Preventing Renal Complications in Type 2 Diabetes: Results of the Diabetics Exposed to Telmisartan and Enalapril Trial

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Patients with type 2 diabetes are prone to hypertension and persistent protein leakage from the kidney (microalbuminuria or macroalbuminuria). A progressive decline in renal function can lead to overt diabetic nephropathy and ESRD. The likelihood of cardiovascular disease also is increased. Control of hypertension is paramount to prevent these life-threatening complications. Agents that target the renin-angiotensin system—angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers—have been shown to be renoprotective. The groundbreaking Diabetics Exposed to Telmisartan And enalapril IL (DETAIL) trial was designed to address the absence of comparative data on the long-term effects of an angiotensin II receptor blocker versus an angiotensin-converting enzyme inhibitor on renoprotection and survival in 250 patients with hypertension and early type 2 diabetic nephropathy. The primary purpose of the 5-yr double-blind, double-dummy, randomized study was to establish whether 40 to 80 mg of telmisartan conferred similar (i.e., noninferior) renoprotection to 10 to 20 mg of enalapril as determined by the change from baseline in GFR, measured by the plasma clearance of iohexol. Secondary end points included the emergence of ESRD and all-cause mortality. Telmisartan was not inferior to enalapril in reducing the decline in GFR: Mean annual declines in GFR were 3.7 and 3.3 ml/min per 1.73 m² with telmisartan and enalapril, respectively. During the 5-yr study period, no patient developed a serum creatinine >200 µmol/L, and none required dialysis. There were only six deaths in each treatment group during the study, with half being due to cardiovascular events.


The prevalence of type 2 diabetes has escalated in recent years, mainly as a result of changes in lifestyle and increasing obesity (1). This has serious public health implications: Life expectancy of men and women who receive a diagnosis of type 2 diabetes at age 40 is reduced by 11.6 and 14.3 yr, respectively (2). Death is usually due to cardiovascular disease, especially if nephropathy is already present (3). In type 2 diabetes, hypertension is a frequent comorbidity, often being present when diabetes is diagnosed (4). Hypertension is associated with thickening of the glomerular basement membrane and glomerulosclerosis, leading to albuminuria (5). Up to 30% of patients with type 2 diabetes develop macroalbuminuria (6).

Aggressive BP control to prevent the onset of nephropathy, or its progression if already present, is emphasized in recent guidelines (7,8). Many classes of antihypertensive agents are available, and their use will overcome the GFR decline and development of ESRD (9). In particular, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB), both of which target the renin-angiotensin system, have been shown to be renoprotective (10).

Although ACE inhibitors are the agents of choice for renoprotection in type 1 diabetes, their efficacy in type 2 diabetes varies. This may be due partly to the generation of angiotensin II by renal non-ACE pathways, which are not susceptible to ACE inhibitors (11). In patients with diabetes, these alternative pathways produce approximately 40% of angiotensin II, possibly explaining the findings of a recent meta-analysis that showed that ACE inhibitors did not prevent ESRD or doubling of serum creatinine (12). By contrast, ARB act by preventing binding of angiotensin II to type 1 (AT₁) receptors (13), which are implicated in angiotensin II’s pathologic effects. Therefore, ARB may provide more complete renin-angiotensin system blockade. Furthermore, angiotensin II is available to stimulate AT₂ receptors, which may counteract the harmful effects of AT₁ stimulation (14).

Before the Diabetics Exposed to Telmisartan And enalapril IL (DETAIL) trial (15), six studies had evaluated ARB in type 2 diabetic nephropathy. Their duration differed, with none lasting more than 3.4 yr. Four were performed in patients with microalbuminuria (16–19), and two were performed in patients with overt nephropathy (20,21). Irbesartan in patients with type 2 diabetes and MicroalbuminuriA (IRMA 2) (18) provides the most conclusive evidence for ARB use in incipient nephropathy. The 2-yr study showed that irbesartan significantly improved albumin excretion rate compared with placebo and slowed progression to overt nephropathy. For established nephropathy, Irbesartan in Diabetic Nephropathy Trial (IDNT) (20) and Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) (21) demonstrated benefits.

Purpose of DETAIL

The primary purpose of the 5-yr, double-blind, double-dummy, randomized DETAIL study was to establish whether telmisartan conferred similar (i.e., noninferior) renoprotection...
to enalapril (15). Until DETAIL, only the 1-yr study by Lacourcière et al. (16) had compared the effects of an ACE inhibitor versus an ARB. It is known that enalapril has a long-term stabilizing effect on plasma creatinine and proteinuria in normotensive patients with type 2 diabetes (22). Of the available ARB, telmisartan has the highest lipophilicity (23), which assists in tissue penetration; has the longest half-life of approximately 24 h (24); and is almost exclusively excreted in feces (25). Telmisartan has well-documented antihypertensive efficacy (26) and reduces BP and proteinuria as effectively as enalapril in hypertensive patients with moderate renal failure (27).

**DETAIL Patients**

Enrolled patients were mild to moderately hypertensive (resting systolic/diastolic BP <180/95 mmHg) and had type 2 diabetes treated by diet and/or oral hypoglycemics or insulin (provided that diabetes had been diagnosed after 40 yr of age and oral hypoglycemics had been given for at least 1 yr before starting insulin). All patients had to have been treated with an ACE inhibitor to eliminate anyone who was intolerant of these agents. Patients with an albumin excretion rate of 11 to 999 µg/min and normal gross renal morphology were eligible, but those with serum creatinine >140 µmol/L and/or GFR <70 ml/min per 1.73 m² were excluded.

**DETAIL Study Design**

The 250 eligible patients received their current antihypertensive therapy for 1 mo before being randomly assigned to 40 mg of telmisartan or 10 mg of enalapril for 1 mo. Thereafter, the dose of the assigned drug was doubled, but it could be reduced again after an additional 3 mo if hypotension occurred. Additional antihypertensive agents were allowed if hypertension persisted. The primary end point was change from baseline in GFR, determined by plasma clearance of iohexol (28), after 5 yr. Noninferiority was established when the upper boundary of the 95% confidence interval (CI) for the difference between telmisartan and enalapril in the 5-yr cumulative reduction in GFR was less than -10 ml/min per 1.73 m². Secondary end points included emergence of ESRD and incidences of cardiovascular and all-cause mortality.

**Renoprotection in DETAIL**

There was no significant difference in GFR or in change in GFR according to treatment after 5 yr (Figure 1) (15). The difference between telmisartan and enalapril in GFR was -3.1 ml/min per 1.73 m² (95% CI -7.6 to 1.6). The 95% CI of the difference between treatments was less than -10 ml/min per 1.73 m²; therefore, telmisartan was noninferior to enalapril. The GFR decline was steepest for year 1 (Figure 2). This may be due to the hemodynamic effect associated with systemic BP lowering and consequent intraglomerular pressure reduction (29). After year 1, annual rate of decline was markedly reduced with a consistent, year-on-year effect. In telmisartan patients, mean annual GFR decline was 3.7 ml/min per 1.73 m² for those who completed the study and 3.6 ml/min per 1.73 m² in the last observation carried forward data set. In enalapril-treated patients, respective mean annual declines were 3.3 and 3.1 ml/min per 1.73 m². During the study, no patient had serum creatinine >200 µmol/L, and none required dialysis.

The annual GFR decline is approximately 10 to 12 ml/min per 1.73 m² in patients with type 2 diabetes and untreated nephropathy (30), compared with approximately 1 ml/min per 1.73 m² in normal individuals (31). In DETAIL, the initial steep decline stabilized after 3 yr; thereafter, both telmisartan and enalapril resulted in an annual GFR decline of approximately 2 ml/min per 1.73 m² (Figure 2), which is close to the target annual decline of <2 ml/min per 1.73 m² (32). The annual decline in DETAIL is comparable to that in IRMA 2 (18), IDNT (20), and RENAAL (21) of 4.9, 5.5, and 4.4 ml/min per 1.73 m², respectively (all of which calculated GFR from serum creatinine). Furthermore, the annual GFR decline of 3.7 ml/min per 1.73 m² compares very favorably with the annual decline of 5.2 ml/min per 1.73 m² achieved with best-practice care in early diabetic nephropathy (33).

**Mortality in DETAIL**

There were only six deaths in each treatment group during the study, representing a mortality rate of approximately 5%; only half were due to cardiovascular events (15). By comparison, a population study found that the mortality rate over 5 yr was approximately 35% in older patients with type 2 diabetes and microalbuminuria and approximately 50% when macroalbuminuria was present (34). Although ARB have been
shown to reduce ESRD significantly (18,20,21), until now, there has been no evidence that they have a positive impact on mortality in type 2 diabetic nephropathy (12).

Conclusions

DETAIL is a groundbreaking study, being the first long-term head-to-head comparison of an ARB and an ACE inhibitor in patients with hypertension and early type 2 diabetic nephropathy (15). Determination of GFR using iohexol, a safe and accurate method of evaluating renal function (35), distinguishes it from previous ARB studies (16–21). Pharmacologic intervention is essential to prevent the inevitable decline in renal function and to minimize the likelihood of early death (10). DETAIL shows that telmisartan is comparable to enalapril in reducing GFR decline and that it provides renoprotection in type 2 diabetic nephropathy. Before DETAIL, there were no direct comparisons of relative survival advantages of ARB versus ACE inhibitors (12). In DETAIL, telmisartan and enalapril were associated with similar, low rates of all-cause mortality.

References

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