSAID) leads to renal hemodynamic changes, with a reduction in intraglomerular pressure and reduction of proteinuria (35,36). Historically, besides corticosteroids, NSAID were the first drugs with a marked antiproteinuric effect (37,38). Similar antiproteinuric effects were observed in diabetic nephropathy (39). The effect on proteinuria appears related to the degree of prostaglandin E-2 (PGE-2) inhibition in the urine (40,41). Moreover, when ACE inhibitors are compared with NSAID, it is reported that there is equal reduction in urinary protein excretion (42,43). A combination of both treatments resulted even in a more potent antiproteinuric effect (43,44). Interestingly, Vriesendorp et al. (45) reported on the renoprotective effect of indomethacin when used as an antiproteinuric tool in patients with proteinuria. Unfortunately, this was a retrospective open-label, nonrandomized study, and prospective studies have never been carried out.

Of note, the antiproteinuric effect of NSAID, and also of RAAS intervention, appears to occur only under special conditions. First, it is clearly dependent on the dose of the drugs. For indomethacin, naproxen, and flurbiprofen, the maximal allowed chronic dose had to be used for achieving an optimal antiproteinuric effect (46,40). Second, not only the dose of the NSAID, but also the specific NSAID determined the degree of response. Indomethacin was considered to be superior to re-
respectively diclofenac and flurbiprofen (40). Third, the patient has to be on a sodium-restricted diet or use a diuretic to attain the full potential of this antiproteinuric treatment (35).

These findings underscore that without systemic effects on BP specific agents can induce an antiproteinuric response and subsequent renoprotection. Like RAAS intervention, treatment with NSAID as indomethacin or naproxen may have a beneficial effect on renal function. Because of the well-known side effects of NSAID and the required high dose, it is not attractive to study the long-term renoprotective effect in patients with nephropathy.

A Novel Strategy: COX-2 Inhibition

Several recent data suggest that COX-2 inhibition may be a novel and promising renoprotective strategy for diabetic and nondiabetic patients with proteinuria. In animal studies, COX-2 is upregulated in progressive renal disease models, such as ablation and diabetes (47). Moreover, COX-2 inhibition has antiproteinuric and renal protective effects in these animal models (47,48). So far no data on the antiproteinuric or renoprotective action of COX-2 inhibition are available in humans. There are data, however, showing similarity between NSAID and COX-2 inhibitors on renal hemodynamics and sodium handling (49). Thus, it may be worthwhile to investigate whether COX-2 inhibitors also share the antiproteinuric properties of the NSAID, particularly because COX-2 inhibition was reported to have few side effects in comparison with NSAID in patients with rheumatic disease (50,51). Although the VIGOR trial (51) reported a higher incidence of myocardial infarction in the rofecoxib group, a recent analysis could not provide any evidence that this drug (or the COX-2 inhibitor class) has an excess of cardiovascular risk (52). Therefore, it would be interesting to study the influence of COX-2 inhibition on proteinuria and its putative renoprotective action. This would allow studying the antiproteinuric effect with a drug that has a low side effect profile without influencing systemic BP. Thus we would further elucidate the role of proteinuria in progressive renal damage and also test a new application in proteinuric patients in whom to date the optimal reduction of proteinuria cannot always be obtained due to the drug-induced symptomatic hypotension. Moreover, the additive effect of NSAID and ACE inhibition on proteinuria suggests that COX-2 inhibitors added to ACE inhibitors may be a fruitful strategy to reduce residual proteinuria during RAAS blockade.

Conclusion

In summary, agents that reduce BP provide renoprotection in chronic renal diseases. An additional renoprotective effect is suggested to be achieved by intervention in the RAAS. ACE inhibitors and AngII antagonists show this additional, non-pressure-related effect on decline of renal function. The characteristic potential of both agents to reduce the proteinuria appears to be the strongest marker for renal outcome. We therefore conclude that the antiproteinuric characteristics of the specific agent used for lowering BP determines the degree of renoprotection more than reduction in BP alone. We conclude that it is not only the BP reduction that is important for renal protection. The particular agent (RAAS intervention) has a specific renal protective effect and is thus the agent of choice in patients with (a chance of) progressive renal function loss.

To obtain more effective renoprotective strategies in the future, it would be of interest to specifically explore the renoprotective action of non-antihypertensive agents.

References


45. Vriesendorp R, Donker AJM, de Zeeuw D, de Jong PE, van der Hem GK, Brentjens JRH: Effects of nonsteroidal anti-