Reduction of proteinuria with angiotensin receptor blockers

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SUMMARY

Renal pathophysiology is elicited by activation of angiotensin II type 1 (AT1) receptors at all stages of renovascular disease. Angiotensin receptor blockers (ARBs) that specifically block the AT1 receptor offer the potential to prevent or delay progression to end-stage renal disease independently of reductions in blood pressure. Proteinuria — an early and sensitive marker for progressive renal dysfunction — is reduced by ARB use in patients with type 2 diabetic nephropathy and microalbuminuria or macroalbuminuria. Retrospective analysis of data available from early trials has confirmed this finding, and has shown that albuminuria reduction is associated with lessening of cardiovascular risk. The ARB telmisartan is equivalent to enalapril in preventing glomerular filtration rate decline, and equivalent to valsartan in reducing proteinuria. Telmisartan is more effective than conventional therapy in lowering the risk of transition to overt nephropathy in hypertensive and normotensive patients. An additive effect has been seen in smaller studies when telmisartan has been added to lisinopril therapy, and high-dose telmisartan reduces albuminuria better than low-dose telmisartan. Similar data were obtained with other ARBs such as candesartan, losartan, valsartan, or irbesartan. These data support the proposition that blockade of the renin–angiotensin system in beyond that required for maximum blood pressure reduction provides optimum renal protection.

KEYWORDS angiotensin receptor blockers, diabetes, proteinuria, renal disease, renin–angiotensin system blockade

INTRODUCTION

Proteinuria is an early and sensitive marker for progressive renal dysfunction.1 In the early stages of kidney disease, very small amounts of protein are detectable in the urine (microalbuminuria). As the disease progresses to clinical or overt nephropathy, larger quantities of urinary protein can be measured (macroalbuminuria). Hemodynamic injury to the vascular endothelium and glomerulus can be induced by both systemic and glomerular hypertension, which is promoted by an activated renin–angiotensin system (RAS). Angiotensin II, the primary agent of this system, is centrally involved in all stages of renal pathophysiology.2

Angiotensin-II-receptor blockers (ARBs) are primarily prescribed as antihypertensive drugs, and several guidelines recommend these agents as first-line therapy for patients with arterial hypertension.3–5 The benefits of ARBs extend, however, beyond lowering of blood pressure. Their use to selectively inhibit the angiotensin II type 1 (AT1) receptor can protect against the progression of kidney disease.

This article addresses the central role of angiotensin II in the risk, development and progression of cardiovascular and renovascular disease and considers the potential of RAS blockade for preventing target-organ damage in patients with diabetic nephropathy. It also summarizes the findings from several trials, addressing the efficacy of ARB therapy (specifically with telmisartan) in comparison with that for an angiotensin-converting enzyme (ACE) inhibitor with enalapril, another ARB (valsartan), and conventional treatment in patients with and without hypertension.

This information was first presented at a meeting sponsored by Boehringer Ingelheim and held in Lisbon on 28 and 29 April, 2006. The meeting, which addressed a range of topics related to RAS blockade, was endorsed by the European Society of Hypertension and the International Society of Nephrology. The meeting was called A new dawn in cardiovascular protection: total cardiovascular risk: rigorous treatment of risk factors.
ANGIOTENSIN II IN RENOVASCULAR AND CARDIOVASCULAR DISEASE
Renal disease and coronary artery disease both develop through a general progression of pathophysiologic events, beginning with cardiovascular risk factors and culminating with end-organ disease. Risk factors such as high blood pressure, raised concentrations of cholesterol, diabetes mellitus, and insulin resistance elicit pathological changes in the heart and vasculature. Changes include atherosclerosis, left ventricular hypertrophy, coronary vascular obstruction, and myocardial ischemia. Patients can go on to experience myocardial infarction and arrhythmia, which can lead to sudden death. In patients who survive, ventricular wall remodeling eventually occurs, leading to increased muscle mass and cardiac dilatation, ultimately resulting in congestive heart failure. In renovascular disease, the same cardiovascular risk factors elicit pathological changes, such as endothelial dysfunction and microalbuminuria. These changes can lead to increased risk of coronary heart disease and nephrotic syndrome, reduced glomerular filtration rate (GFR), and nephrosclerosis. Eventually, end-organ damage occurs in the form of chronic kidney disease stage V.

Angiotensin II is centrally involved in target-organ damage at every stage of cardiovascular and renal pathophysologies. Figure 1 illustrates the roles of angiotensin II in renal disease. The major biological actions of angiotensin II in the kidney are mediated by two functionally distinct receptors, AT$_1$ and AT$_2$. Activation of AT$_1$ receptors is responsible for the pathophysiologic effects of angiotensin II, whereas activation of AT$_2$ receptors plays a part in opposing these pathophysiologic effects. AT$_1$ receptors are abundant in the efferent arterioles of each nephron of the kidney. Receptor activation by angiotensin II induces vasoconstriction, which raises glomerular capillary pressure and increases glomerular filtration, and leads to proteinuria. In addition to renal vasoconstriction induced by angiotensin II, direct profibrotic and proinflammatory actions of angiotensin II and aldosterone can promote kidney damage, seen as, for example, activation of plasminogen activator inhibitor 1 or transforming growth factor β (Figure 1).2

BLOCKING THE RAS TO PREVENT TARGET-ORGAN DAMAGE
Potential of ARBs versus ACE inhibitors
Angiotensin II is a central mediator of hemodynamic and nonhemodynamic processes of renal injury. Use of antihypertensive agents that block the RAS will, therefore, cause vasodilatation of the efferent arterioles in addition to lowering blood pressure. These actions should reduce intraglomerular pressure, thereby lessening proteinuria and providing renoprotective effects in patients with nephropathy. Although ACE inhibitors and ARBs both target the RAS, they do so in different ways. This difference might affect their potential benefits in end-organ protection. ACE inhibitors reduce blood pressure by blocking the conversion of angiotensin I to angiotensin II, as well as by preventing the breakdown of bradykinin and other vasactive peptides. Other enzymatic pathways can, however, also lead to the generation of angiotensin II. Over time, therefore, these pathways might compensate for the effect of ACE inhibition, leading to a gradual return of angiotensin II to baseline levels. This phenomenon is known as angiotensin II escape. By contrast, ARBs specifically block the AT$_1$ receptor, thereby effectively inhibiting the pathophysiologic effects of angiotensin II. This action offers the potential for additional benefit beyond blood pressure reduction, including reduced proteinuria and the progression to end-stage renal disease (ESRD) in patients with type 2 diabetes and nephropathy.
### Clinical trials assessing reductions in proteinuria and progression to ESRD

ACE inhibitors and ARBs have been chosen for study in numerous clinical trials.\(^{10}\) ACE inhibitors have been investigated in patients with type 1 or type 2 diabetes.\(^{11–14}\) Overall, studies of these drugs in type 2 diabetes have provided no convincing evidence of efficacy beyond blood pressure control.\(^{15}\)

ARBs have been shown to reduce the incidence of hard endpoints (i.e. relate directly to renal function), such as doubling of baseline serum creatinine concentration or development of ESRD. The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study\(^ {16,17}\) included 1,513 patients with type 2 diabetes and nephropathy. The risk of developing these two hard endpoints was reduced by 25% and 28%, respectively, when compared with placebo.\(^ {16}\) Reduced progression of renal disease was seen in all three tertiles of baseline serum creatinine concentration.\(^ {17}\) In the Irbesartan Diabetic Nephropathy Trial (IDNT),\(^ {18}\) a total of 1,715 hypertensive patients with type 2 diabetes and urinary protein excretion of at least 900 mg/day were randomly assigned 300 mg irbesartan, 10 mg amlodipine, or placebo daily for a mean duration of 2.6 years. The risk of the primary composite endpoint (doubling of serum creatinine, development of ESRD, or death) was reduced in the ARB-treated patients by 20% compared with placebo (\(P = 0.02\)) and by 23% compared with amlodipine group (\(P = 0.006\)). In both RENAAL and IDNT, the superiority of ARB therapy was evident despite very similar changes in blood pressure in the comparator groups.

As early as 2002, the results from these and other trials (Table 1) motivated the American Diabetes Association to recommend that use of ARBs should be standard in the treatment of diabetic nephropathy in patients with type 2 diabetes.\(^ {19}\) Evidence that has become available since that guideline was published has strengthened the case, and the Association’s position has been reiterated.\(^ {20}\) For example, a post hoc subanalysis of the IDNT trial provided strong evidence of the blood-pressure-independent effects of irbesartan compared with amlodipine.\(^ {21}\) Figure 2 shows the relative risk of a renal endpoint in relation to systolic blood pressure and treatment (irbesartan, amlodipine, or placebo). In each treatment group, falls in systolic blood pressure during follow-up were associated with an reduced risk of reaching a renal endpoint. However, in all quartiles of systolic blood pressure, ARB-treated patients experienced improved renal outcomes compared with patients receiving amlodipine or placebo. The relative risk of a renal endpoint in patients taking amlodipine was similar to that in placebo-treated patients. Placebo was, however,
The close relationship between systolic blood pressure and the risk of renal endpoint in the Irbesartan Diabetic Nephropathy Trial subanalysis. Figure 2

Administrated on a background of standard antihypertensive therapy with drugs other than calcium-channel blockers or RAS inhibitors. As well as hard endpoints, ARBs have been extensively investigated in relation to so-called soft endpoints, especially proteinuria. Although this disorder does not directly cause death or disability, it is a key marker of various underlying pathophysiologicals and is linked to decline in renal function, systemic endothelial dysfunction, target-organ damage, and cardiovascular mortality. ARBs have effectively reduced urinary protein concentrations in patients with type 2 diabetic nephropathy, independently of blood pressure lowering. These drugs act either by reducing microalbuminuria in early-stage kidney disease or macroalbuminuria in later-stage disease when GFR is already reduced (Table 1). Overall, reductions in proteinuria seen with ARB treatment have been reported as greater than those with placebo or the calcium-channel blocker amlodipine, despite similar blood pressure reductions in the ARB and calcium-channel blocker groups.

Albuminuria can be employed in risk stratification and treatment assessment. In a post hoc analysis of the LIFE study, decreased microalbuminuria after ARB treatment translated into a reduction in cardiovascular events in hypertensive patients without overt renal disease. The primary analysis of the LIFE study demonstrated that, in 9,193 patients with hypertension and left ventricular hypertrophy, the risk of the primary composite endpoint over 4 years (death, myocardial infarction, or stroke) was significantly lower among patients receiving the ARB losartan than among those taking the β-blocker atenolol, despite similar blood pressure reductions in both groups (23.8 versus 27.9 incidences per 1,000 patient-years, P = 0.021). In the post hoc analysis, the incidence of the primary composite endpoint was assessed in 8,206 patients according to four levels of baseline and in-treatment values of urinary albumin-to-creatinine ratio (<0.5, 0.5–1.0, 1.0–3.0, and >3.0 mg/mmol). Albuminuria concentrations during therapy were closely associated with the risk of developing the primary composite endpoint. When urinary albumin-to-creatinine ratio decreased during treatment, with values moving from the lowest to the highest stratum, the risk for a cardiovascular endpoint increased by threefold to fourfold. This observation, which was independent of blood-pressure-lowering effects, strongly suggests that treatment-induced reductions in albuminuria lead to decreased cardiovascular risk. The distribution of patients across the urinary albumin-to-creatinine ratio strata changed during the study: at baseline, the ratio for 43% of patients was less than 1 mg/mmol, but at 4 years the equivalent value was seen in 53%.

Response to treatment was marked by movement of patients’ ratio values into a stratum that was associated with reduced cardiovascular risk. Monitoring of albuminuria could, therefore, be an important part of the management of hypertensive patients with albuminuria. Intensification of antihypertensive treatment might be considered to reduce urinary protein in patients with ratios in the highest-risk strata.

The importance of minimizing the progression of albuminuria in patients with type 2 diabetes poses the question of whether ARBs should be considered for all such patients, whether they have hypertension or not. Only one major study has thus far assessed an ARB in this role: The INcipieNt to OV ert—Angiotensin II receptor blocker, Telmisartan, Investigation On type II diabetic Nephropathy (INNOVATION) study. The results of this study have not yet been published.

Choice of intervention for RAS blockade

Although ARBs and ACE inhibitors are now established as the therapies of choice for...
patients with diabetic nephropathy, much research remains to be done. A key question is whether one of these drug classes should be the preferred over the other. Only one study, the Diabetics Exposed to Telmisartan And enalapril (DETAIL) study, has so far attempted to address this issue.\(^{32}\)

DETAIL was a 5-year, prospective, multicenter, randomized, double-blind study done in 250 patients with type 2 diabetes and mild to moderate hypertension (seated diastolic/systolic blood pressure during therapy ≤95/180 mmHg), a urinary albumin excretion rate higher than 10 μg/min and lower than 1,000 μg/min, and normal or only mildly impaired GFR [Author: Correct?] (≥70 ml/min/1.73 m²). Telmisartan has the longest plasma half-life and highest volume of distribution of all agents in the ARB class.\(^{30}\) In patients with type 2 diabetes at the earliest stage of renal disease this drug can improve renal endothelial function.\(^{33}\) Enalapril had previously been shown in a 6-year study to significantly reduce the decline of renal function in patients with type 2 diabetes and microalbuminuria.\(^{34}\) Eligible patients received forced titration with either 40–80 mg telmisartan or 10–20 mg enalapril, with optional dose reduction to 40 mg or 10 mg, respectively. The primary endpoint was change in GFR, measured by the iothalamate method, after 5 years of treatment. The two treatments produced similar reductions in blood pressure. The GFR at 5 years was reduced to a similar degree by telmisartan or enalapril therapy (Figure 3), and the rate of decline reduced progressively during the study.\(^{31}\) The typical annual rate of GFR decline in untreated diabetics with proteinuria is 10–12 ml/min/1.73 m².\(^{35}\)

By year 3 of the DETAIL study, the annual decline in GFR had stabilized to approximately 2 ml/min/1.73 m², which is similar to the age-related decline expected in healthy individuals.\(^{36}\)

Interestingly, the mortality in DETAIL was unexpectedly low given the link between renal and cardiovascular disease. Only six patients died in each treatment group, which represented about 5% of the study population. By contrast, the expected mortality rate in older patients with type 2 diabetes of more than 5 years’ duration [Author: Correct?] is around 35% in those with microalbuminuria and 50% in those with macroalbuminuria.\(^{37}\)

The GFR-preserving effect provided by telmisartan in the DETAIL study may be compared with that of other ARBs in studies of renal disease progression, although the populations and treatment durations differ between studies.\(^{38}\) In DETAIL, the mean yearly decline in measured GFR was 3.7 ml/min/1.73 m² after 5 years of treatment with 40–80 mg telmisartan.\(^{32}\) In RENAAL, the yearly decline in estimated GFR was 4.4 ml/min/1.73 m² after 3.4 years of treatment with 100 mg losartan.\(^{16}\)

In the IRbesartan in patients with type 2 diabetes and Microalbuminuria (IRMA 2) study,\(^{21}\) the corresponding value was −5.7 ml/min/1.73 m² after 2 years of treatment with 300 mg irbesartan,\(^{21}\) and in IDNT it was −5.5 ml/min/1.73 m² after 2.6 years of treatment with the same dose.\(^{26}\)

A comparison of the antiproteinuric effects of different ARBs has been investigated in only one large study, a trial to investigate the efficacy of telmisartan versus valsartan in hypertensive type-2 diabetic patients with overt nephropathy (VIVALDI).\(^{39}\) This study was a prospective, 1-year, multicenter, randomized, double-blind, parallel-group trial of patients with type 2 diabetes, hypertension (seated systolic/diastolic blood pressure >130/>80 mmHg), macroalbuminuria (≥900 mg/day) and serum creatinine 97–265 μmol/l in women and 115–265 μmol/l in men. Patients were randomized to receive 80 mg
telsmisartan or 160 mg valsartan once daily, with add-on therapy as required to achieve blood pressure control (<130/80 mmHg). The primary analysis was a noninferiority test of the 24 h urinary protein excretion rate. Since valsartan is an established, renoprotective therapy, these data confirm that telsmisartan is an attractive option in these patients.

A sister trial to VIVALDI, A trial to compare telmisartan 40 mg titrated to 80 mg versus losArtan 100 mg in hypertensive type-2 Diabetic patients with overt nephropathy (AMADEO), is currently ongoing and will provide further valuable information on the relative renoprotective effects of ARBs. A prespecified meta-analysis based on the pooled data of the AMADEO and VIVALDI trials will also be performed.

Maximizing blockade to increase efficacy
Increasing evidence shows that the doses of ARBs and ACE inhibitors that provide maximum blood-pressure-lowering effects might not provide maximum renoprotective effects. High-dose ARB therapy (not high-dose ACE inhibitor therapy, as this is unlikely to be well tolerated) or combined ARBs and ACE inhibitor therapy have been investigated in several trials. In an open-label, randomized study of 78 hypertensive patients with chronic, nondiabetic, biopsy-proven nephropathies, reductions in proteinuria were compared for patients receiving 80 mg telsmisartan once daily and patients taking 80 mg twice daily over 25 months. Significant decreases were reported in proteinuria in both treatment groups (P <0.01), but urinary protein concentrations were reduced significantly more among patients receiving double-dose telsmisartan (P <0.01). Reduction of proteinuria to lower than 0.3 g/day was achieved in 40% of patients treated with the double dose compared with 15% taking the once-daily regimen. In addition, in patients taking 80 mg twice daily, serum creatinine values remained stable.

ACE inhibitors and ARBs act on different stages of the RAS cascade. An attractive alternative to high-dose ARB therapy, therefore, is combination therapy. A meta-analysis included 21 studies of combination ACE inhibitor and ARB therapy in 654 patients with proteinuric renal disease. The addition of an ARB to ACE inhibitor therapy resulted in reductions of proteinuria in patients with or without diabetes (210 mg/day and 582 mg/day, respectively). In one trial, 192 patients received lisinopril or telsmisartan for 6 months, after which half received add-on telsmisartan or lisinopril. All patients who received combination therapy derived additional benefit, amounting to around 30% further reductions in albuminuria.

CONCLUSIONS
Angiotensin II represents an important therapeutic target for effective reduction of blood pressure and for protection from progressive renal damage in susceptible patients. Specific blockade of the AT1 receptor by ARBs inhibits the pathophysiological effects of angiotensin II. The renoprotective effects of ARBs are convincing, with data consistently showing effective reductions in proteinuria that are independent of effects on hypertension in patients with type 2 diabetic nephropathy. Furthermore, reductions in proteinuria correlate with reduced cardiovascular risk.

In comparative studies of telsmisartan and other blood-pressure-lowering therapies or placebo, renoprotection, reduced proteinuria and decline in GFR to levels similar to expected age-related decline have been reported. Further reductions in proteinuria can be achieved by increasing the dose or by combining treatment with an ACE inhibitor. ARBs can, therefore, play an important part in reducing the progression of renal disease and can be expected to play an increasing role in treatment of patients with either established nephropathy or with known risk factors, such as diabetes or hypertension.

KEY POINTS

- Injury to the vascular endothelium and glomerulus can be promoted by an activated renin-angiotensin system and, therefore, inhibition of this system provides renoprotection
- RAS inhibition reduces proteinuria, which is a key factor in the progression of renal disease
- Blood pressure control is essential to prevent progression to end-stage renal disease, but because the mechanisms of angiotensin receptor blockers and angiotensin-converting-enzyme inhibitors differ, the effectiveness of the latter might decline over time
- Combination therapy with angiotensin receptor blockers and angiotensin-converting-enzyme inhibitors seems to produce additional blood-pressure-lowering effects to monotherapy
References


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Competing interests
[Author: Please sign the competing interests form and add the appropriate information here.]