Prevention of Loss of Renal Function Over Time in Patients with Diabetic Nephropathy

Anthony Barnett, MD
Division of Medical Sciences, University of Birmingham and Birmingham Heartlands and Solihull National Health Service Trust, Birmingham, United Kingdom

ABSTRACT

Management of hypertension is the mainstay of prevention and treatment of diabetic renal disease; evidence suggests that tight blood pressure control slows renal disease progression in established diabetic nephropathy. Inhibition of the renin-angiotensin-aldosterone system (RAAS) has renoprotective effects over and above those achieved by lowering systemic blood pressure. To date, however, no long-term study using hard end points has directly compared current mechanisms for RAAS inhibition, angiotensin II receptor blockade (ARB) and angiotensin-converting enzyme (ACE) inhibition. This issue was addressed in the recently published Diabetics Exposed to Telmisartan and Enalapril (DETAIL) study, a head-to-head comparison of telmisartan and enalapril in 250 patients with hypertension and type 2 diabetes mellitus and early-stage nephropathy. After 5 years’ treatment, change in glomerular filtration rate (GFR), the primary efficacy end point, was equivalent in the 2 treatment groups, as were all secondary end points. The expected steep decline in GFR in the first year was followed by a lesser decrease in the second year and then almost complete stabilization of renal function at ≥3 years. Over 5 years, no patient went into end-stage renal disease or required dialysis. There were also no increases in albumin excretion rate, nor was there an increase in creatinine beyond 200 μmol/L. Incidence of cardiovascular morbidity and mortality was extremely low in both treatment groups, a remarkable outcome given that almost 50% of patients had evidence of cardiovascular disease at randomization. Inhibition of the RAAS should play a major part in management of patients with type 2 diabetes with nephropathy, for which both telmisartan and enalapril provide long-term renoprotection. © 2006 Elsevier Inc. All rights reserved.

KEYWORDS: Angiotensin-converting enzyme inhibitor; Angiotensin II receptor blocker; Antihypertensive therapy; Type 2 diabetes mellitus; Diabetic nephropathy; Telmisartan

Diabetic nephropathy is a progressive, irreversible disease characterized by increasing blood pressure, microalbuminuria, proteinuria, and a continuous decline in glomerular filtration rate (GFR). Without therapeutic intervention, serum creatinine levels increase and patients go on to develop end-stage renal disease (ESRD). Among patients with type 2 diabetes mellitus, diabetic nephropathy predisposes to significantly increased risk of death from cardiovascular disease; twice as many patients with type 2 diabetes and significant microalbuminuria die within 10 years of diagnosis compared with normoalbuminuric patients.

The leading risk factors for ESRD are diabetes and hypertension and, as the incidence of these factors increases worldwide, there has been a concomitant increase in the incidence of ESRD. As a result, diabetic renal disease is now the single most common cause of chronic renal failure and of the need for dialysis in many parts of the world. In Europe, for example, the annual number of new cases of ESRD due to diabetes increased from a handful of cases in 1970 to around 4,000 cases 20 years later. In the United States, diabetes (mostly type 2) is the primary diagnosis in approximately 45% of new dialysis cases, whereas hypertension is the primary diagnosis in 30% of new cases. The increasing incidence of ESRD is also driven by better treatment and improved prognosis, which has led to longer survival times for patients on dialysis, as well as by the increasing age of the population in many countries.
The prevalence of type 2 diabetes is projected to double within the next 15 years, and the incidence of ESRD is expected to continue rising. As patients with type 2 diabetes live longer and are at greater risk of diabetes-related complications, more people are developing the disease. Meeting the needs of this growing patient population represents a major therapeutic challenge.

Management of hypertension is the mainstay of prevention and treatment of diabetic renal disease. Over the last decade, aggressive antihypertensive therapy has had a significant effect on slowing the progression of renal disease in established diabetic nephropathy, although better treatment and improved prognosis have, in part, been responsible for the paradoxical increase in the number of patients with ESRD.

Among currently available antihypertensive drugs, those that act on the renin-angiotensin-aldosterone system (RAAS) are known to have renoprotective effects over and above their systemic blood pressure–lowering properties. This makes them particularly suitable therapy for the patient with hypertension and diabetes. To date, however, no long-term studies using hard end points have directly compared the 2 mechanisms for RAAS inhibition—that is, angiotensin II receptor blockade (ARB) and converting enzyme (ACE) inhibition—or whether different modes of action may have clinical significance in patients at risk for diabetic nephropathy. This review looks at the renoprotective properties of these agents and describes in detail the results of the Diabetics Exposed to Telmisartan and Enalapril (DETAIL) study, a head-to-head comparison of telmisartan and enalapril in hypertensive patients with type 2 diabetes and early-stage nephropathy.

**RENN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITION AND DIABETIC NEPHROPATHY**

Activation of the RAAS system plays a crucial role in the pathophysiology of diabetic nephropathy, with angiotensin II exerting a potent effect on renal structure and function. Although angiotensin II constricts both afferent and efferent arterioles and directly affects sodium bicarbonate excretion, it also controls mesangial cell function and release of norepinephrine from sympathetic nerves and renin from the juxtaglomerular cells of the kidney. In addition, angiotensin II is central to the pathophysiology of diabetic renal disease. It stimulates the generation of reactive oxygen species, leading to renal endothelial dysfunction, and it also stimulates the expression of chemokines, chemotaxins, and cell adhesion molecules, all of which contribute to cell proliferation and renal fibrosis.

Blocking the RAAS has a number of advantages with respect to renal function that extend beyond the imperative of lowering systemic blood pressure in the patient with hypertension and type 2 diabetes. In the kidneys, inhibition of RAAS is associated with relaxation of the efferent arterioles and a reduction in intraglomerular pressure and proteinuria, thereby slowing progression of chronic renal failure. By decreasing efferent arteriolar resistance and blocking the arteriolar hypertrophic effects of angiotensin II, ARBs and ACE inhibitors have the potential to arrest the sequence of events that lead inexorably to ESRD.

Experimental evidence indicates that blockade of the RAAS does indeed have a favorable effect on renal hemodynamics and pathophysiology. Acute administration of irbesartan to patients with type 2 diabetes and obesity was found to cause substantial renal vasodilation. In a rodent model of type 2 diabetes, losartan suppressed glomerular mesangial expansion and mesangiocapillary glomerulonephritis. Interestingly, this study found little effect of enalapril on these outcomes. In a rodent model of nonhypertensive renal fibrosis, both candesartan and ramipril reduced glomerular and tubulointerstitial fibrosis, although the effect of ramipril was greater. Similarly, in a model of progressive glomerulosclerosis, both cilazapril and candesartan ameliorated glomerular and tubulointerstitial injury. In patients with type 1 diabetes and microalbuminuria, enalapril treatment for 5 years reduced the increase in glomerular volume and mesangial volume. Therapy with perindopril for 3 years in patients with type 1 and type 2 diabetes also appeared to reduce interstitial fibrosis and ameliorate the increase in glomerular basement membrane thickness.

Although both ARBs and ACE inhibitors interrupt the RAAS, the differences in their modes of action may have clinical significance. There are 2 principal angiotensin II receptor subtypes in the kidney: type 1 (AT1) and type 2 (AT2). The 2 receptors act in largely antagonistic ways, with the AT2 receptor causing, for example, renal vasodilation and decreased inflammation. In adult humans, 90% of angiotensin II receptors in the kidney are type 1, with the result that the pathologic effects predominate. ACE inhibitors, by lowering levels of angiotensin II, reduce activation of both AT1 and AT2 receptors. ARBs, in contrast, actually stimulate levels of angiotensin II as a result of negative feedback. The continued activation of AT1 receptors, despite AT1-receptor blockade with ARBs, could conceivably afford greater renoprotection than with ACE inhibition, although such an effect has yet to be demonstrated.

**CLINICAL EVIDENCE FOR THE USE OF ANGIOTENSIN II RECEPTOR BLOCKERS AND ANGIOTENSIN-CONVERTING ENZYME INHIBITORS IN DIABETIC RENAL IMPAIRMENT**

ARBs and ACE inhibitors are well-established antihypertensive agents. In nondiabetic patients with hypertension, telmisartan and enalapril exhibit comparable antihypertensive efficacy. They have also shown comparable anti-hypertensive efficacy in hypertensive patients with moderate renal impairment, in whom systemic blood pressure lowering was accompanied by reductions in proteinuria. The incidence of adverse events, particularly cough and hypotension, is markedly lower with telmisartan, how-
ever, and consistent with the known adverse event profile of the 2 classes.

The US National Kidney Foundation recommends both ARBs and ACE inhibitors as first-line treatment for diabetic renal disease. Data from large-scale clinical studies on the use of ARBs in patients with hypertension and type 2 diabetes and nephropathy provide convincing evidence of their renoprotective effects in this patient population. Significant reductions in the risk of developing ESRD were observed following long-term treatment with ARBs in both the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and the Irbesartan Diabetic Nephropathy Trial (IDNT) studies. Fewer data support the use of ACE inhibitors in this patient population.

The antiproteinuric effects of telmisartan have been demonstrated in patients with nondiabetic renal disease. Cupisti and colleagues showed that telmisartan was effective in reducing microalbuminuria and proteinuria in patients without diabetes with chronic kidney disease who were either normotensive or mildly hypertensive. The reduction of albuminuria occurred despite only small changes in reduction of systemic blood pressure; this is suggestive of a direct effect on the kidney of AT1-receptor blockade. A reduction in albuminuria with telmisartan has also been shown in patients with isolated systolic hypertension and with mild-to-moderate hypertension.

Among normotensive patients with type 2 diabetes and evidence of microalbuminuria, treatment with enalapril for 5 years has been shown to stabilize the decline in GFR, as measured by plasma creatinine levels, as well as to reduce proteinuria when compared with placebo. These findings also hold true for patients with type 2 diabetes and hypertension, in whom treatment with enalapril for 5 years has been shown to stabilize creatinine clearance over time. Crucially, this study showed the importance of initiating therapy before the onset of overt albuminuria and of maintaining tight blood pressure control to within current target goals.

Before DETAIL, few studies had compared an ARB with an ACE inhibitor in diabetic nephropathy, and none had a duration sufficient to detect effects on the progression of the disease. The longest, conducted by Lacourcière and colleagues, was a 1-year head-to-head comparison of losartan with enalapril in early diabetic renal nephropathy. This study showed that both classes of drugs were equally effective in reducing proteinuria over a 12-month period, as well as in maintaining GFR.

## THE DETAIL STUDY

The DETAIL study sought to compare the effects of telmisartan with enalapril on the progression of renal disease in patients with type 2 diabetes. It was a 5-year prospective, multicenter, randomized, double-blind, parallel-group study in patients with hypertension and concurrent type 2 diabetes and early-stage nephropathy who were randomized to telmisartan 40 to 80 mg/day or enalapril 10 to 20 mg/day. A unique feature of this study was the decision to use change in GFR at 5 years rather than albuminuria as the primary end point, as has been common in most other diabetic nephropathy studies. Albuminuria correlates only weakly with GFR, and few would dispute that GFR is the best overall index of renal function. In DETAIL, GFR was measured by plasma clearance of iohexol, an exogenous marker of GFR. Secondary outcome measures included the annual change in GFR, serum creatinine level, urinary albumin excretion, and blood pressure, as well as incidence of ESRD, myocardial infarction, cerebrovascular accident, congestive heart failure, and all-cause mortality.

The study included men and women aged 35 to 80 years. All had type 2 diabetes that had been treated with diet, diet plus oral hypoglycemic agents, or insulin preceded by oral hypoglycemic agents for ≥1 year, along with evidence of early-stage diabetic nephropathy. This was defined as normal renal morphology, urinary albumin excretion rate (UAER) within the range 10 to 999 μg/mL, glycosylated hemoglobin value <12%, serum creatinine 0 μmol/L, and GFR >70 mL/min per 1.73 m² of body surface area. Approximately 80% of patients had microalbuminuria at study entry, whereas the remainder had early overt proteinuria. Patients also had mild-to-moderate hypertension (resting blood pressure ≤180/95 mm Hg) and all had been on an ACE inhibitor for ≥3 months before study entry.

From an original study population of 250 patients, of whom 120 were randomized to telmisartan and 130 to enalapril, analyses of GFR values based on last observation carried forward (LOCF) were available for 103 and 113 patients, respectively. After 5 years, the change in GFR was equivalent in the 2 groups, with a mean decline of approximately 16 mL/min per 1.73 m². The mean change in GFR in the telmisartan and enalapril treatment groups over this period was −17.5 mL/min per 1.73 m² and −15.0 mL/min per 1.73 m², respectively, within the statistical bounds of noninferiority. In both treatment groups, there was the expected steep decline in GFR in the first year of the study, a much lesser decline in the second year, and then almost complete stabilization of renal function at ≥3 years. No patient went into kidney failure or required dialysis during the 5-year study period and, indeed, no patient in either treatment group had an increase in UAER or an increase in serum creatinine to >200 μmol/L.

Incidence of cardiovascular morbidity and mortality was extremely low in both treatment groups over the 5-year study period, a remarkable finding given that almost 50% of patients had evidence of cardiovascular disease at randomization in addition to long-standing hypertension and diabetes. Epidemiologic data suggest an expected mortality rate of 35% to 50% in this patient population by 5 years, a rate 10 times higher than that observed in the DETAIL trial. Use of concomitant cardiovascular medication more than doubled during the trial.

This fact, together with sustained systemic blood
pressure lowering, with both treatments equally effective in reducing systemic blood pressure over the 5-year treatment period, may have contributed to these findings. The specific contribution to reducing mortality by inhibition of the RAAS by both treatments is undetermined.

Study medications were well tolerated following long-term administration; tolerance to ACE-inhibitor therapy was a precondition of study eligibility and so no major differences in adverse events (such as cough) between treatments were anticipated. Adverse events were responsible for premature withdrawal in only 17% of telmisartan-treated patients and 23% of enalapril recipients; few patients withdrew due to worsening of diabetic nephropathy (<2%) or worsening of other diseases (<5%).

**IMPLICATIONS OF THE DETAIL STUDY**

The DETAIL trial is the first long-term study to compare the renoprotective effects of an ARB (telmisartan) and an ACE inhibitor (enalapril) in patients with hypertension and type 2 diabetes.

---

**Table 1** Baseline characteristics of patients randomized to treatment in the Diabetics Exposed to Telmisartan and Enalapril (DETAIL) trial

<table>
<thead>
<tr>
<th></th>
<th>Telmisartan (n = 120)</th>
<th>Enalapril (n = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, n (%)</td>
<td>87 (73)</td>
<td>95 (73)</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>118 (98)</td>
<td>128 (98)</td>
</tr>
<tr>
<td>Age (yr), mean ± SD</td>
<td>61.2 ± 8.5</td>
<td>60.0 ± 9.1</td>
</tr>
<tr>
<td>Body weight (kg), mean ± SD</td>
<td>90.6 ± 14.9</td>
<td>90.6 ± 17.4</td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>30.8 ± 4.4</td>
<td>30.6 ± 5.1</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²), mean ± SD</td>
<td>91.4 ± 21.5</td>
<td>94.3 ± 22.1</td>
</tr>
<tr>
<td>UAER (µg/mL), median (range)</td>
<td>46.2 (4-1101)</td>
<td>60.0 (9-969)</td>
</tr>
<tr>
<td>Microalbuminuria, n (%)</td>
<td>98 (82)</td>
<td>106 (82)</td>
</tr>
<tr>
<td>Macroalbuminuria, n (%)</td>
<td>22 (18)</td>
<td>23 (18)</td>
</tr>
<tr>
<td>Hypertension (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean duration ± SD</td>
<td>10.0 ± 8.3</td>
<td>8.7 ± 9.2</td>
</tr>
<tr>
<td>Median duration (range)</td>
<td>8.0 (0-34)</td>
<td>5.5 (0-49)</td>
</tr>
<tr>
<td>Diabetes (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean duration ± SD</td>
<td>9.2 ± 6.6</td>
<td>9.1 ± 6.3</td>
</tr>
<tr>
<td>Median duration (range)</td>
<td>8.0 (0-25)</td>
<td>8.0 (0-37)</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>41 (34)</td>
<td>47 (36)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>54 (45)</td>
<td>55 (42)</td>
</tr>
<tr>
<td>Smoker</td>
<td>25 (21)</td>
<td>28 (22)</td>
</tr>
<tr>
<td>Alcohol history, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondrinker</td>
<td>29 (24)</td>
<td>35 (27)</td>
</tr>
<tr>
<td>Average consumption</td>
<td>90 (75)</td>
<td>94 (72)</td>
</tr>
<tr>
<td>Excessive consumption</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

BMI = body mass index; GFR = glomerular filtration rate; UAER = urinary albumin excretion rate.

Reprinted with permission from *J Diabetes Complications*.46

---

**Figure 1** Effect of telmisartan on albuminuria in patients with mild-to-moderate hypertension. *P <0.01 vs. baseline. (Reprinted with permission from *Pharmacogenomics J*.)
diabetes who have early-stage diabetic nephropathy, and it is the first to measure directly change in GFR as a primary end point.13 The study demonstrated telmisartan is as effective as enalapril in reducing the decline in GFR in patients with early evidence of diabetic nephropathy.

Healthy individuals show an age-related decline in GFR of about 1 mL/min per 1.73 m$^2$ per year48 compared with a decline of 10 to 12 mL/min per 1.73 m$^2$ per year in patients with untreated type 2 diabetes and overt proteinuria.1,2 The objective of treatment with drugs that inhibit the RAAS, either via ACE inhibition or blockade of the AT$_1$ receptor, is to protect the kidney by reducing proteinuria to $<0.5$ g/day, while simultaneously reducing the decline in GFR to $<2$ mL/min per 1.73 m$^2$ per year.15 In the DETAIL study, the initial steep decline in GFR that occurred in both treatment groups in the first year had by year 3 stabilized to $<2$ mL/min per 1.73 m$^2$ per year. Among patients who completed the study, the mean yearly decline in the telmisartan (n = 62) and enalapril (n = 74) groups was 3.5 mL/min per 1.73 m$^2$ and 3.0 mL/min per 1.73 m$^2$, respectively. This may be compared with the expected rate of decline in these patients, if left untreated, of 10 to 12 mL/min per 1.73 m$^2$ per year (Figure 3).6

These findings are consistent with data from the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA)-2 study, a 2-year study in which the cohort of 300 patients closely resembled those enrolled in the DETAIL trial.12 In the IRMA-2 study, treatment with irbesartan produced a mean decline in GFR of 6.6 mL/min per 1.73 m$^2$ in the first year and of 4.8 mL/min per 1.73 m$^2$ in the second year, similar in fact to the first 2 years of data in the DETAIL trial.13 In both the RENAAL and IDNT trials, which studied patients with more advanced nephropathy (macroalbuminuria), median decline in GFR following 12 months of treatment was 4.4 mL/min per 1.73 m$^2$ with losartan and 5.5 mL/min per 1.73 m$^2$ with irbesartan, respectively.36,37

Although the DETAIL trial was not powered to assess the impact of treatment on mortality, the very low rates of cardiovascular morbidity and mortality were still striking when compared with historical data. In each treatment group, 6 deaths (approximately 5%) occurred, of which only 50% were due to cardiovascular events. Interestingly, in the IRMA-2 study, Parving and colleagues12 also observed a low rate of death from cardiovascular causes. Previous studies have provided consistent evidence that treatment with ACE inhibitors and ARBs reduces significantly the risk of ESRD in patients with diabetic nephropathy.12,36,37 Studies such as the Heart Outcomes Prevention Evaluation (HOPE) and Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trials provide evi-
data that treatment with ACE inhibitors or ARBs reduces the risk of cardiovascular events in patients with type 2 diabetes. Significant reductions in cardiovascular end points have yet to be demonstrated, however, in patients with type 2 diabetes and nephropathy. Data from the DETAIL trial provide, nonetheless, early encouraging evidence for cardiovascular protection in association with RAAS inhibition in a very-high-risk group of patients with type 2 diabetes. Brenner and associates, in a reexamination of data from the RENAAL trial, have suggested that it is the reduction in proteinuria associated with ARB therapy that appears to confer cardiovascular protection in patients with type 2 diabetes with nephropathy: the greater the reduction, the greater the cardiovascular protection.

Given the apparent equivalent efficacy of telmisartan and enalapril seen in the DETAIL study, it is important to consider the question of tolerability. Although the patients were selected for tolerance of ACE inhibitors, in a previous 1-year study in a similar patient population, the ARB was better tolerated than was the ACE inhibitor, mainly due to a much lower incidence of cough. Cough is a common side effect of ACE-inhibitor treatment that affects patient adherence to therapy, and this probably explains why persistence with ACE-inhibitor treatment is lower than that with ARB treatment. As with other ARBs, telmisartan has been shown to be notably better tolerated than ACE inhibitors in patient populations not selected for ACE-inhibitor tolerance.

**SUMMARY**
Overall, results from the DETAIL trial show that long-term treatment with telmisartan provides comparable renoprotective efficacy to enalapril in patients with type 2 diabetes with early-stage nephropathy, but it has the potential for greater tolerability as demonstrated in earlier comparative

---

**Table 3** Use of concomitant cardiovascular medication for ≥6 consecutive months before and during the Diabetics Exposed to Telmisartan and Enalapril (DETAIL) trial

<table>
<thead>
<tr>
<th></th>
<th>Telmisartan (n = 120)</th>
<th>Enalapril (n = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Study, n (%)</td>
<td>During Study, n (%)</td>
</tr>
<tr>
<td>Any medication</td>
<td>104 (87)</td>
<td>102 (85)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>92 (77)</td>
<td>NA</td>
</tr>
<tr>
<td>Diuretics</td>
<td>26 (22)</td>
<td>63 (53)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>23 (19)</td>
<td>47 (39)</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>32 (27)</td>
<td>55 (46)</td>
</tr>
<tr>
<td>Other antihypertensive agents and heparin</td>
<td>14 (12)</td>
<td>42 (35)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>21 (18)</td>
<td>44 (37)</td>
</tr>
<tr>
<td>Statins</td>
<td>14 (12)</td>
<td>51 (43)</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; NA = not applicable.

Reprinted with permission from *J Diabetes Complications*.46

---

**Figure 3** Glomerular filtration rate (GFR) decline with telmisartan compared with expected diabetic population norm. ESRD = end-stage renal disease. *All patients, last observation carried forward. (Adapted from *Semin Nephrol* and *N Engl J Med*.13)
studies. Both study treatments showed comparable efficacy in lowering systemic blood pressure, which makes telmisartan a valid first-line treatment for hypertension in patients who have type 2 diabetes, with or without renal nephropathy. Although the study results are consistent with the proven renoprotective profile of ACE inhibitors and ARBs in diabetic nephropathy, they also provide early data supporting clinical equivalence in various states of cardiovascular risk.

References


