ACE Inhibitors versus AT₁ Receptor Antagonists in Patients with Chronic Renal Disease

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The success of Angiotensin-converting enzyme (ACE) inhibitors in preventing the progression of chronic renal insufficiency has led investigators to study the effects of other inhibitors of the renin-angiotensin system (RAS). Recently, the results of the first large-scale trials with angiotensin II type 1 receptor (AT₁) antagonists became available (1,2). This article discusses the relative merits of ACE inhibitors, AT₁ antagonists, and the combination of both drug classes in the treatment of chronic renal disease. First, we will review the potential differences between the effects of both drug classes on the basis of pathophysiologic considerations. Then we will provide a brief overview of clinical trials on the progression of renal diseases. Finally, we will review the clinical studies that have compared head-to-head ACE inhibitors and AT₁ antagonists and discuss combination therapy with both drug classes. Except for the first part, we will limit our discussion to clinical studies in patients or volunteers.

Differential Effects of ACE Inhibitors versus AT₁ Antagonists

The main common action of ACE inhibitors and AT₁ antagonists is the reduction of the stimulation of the AT₁ receptor by its ligand angiotensin II (AngII) (Figure 1). ACE inhibitors achieve this effect by blocking ACE, thus limiting the amount of AngII available for binding to the AT₁ receptor, whereas AT₁ antagonists directly inhibit the binding of AngII to AT₁. Both RAS blockers induce a compensatory upregulation of renin, with more AngI being formed. In addition to AngII, several other products of AngI exert physiologic actions, including peptides generated by ACE-independent pathways (Figure 1). AngIII binds to AT₁ receptors (3). Additional specific receptors have been demonstrated for AngIV (3) and postulated for angiotensin(1–7) (4). The plasma levels of angiotensin(1–7) may contribute to vasodilation but are unlikely to account for differential effects of both drug classes. In contrast, AngIV plasma levels increase after AT₁ antagonists (5) but decrease after ACE inhibitors (6). AngIV may contribute to the effects of AT₁ antagonists via the AT₄ receptor, which mediates vasodilation (3). There are, however, no convincing data, particularly in humans, to prove a role of AngIV/AT₄ in mediating the effects of AT₁ antagonists.

Of several enzymes other than ACE that can generate AngII (Figure 1), human heart chymase cloned by Urata et al. (7) has attracted particular attention. The majority of AngI-forming activity in human heart tissue homogenates was due to chymase, not ACE (7). Initial studies suggested that humans possess an AngII-generating chymase, whereas rodents exhibit only AngII-degrading chymase-like activity (8). However, more recent data have unequivocally shown that rodent chymase enzymes can generate AngII (9) and cause hypertension when overexpressed as a transgene (10), a crucial point that has never been demonstrated for human chymase. Like other non-ACE enzymes, human chymase activity is readily detectable in extracts of tissue homogenates, but its contribution to AngII generation in intact tissues in vivo is questionable (11,12). If chymase substantially contributes to AngII generation in the human kidney, one would expect a much higher degree of blockade of the RAS by AT₁ antagonists than by ACE inhibitors, as pointed out by Hollenberg et al. (8). We do not think that the available data from head-to-head comparisons of both drug classes, as reviewed below, provide support for this hypothesis. More research with chymase-specific inhibitors will be needed.

Two important differences between ACE inhibitors and AT₁ antagonists are depicted in Figure 2: the blockade of bradykinin degradation by ACE inhibitors and the unopposed activation of the AngII type 2 receptor (AT₂) when AT₁ antagonists are administered. The latter mechanism may explain the recent observation that AT₁ antagonists can also increase bradykinin levels, e.g., in vessels (13) or in the kidney (14). However, the magnitude of bradykinin increases after AT₁ antagonists is presumably much less than after ACE inhibitors. In addition, the bradykinin-stimulating action of AT₁ antagonists has been most conclusively demonstrated in genetically altered rodents with either overexpression (13) or deletion (14) of AT₂.
Whether this mechanism occurs in humans has yet to be tested. In contrast, ACE unequivocally plays a major role in degrading bradykinin and leads to a substantial and lasting increase in the concentration of this peptide. Kinins contribute significantly to the BP lowering effects of ACE inhibitors in patients and healthy volunteers (15). Studies with B2 bradykinin receptor antagonists in humans revealed that up to 30 to 50% of the acute hypotensive response to a single ACE inhibitor dose may be due to kinins (15). Kinins also promote some unwanted side effects of ACE inhibitors such as cough (16), angioneurotic edema (16), or anaphylactoid reactions to dialysis membranes (17).

Less is known about the contribution of kinins to the various intrarenal effects of ACE inhibitors. In rats, kinins may contribute to the acute hemodynamic effects of ACE inhibitors on the kidney, especially to efferent glomerular vasodilation (18). In humans, however, the renal vasodilator response to an ACE inhibitor was not affected by a bradykinin B2 receptor antagonist (15). Circumstantial evidence from studies comparing ACE inhibitors and AT1 antagonists does not point to a major role of kinins in the reduction of proteinuria by ACE inhibitors in humans (19).

AT1 antagonists but not ACE inhibitors lead to an exaggerated stimulation of the AT2 receptor (Figure 2). AT2 is present in the adult human kidney (20), but its physiologic function is still a matter of research. The present knowledge on its expression and signal transduction was comprehensively reviewed by De Gasparo et al. (3). Most studies indicate that AT2 counteracts the vasoconstrictor (14) and proliferative actions (21) of AT1, e.g., by promoting apoptosis (22,23). A very recent article suggested that part of this antagonism between AT1 and AT2 may be due to the formation of AT1–AT2 heterodimers, i.e., the AT2 protein itself may directly inhibit AT1 (24). The expression of AT2 is highest and most widespread during early embryonic development (20,25). Nevertheless, lack of AT2 does not induce major developmental abnormalities (26), in contrast to the renal abnormalities induced by deletion mutations of virtually all other major components of the RAS (25).

Renal interstitial fibrosis after ureteral obstruction was enhanced in rats with pharmacologic blockade of AT2 (22) and in mice with a targeted deletion mutation of AT2 (23), probably due to a reduction of the number of interstitial cells undergoing apoptosis (22,23). The notion that AT2 promotes apoptosis and decreases fibrosis is intriguing because it suggests that AT1 antagonists may have a greater potential for preventing the progression of renal scarring than ACE inhibitors. The role of
Figure 2. Simplified schematic drawing of differential effects of angiotensin-converting enzyme (ACE) inhibitors (upper panel) and AT$_1$ receptor antagonists (lower panel) on the renin-angiotensin and bradykinin systems. ACE inhibitors decrease the formation of AngII and the breakdown of bradykinin (gray shaded areas). Consequently, AT$_1$ and AT$_2$ receptors for AngII are activated less (gray shaded area), whereas B1 and B2 receptors for bradykinin are activated more (green shaded area). Plasma renin and AngI are increased by ACE inhibitors as well as by AT$_1$ antagonists (green shaded areas). AT$_1$ antagonists, on the other hand, also increase AngII, leading to activation of the AT$_2$ receptor (green shaded area) while AT$_1$ is blocked (gray shaded box). The AT$_2$-mediated, slight increase of bradykinin by AT$_1$ antagonists is indicated (light green shaded area).
unopposed stimulation of \( \text{AT}_2 \) for the effects of \( \text{AT}_1 \) antagonists will have a major bearing on the question of whether combined therapy with \( \text{AT}_1 \) antagonists and ACE inhibitors will exert additive benefit. On the other hand, stimulation of \( \text{AT}_2 \) may contribute to the proinflammatory actions of AngII in the kidney (27), an action that is also transduced by the \( \text{AT}_1 \) receptor (28). Very little is known about the function of \( \text{AT}_2 \) in humans. Circumstantial evidence suggests that a polymorphism of the gene for \( \text{AT}_2 \) may modulate left ventricular hypertrophy in patients with hypertension (29). Functional studies with \( \text{AT}_2 \) inhibitors in humans are only now beginning (30), and more research will be needed.

**ACE Inhibitors and \( \text{AT}_1 \) Antagonists and the Progression of Kidney Diseases**

By the mid-1980s, animal studies had shown that ACE inhibitors were superior to other antihypertensive drugs in preventing structural damage to the kidney in models of renal injury (31). Within a few years, several retrospective or small-scale open studies suggested that ACE inhibitors had the same effects in patients with type 1 diabetes and nephropathy (32) or other chronic kidney diseases (33).

On the basis of this sound experimental and pilot clinical evidence, several large-scale multicenter, prospective, randomized clinical trials on the effects of ACE inhibitors in progressive kidney diseases were initiated in the late 1980s. In most of these studies, the occurrence of end-stage renal failure or doubling of serum creatinine or a composite of both of these end points and death were defined as the primary end points. Table 1 provides an overview of these studies. A relative risk reduction of 45 to 56% by ACE inhibitors was reported for patients with type 1 diabetes and nephropathy (34), for hypertensive nephrosclerosis (35) and for chronic nondiabetic glomerular (36,37) as well as interstitial (36,38) kidney diseases. The absolute benefit of ACE inhibitors is bigger in patients with high-grade proteinuria but extends to patients with low-grade proteinuria (37,38) or interstitial kidney disease (36). Longer observation periods are necessary in cases with low-grade proteinuria because progression tends to be very slow. For example, in the Angiotensin-Converting Enzyme Inhibition in Progressive Renal Insufficiency trial (36), the relative benefit of ACE inhibitors therapy was greater in patients with low-grade proteinuria than with high-grade proteinuria, and the reverse was true for the absolute benefit.

In patients with type 2 diabetes, ACE inhibitors were found to be superior to placebo in preventing progression of microalbuminuria to overt proteinuria (39–41). Ravid et al. (39) followed 94 normotensive patients for 5 yr and reported that enalapril reduced urine albumin excretion, BP, and the rate of decline of renal function if compared with placebo. However, ACE inhibitors were not shown to be superior to other antihy-

### Table 1. Overview of large-scale, multicenter, prospective, randomized clinical end point trials of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II (AngII) type 1 receptor (\( \text{AT}_1 \)) antagonist on the progression of chronic kidney disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>Comparison</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril study (34)</td>
<td>1993</td>
<td>( n = 409; \text{ type 1 diabetes and proteinuria} )</td>
<td>captopril versus placebo</td>
<td>45%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>AIPRI (36)</td>
<td>1996</td>
<td>( n = 583; \text{ chronic nephropathies, mostly nondiabetic} )</td>
<td>benacepril versus placebo</td>
<td>53%</td>
</tr>
<tr>
<td>REIN stratum 2 (37)</td>
<td>1997</td>
<td>( n = 117; \text{ nondiabetic chronic nephropathies, proteinuria} \geq 3 \text{ g/d} )</td>
<td>ramipril versus placebo</td>
<td>52%</td>
</tr>
<tr>
<td>UKPDS 39 (43)</td>
<td>1998</td>
<td>( n = 758; \text{ type 2 diabetes and hypertension} )</td>
<td>captopril versus atenolol</td>
<td>NS</td>
</tr>
<tr>
<td>REIN stratum 1 (38)</td>
<td>1999</td>
<td>( n = 186; \text{ nondiabetic chronic nephropathies, proteinuria} \geq 1 \text{ g/d} ) but (&lt; 3 \text{ g/d} )</td>
<td>ramipril versus placebo</td>
<td>56%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>AASK interim analysis: ramipril and amlodipine arms (35)</td>
<td>2001</td>
<td>( n = 653; \text{ African Americans with hypertension and probable hypertensive nephrosclerosis} )</td>
<td>ramipril versus amlodipine</td>
<td>48%</td>
</tr>
<tr>
<td>IDNT (2)</td>
<td>2001</td>
<td>( n = 1715; \text{ type 2 diabetes and hypertension} )</td>
<td>irbesartan versus placebo</td>
<td>20%</td>
</tr>
<tr>
<td>RENAAL (1)</td>
<td>2001</td>
<td>( n = 1513; \text{ type 2 diabetes and nephropathy} )</td>
<td>losartan versus placebo</td>
<td>16%</td>
</tr>
</tbody>
</table>

<sup>a</sup> RR, risk reduction for the composite of end-stage renal failure, death, or doubling of serum creatinine or 50% reduction of clearance. AIPRI, Angiotensin-Converting Enzyme Inhibition in Progressive Renal Insufficiency study group; REIN, Ramipril Efficacy in Nephropathy trial; UKPDS, UK Prospective Diabetes Study Group; AASK, African American Study of Kidney Disease and Hypertension; IDNT, Irbesartan Diabetic Nephropathy Trial; RENAAL, Reduction of Endpoints in Non-insulin–dependent diabetes mellitus with Angiotensin II Antagonist Losartan trial; NS, no significant reduction.

<sup>b</sup> End point doubling of serum creatinine only.

<sup>c</sup> End point end-stage renal failure only.
pertensive drugs. A small prospective randomized study in 74 patients with type 2 diabetes, hypertension, and albuminuria did not detect a difference between captopril and other antihypertensive drugs (metoprolol and hydrochlorothiazide) with regard to the time course of GFR (42). The same was true for two large-scale end point studies, UK Prospective Diabetes Study Group 39 (43)(Table 1) and the Appropriate Blood Pressure Control in non–insulin-dependent Diabetes mellitus (ABCD) trial (44) with 470 patients, which compared ACE inhibitors with other antihypertensive treatment. However, both studies had very few renal end points, either because only patients with newly diagnosed type 2 diabetes were included (43) or because the trial ended prematurely due to excess cardiovascular events in the non–ACE inhibitor arm (45).

The lack of powerful long-term trials on the course of nephropathy in type 2 diabetes was disturbing because this disease is becoming an ever more important cause of end-stage renal failure worldwide (46). This therapeutic gap has now been filled by AT1 antagonists (Table 1). Two large-scale trials demonstrated that AT1 antagonists ameliorate the progression of overt nephropathy of type 2 diabetes compared with placebo (1) or a dihydropyridine calcium antagonist (2). Additionally, a mid-scale, prospective randomized trial showed that AT1 antagonists prevented or delayed the development of overt proteinuria in type 2 diabetic patients with hypertension and microalbuminuria at baseline (47). The Irbesartan Diabetic Nephropathy trial (IDNT) (2) comprised an amlodipine arm in addition to the irbesartan and placebo arms. Although irbesartan and amlodipine caused slight and identical reductions of BP compared with placebo, renal protection was only afforded by irbesartan (2). The most obvious question, i.e., whether ACE inhibitors and AT1 antagonists are any different as nephroprotective agents, was not answered by the most recent trials, which raised serious criticism for the design of the studies and potential nonscientific influence of the sponsors on trial design (48).

These recent studies with AT1 antagonists and the ACE inhibitors trials (Table 1) reassure us that blockade of the RAS retards the progression of nephropathy of almost any etiology, including patients with type 2 diabetes. Unfortunately, people with adult dominant polycystic kidney disease are an exception (36). One may ask whether the nephroprotective effect of inhibition of the RAS by AT1 antagonists indicates that ACE inhibitors will have the same effect in patients with type 2 diabetes. Some arguments support this assumption, but the principles of evidenced-based medicine mitigate against it. ACE inhibitors have been shown to be nephroprotective, independent of their effects on BP in type 1 diabetes (34) as well as in other nephropathies (Table 1). Clinical and histologic aspects of nephropathy in type 1 and 2 diabetes are very similar (46). At the present stage it appears unlikely that renal end point studies comparing AT1 antagonists with ACE inhibitors will ever be undertaken, due to the very large sample size that would be required to detect differences.

Finally, the effect of ACE inhibitors on cardiovascular end points apart from the kidney deserve some consideration, although a review of these studies is beyond the scope of this article. Patients with renal disease, particularly type 2 diabetics, are clearly at a high risk for myocardial infarction, heart failure, and cardiovascular death and are therefore candidates for ACE inhibitors treatment regardless of the progression of nephropathy (49). A recent subgroup analysis of the Heart Outcomes Prevention Evaluation (HOPE) study (50) reinforced this notion and demonstrated not only that patients with renal disease do carry a high risk of cardiovascular events but also that this risk can be ameliorated by ACE inhibitors. These data show that ACE inhibitors should not be withheld from patients with type 2 diabetes and nephropathy and did in fact prompt the early termination of the RENAAL study (1).

Direct Comparisons of Renal Effects of ACE Inhibitors and AT1 Antagonists

In patients with heart failure, large-size randomized prospective trials with clinical end points have shown similar effects of AT1 antagonists and ACE inhibitors (51). It appears unlikely that comparable studies in patients with renal disease will ever be done. Comparisons between AT1 antagonists and ACE inhibitors in patients with renal diseases have been limited to the investigation of surrogate parameters. The effects of AT1 antagonists and ACE inhibitors on proteinuria are probably the best available evidence for comparing the efficacy of both drug classes for the amelioration of progressive glomerular disease because proteinuria predicts subsequent loss of renal function (37).

In a meta-analysis of several studies on the renal blood flow effects of AT1 antagonists and ACE inhibitors, Hollenberg et al. (8) hypothesized that AT1 antagonists are more effective because AngII generated by chymase is also antagonized. Direct comparisons of the renal hemodynamic effects of AT1 antagonists and ACE inhibitors in patients with hypertension or renal diseases did not support this hypothesis but yielded similar renal vasodilation by both classes of drugs (15,19). Comparing acute renal hemodynamic effects is subject to confounding factors such as different pharmacokinetic or hypotensive properties of the drugs.

Earlier small-scale studies on protein excretion, or dextran sieving, pointed out subtle differences between the effects of AT1 antagonists and ACE inhibitors on the glomerular filtration barrier. For example, losartan but not enalapril was found to decrease the fractional clearance of mid-size dextrans (52). Furthermore, losartan decreased proteinuria only after prolonged treatment compared with enalapril (19). However, more recent, larger-scale studies in patients with renal disease have rather emphasized the similarity of the effects of AT1 antagonists and ACE inhibitors on protein excretion; Remuzzi et al. (53) reported similar effects of enalapril and irbesartan on proteinuria and dextran sieving coefficients in patients with IgA nephropathy. Lacourcière et al. (54) treated 92 patients with type 2 diabetes and microalbuminuria for 1 yr with either enalapril or losartan. Both drugs reduced microalbuminuria to a comparable degree, with a trend in favor of enalapril (54). The multicenter Candesartan and Lisinopril Microalbuminuria (CALM) study (55) included 197 patients with type 2 diabetes and microalbuminuria. Candesartan and lisinopril lowered BP
and albumin excretion to the same degree. Again, the ACE inhibitor was slightly more effective (55).

In accordance with the similar renal hemodynamic effects of AT1 antagonists and ACE inhibitors, acute decreases of GFR can occur with similar frequency after starting treatment with both drug classes (56). Otherwise, AT1 antagonists are clearly better tolerated than ACE inhibitors and induce fewer adverse events (e.g., cough, angioneurotic edema) (51,54,56). In patients with renal insufficiency, AT1 antagonists increase serum potassium less than ACE inhibitors (57). Consequently, the limited evidence available to date indicates that a carefully supervised trial of AT1 antagonists can be justified in many patients in whom ACE inhibitors were withdrawn because of unwanted side effects (58).

**Combination Therapy with ACE Inhibitors and AT1 Antagonists**

The rationale for a combination therapy with AT1 antagonists and ACE inhibitors is based on the assumption that certain nonclassical pathways of the RAS produce substantial amounts of AngII. AT1 antagonists would counteract the AT1-mediated effects of residual AngII formation by non-ACE enzymes like chymase (Figure 1), whereas ACE inhibitors would additionally increase kinins (Figure 2). Furthermore, both AT1 antagonists and ACE inhibitors would synergistically elevate the levels of angiotensin(1–7), which may also promote vasodilation (4). On the other hand, adding an ACE inhibitor to AT1 antagonists may be detrimental if stimulation of the AT2 receptor contributes substantially to the beneficial effects of AT1 antagonists (Figure 2). Finally, combining both drug classes might simply provide a higher degree of blockade of classical RAS pathways (Figure 1) than either drug class alone. Especially in human studies, where very high doses of drugs cannot be safely administered, the question of whether the combination of ACE inhibitors and AT1 antagonists is doing more than maximal doses of one of the two will probably remain unanswered.

The potential concern that combining AT1 antagonists and ACE inhibitors may lead to more side effects, e.g., hyperkalemia, has been alleviated by two studies with reasonable sample size (54,55). The combination of candesartan and lisinopril turned out to be safe in 67 patients with type 2 diabetes and albuminuria (55), and the combination of valsartan and benazepril in 86 patients with renal insufficiency of various etiologies (54). In both studies, side effects and tolerability of the combination were comparable to those of the ACE inhibitors alone. However, one must add the cautionary note that these studies had insufficient power to address the frequency of rare serious adverse events, e.g., angioneurotic edema.

Combination therapy with AT1 antagonists and ACE inhibitors at usual clinical doses decreases BP to a greater extent than either drug alone (54,55,59). Limited data are available on the effects of combination therapy on proteinuria or albuminuria. In two small studies in selected patients with IgA nephropathy, Russo et al. (59,60) observed that the combination of losartan and ACE inhibitors was at least additive in decreasing protein excretion, whereas doubling the dose of either monotherapy had no effect (59,60). However, Agarwal (61) reported that combination therapy was not superior to ACE inhibitors alone in decreasing proteinuria in patients with various diseases, mostly diabetic nephropathy. The study by Agarwal (61) is the only one to date in which AT1 antagonists were added on top of what can be considered, for clinical purposes, as a maximal dose of ACE inhibitors (40 mg of lisinopril).

Protein or albumin excretion, respectively, was also measured in the two larger trials of combination treatment mentioned above (54,55). Ruilope et al. (54) reported that the combination of AT1 antagonists and ACE inhibitors reduced proteinuria by 59%, compared with 45% reduction by the same dose of AT1 antagonists alone (P = 0.047). However, monotherapy with ACE inhibitors was not tested. Moreover, this study (54) was designed mainly to test the safety of combination therapy, and the treatment periods may have been too short to evaluate the full extent of the antiproteinuric effects. In contrast, the CALM study (55) was designed to compare the efficacy of AT1 antagonists and ACE inhibitors for lowering microalbuminuria in patients with type 2 diabetes. Combination therapy decreased albumin excretion (by 50%) significantly more than candesartan alone (24%) but not significantly more than lisinopril alone (39%).

Several very recent trials presented at the 2001 American Society of Nephrology/International Society of Nephrology meeting reported a consistently greater antiproteinuric effect of the combination therapy than with ACE inhibitors or AT1 antagonists alone. One prospective trial evaluated clinical end points (doubling of serum creatinine or end-stage renal failure) in 245 patients with nondiabetic renal insufficiency followed for 4 yr (62). Treatment withtrandolapril, losartan, and the combination resulted in 25, 24, and 13 renal end points, a significant difference (62). As indicated above, one has to scrutinize those data, once published, for the doses of the drugs used.

**Conclusions**

ACE inhibitors are currently the best-documented treatment to delay the progression of chronic nondiabetic renal diseases and nephropathy in patients with type 1 diabetes. The beneficial effects of ACE inhibitors, like those of AT1 antagonists, cannot be explained by BP lowering alone. Clearly, the blockade of the formation or action of AngII exerts additional effects on fibrotic and/or inflammatory processes in the kidney. The benefits of ACE inhibitors are most apparent in glomerular diseases with proteinuria above 1 g per day but extend also to kidney diseases with lower proteinuria. Patients with type 1 or type 2 diabetes and microalbuminuria should be treated early with ACE inhibitors because these drugs can prevent, or at least delay, the occurrence of overt nephropathy.

In patients who cannot tolerate ACE inhibitors, AT1 antagonists can be given alternatively, although the comparable efficacy of AT1 antagonists in nondiabetic glomerular diseases is supported only by circumstantial evidence (investigations of surrogate parameters in nondiabetic nephropathies and end point studies in type 2 diabetes). To evaluate the potential of combination therapy with AT1 antagonists and ACE inhibitors,
we will need the results of long-term prospective clinical studies, as well as a better understanding of the role of the AT$_2$ receptor. At present, a trial of combination therapy may be justified in selected patients if BP and/or proteinuria cannot adequately be lowered by AT$_1$ antagonists or ACE inhibitors monotherapy, as a rule in combination with other antihypertensive agents.

The choice of drugs is less obvious in patients with type 2 diabetes. The progression from microalbuminuria to overt nephropathy can be delayed or prevented by AT$_1$ antagonists (55) as well as by ACE inhibitors monotherapy (41), although the only head-to-head comparison between both drug classes indicates that ACE inhibitors may lower microalbuminuria more than AT$_1$ antagonists (55). In patients with type 2 diabetes and overt nephropathy, only AT$_1$ antagonists have been shown to delay the progression of renal insufficiency in clinical end point studies (2,47). Consequently, the notion that AT$_1$ antagonists should be the first-line treatment for nephropathy in type 2 diabetes appears straightforward at first glance. On the other hand, circumstantial evidence indicates that ACE inhibitors are also effective in these patients, as discussed above. ACE inhibitors have simply not been tested in renal end point studies with sufficient power in these patients. Finally, virtually all patients with type 2 diabetes and nephropathy should be treated with ACE inhibitors to reduce their considerable nonrenal cardiovascular risk (50). In our opinion, these considerations justify the selection of ACE inhibitors as first-line therapy also for patients with early and moderate renal disease in type 2 diabetes mellitus.

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