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Preventing renal complications in diabetic patients: the Diabetics Exposed to Telmisartan And enalaprIL (DETAIL) study*

Abstract Diabetic nephropathy is characterised by hypertension and persistent proteinuria. If ineffectively controlled, a progressive decline in renal function can result in end-stage renal disease. Patients with diabetic nephropathy are also at greatly increased risk of cardiovascular disease. Angiotensin-converting enzyme (ACE) inhibitors display additional renoprotective effects beyond systemic blood pressure lowering, perhaps due to reduction in intraglomerular pressure by inhibition of angiotensin II activity. In type 2 diabetics, ACE inhibitors have variable effects, with some studies showing a reduction in microalbuminuria, prevention of the progression to macroalbuminuria and maintenance of renal function. Randomised studies have demonstrated that angiotensin II receptor blockers (ARBs), as well as controlling systemic blood pressure, delay progression of proteinuria in patients with diabetic nephropathy. Telmisartan has a number of features that may make it particularly suitable for the treatment of diabetic nephropathy. In addition to its long duration of action and almost exclusive faecal excretion, its high lipophilicity should assist in tissue penetration. The Diabetics Exposed to Telmisartan And enalaprIL (DETAIL) study was designed to compare the long-term renal outcome of treatment with telmisartan 40–80 mg versus enalapril 10–20 mg (with titration to the higher dose after 4 weeks) in patients with type 2 diabetes, mild-to-moderate hypertension and albuminuria. The primary endpoint is the change in glomerular filtration rate after 5 years' randomised treatment. Secondary endpoints are annual changes in glomerular filtration rate, serum creatinine and urinary albumin excretion, as well as incidences of end-stage renal disease, cardiovascular events, all-cause mortality and adverse events. The groundbreaking DETAIL study revealed that telmisartan conferred comparable renoprotection to enalapril and was associated with a low incidence of mortality.

Key words Diabetic nephropathy • Proteinuria • Angiotensin-converting enzyme inhibitors • Enalapril • Angiotensin II receptor blockers • Telmisartan

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Introduction

Type 2 diabetes is one of the major public-health problems facing us in the 21st century. Its dramatic escalation in recent years is largely attributed to increasing obesity in most parts of the world, with the problem of malnutrition

having been superseded by that of overeating. In the near future, it is likely that being everweight and obese will cause as much, if not more, preventable disease and death as cigarette smoking. Unless appropriate action is taken now, the outlook is highly worrying. The current prediction by the World Health Organization is that, by 2030, there will be at least 350 million people worldwide suffering from type 2 diabetes [1]. The seriousness of the situation for the individual is illustrated by the fact that the life expectancy of men and women diagnosed as having type 2 diabetes at 40 years of age is reduced by 11.6 and 14.3 years, respectively [2].

Natural history of diabetic nephropathy

Hypertension is frequently present at the time of diagnosis of type 2 diabetes [3]. The hypertension causes target-organ damage, including thickening of the glomerular basement membrane and glomerulosclerosis, which result in protein being excreted in the urine [4]. Microalbuminuria is also often present when diabetes is diagnosed. Persistent hypertension will lead to about 35–40% of subjects with type 1 diabetes and 25–30% of those with type 2 diabetes subsequently developing overt diabetic nephropathy, defined as proteinuria and the deterioration of renal function [5]. Without early medical intervention, microalbuminuria almost inevitably progresses to overt nephropathy, with reductions in creatinine clearance and consequent rises in serum creatinine concentration, and culminates in end-stage renal disease that necessitates dialysis or a kidney transplant.

Although some subjects with type 2 diabetes will die of uraemic complications, cardiovascular morbidity poses the biggest threat. Approximately 80% of all patients with diabetes will eventually die of such complications and in many cases death is unnecessarily premature. The probability of cardiovascular morbidity and mortality is magnified if renal impairment is also present. A 10-year study of subjects with type 2 diabetes demonstrated that individuals with even relatively small elevations of urinary albumin at baseline (16–40 μg/ml) had a much poorer prognosis, with fewer surviving, compared with those who were normoalbuminuric (Fig. 1) [6]. This study also showed that for those with baseline urinary albumin concentrations of 41–200 μg/ml, the prospect is very bleak: after 5 years, approximately 50% of the subjects had died. Cardiovascular disease or stroke was the cause of death in 58%, whereas only 3% had died from uraemia.

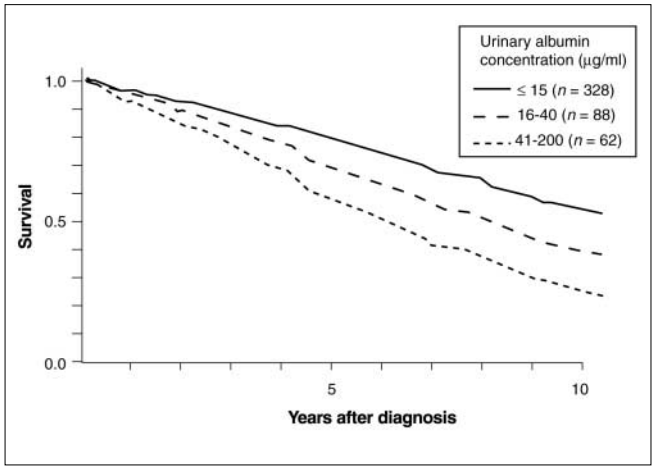

Fig. 1 Microalbuminuria as a risk factor for death in type 2 diabetes. With permission from [6]

Improvement of long-term outcomes

The most important aspect of the management of diabetic patients and the improvement of prognosis is the aggressive control of blood pressure in the early stages of diabetes. Tight control of blood pressure may not only delay the onset or bring about regression of renal disease, but also control the endothelial dysfunction in other tissues and organs that leads to the debilitating micro- and macrovascular disease associated with diabetes. The importance of stringent blood pressure control is acknowledged in recent guidelines, such as The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and European Society of Hypertension – European Society of Cardiology, which propose targets of <130/80 mmHg [7, 8].

Different classes of antihypertensive agents have been shown to have beneficial effects in terms of lowering the decline in the glomerular filtration rate [9]. However, the use of agents that target the renin–angiotensin system (RAS) – angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) – appears to confer renoprotective effects above and beyond those resulting from the control of blood pressure. This is because inhibitors of the RAS are believed to act on the efferent arteriole and prevent angiotensin II-mediated vasoconstriction, with the resultant reduction in intraglomerular pressure providing further renoprotection [10]. Experimental studies have revealed that ACE inhibitors and ARBs produce similar improvements in glomerular haemodynamics and afford equal renoprotection in a variety of experimental models of kidney disease [10].

Renoprotective effects of ACE inhibitors

Extensive studies in patients with type 1 diabetes focusing on renal endpoints have demonstrated the beneficial

effects of ACE inhibitors [11]. The conclusive evidence of long-term protection afforded by ACE inhibitors has resulted in them becoming the agents of choice in type 1 disease. The clinical evidence for the use of ACE inhibitors in type 2 diabetes is less extensive; nevertheless, benefit has been demonstrated in terms of preservation of renal function and/or changes in microalbuminuria in some studies (Table 1) [12–22]. However, in others, there was no significant difference in albumin excretion rate in patients treated with ACE inhibitors compared with those receiving comparators from other antihypertensive classes or even placebo. This may be explained partly by there being marked intraindividual day-to-day variations in albumin excretion rates [23], and an especially high variability has been noted in diabetic subjects [24]. There is also the possibility that the local renal RAS may affect the renoprotective efficacy of ACE inhibitors. Within the kidney, about 40% of angiotensin II is generated by non-ACE pathways, which are not susceptible to ACE inhibition [25]. Furthermore, there is evidence that these non-ACE pathways are substantially more active in diabetic patients [25]. In theory, at least, it is possible that use of ACE inhibitors may result in incomplete blockade of angiotensin II activity. In a recently published meta-analysis of trials, including previously unpublished data, comparing ACE inhibitors with placebo shows strong evidence for the benefit of ACE inhibitors in preventing progression from microalbuminuria to macroalbuminuria and promoting the regression from macroalbuminuria to microalbuminuria, but no benefit in terms of prevention of end-stage renal disease or doubling of serum creatinine [26].

Renoprotective effects of ARBs

The ARBs target the RAS by preventing the binding of angiotensin II to the type 1 (AT_1) receptor, which is implicated in the numerous pathological effects of angiotensin II. Because the action of angiotensin is blocked irrespective of the pathway by which it is generated, these agents have the potential to provide more complete blockade of the RAS. In addition, angiotensin II is available to stimulate the type 2 receptor, which may counteract the detrimental effects of AT_1 stimulation [27].

To date, there have been six studies of varying duration and including between 103 and 1715 patients, but none lasting more than 3.4 years, evaluating the use of ARBs in patients with type 2 diabetes and varying degrees of renal insufficiency (Table 2) [28–33]. Of the four conducted in patients with microalbuminuria [28–31], the IRbesartan in patients with type 2 diabetes and MicroalbuminuriA (IRMA 2) study [28] provides the most conclusive evidence supporting the use of an ARB. Over the 2-year period of the study, irbesartan was associated with a significant improvement in albumin excretion rate compared with placebo ($p<0.001$). In addition, the study showed that irbesartan slowed the progression from microalbuminuria to overt diabetic nephropathy. In the management of macroalbuminuria, both the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) [32] and Irbesartan in Diabetic Nephropathy Trial (IDNT) [33] demonstrated the benefit of ARB treatment.

Table 1 Studies evaluating the renoprotective effects of ACE inhibitors in type 2 diabetic nephropathy [12–22]

Study	n	Control	Renal function[a]	Proteinuria
Microalbuminuria				
Ravid et al. [12]	94	Placebo	Preserved	Decreased
UKPDS [13]	758	Beta-blocker	No difference	No difference
Estacio et al. [14]	470	Calcium channel blocker	No difference	No difference
Ruggenenti et al. [15]	27	Conventional therapy	No difference	Not assessed
HOPE Investigators [16]	3577	Placebo	Not assessed	Decreased
Marre et al. [17]	4912	Placebo	Not assessed	No difference
Macroproteinuria				
Lebovitz et al. [18]	121	Conventional therapy	Preserved	Decreased[b]
Bakris et al. [19]	52	Calcium channel blocker	No difference	No difference
		Beta-blocker	Preserved	Decreased
Ahmad et al. [20]	103	Placebo	No difference	Decreased
Nielsen et al. [21]	43	Beta-blocker	No difference	Decreased
Fogari et al. [22]	107	Calcium channel blocker	No difference	Decreased

[a] Renal function assessed as glomerular filtration rate or creatinine clearance; [b] No effect was seen in patients with microalbuminuria

Table 2 Studies evaluating the renoprotective effects of ARBs in type 2 diabetic nephropathy [28–33]

Study	n	Duration	Drug	Change
Microalbuminuria				
IRMA 2 [28]	590	2 years	Irbesartan 150 mg	–24%
			Irbesartan 300 mg	–38%
			Placebo	–2%
MARVAL [29]	332	24 weeks	Valsartan 80–160 mg	–42%
			Amlodipine 5–10 mg	–3%
CALM [30]	199	12/24 weeks	Candesartan 16 mg	–24%
			Lisinopril 20 mg	–39%
			Candesartan 16 mg+ lisinopril 20 mg	–50%
Lacourcière et al. [31]	103[a]	52 weeks	Losartan 50 mg	–35%
			Enalapril	–55%
Macroproteinuria				
RENAAL [32]	1513	3.4 years	Losartan 50–100 mg	–35%
			Placebo	+18%
IDNT [33]	1715	2.6 years	Irbesartan 300 mg	–33%
			Amlodipine 10 mg	–6%
			Placebo	–10%

IRMA 2, IRbesartan in patients with type 2 diabetes and MicroalbuminuriA; *MARVAL*, MicroAlbuminuria Reduction with VALsartan; *CALM*, Candesartan And Lisinopril Microalbuminuria; *RENAAL*, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; *IDNT*, Irbesartan in Diabetic Nephropathy Trial

[a] Ten patients had baseline urinary albumin excretion of 200–300 μg/min; the remaining 93 displayed microalbuminuria

The Diabetics Exposed to Telmisartan And enalaprIL study

Despite the merits of the ARB studies, none of them were truly long-term, the follow-up period being no more than 3.4 years, and none assessed renal function by the direct measurement of glomerular filtration rate. Also, with one exception [31], they have not compared the renoprotection afforded by targeting the RAS using an ARB compared with an ACE inhibitor. These deficiencies have been addressed in the Diabetics Exposed to Telmisartan And enalaprIL (DETAIL) study [34]. The objectives of DETAIL were to evaluate the long-term renal outcomes achieved with different mechanisms of RAS blockade by comparing enalapril 10–20 mg and telmisartan 40–80 mg. The primary purpose was to establish that telmisartan conferred similar (i.e., non-inferior) renoprotection to the ACE inhibitor.

Enalapril was selected because, at the time of designing the study, it was a widely used ACE inhibitor and had been shown to have a long-term stabilising effect on plasma creatinine and on proteinuria in normotensive type 2 diabetic patients [11]. Telmisartan was chosen because of its unique chemical and pharmacological properties. Of all the available ARBs, telmisartan is the most lipophilic compound [35]; this property assists in tissue penetration. It also has a long half-life of about 24 h [36] and is excreted almost exclusively in the faeces [37]. More recently, it has been reported that, in non-diabetic subjects with hypertension, telmisartan and enalapril have comparable antihypertensive efficacy after administration for 12 weeks [38] and both reduce proteinuria similarly in patients with moderate renal failure [39].

A total of 39 centres in Scandinavia, the Netherlands and the UK participated in the double-blind, double-dummy, randomised DETAIL study. Patients were eligible if they had type 2 diabetes treated by diet and/or oral hypoglycaemics. Any patients treated with insulin could also be included if they were diagnosed as being diabetic at the age of ≥40 years, had been in receipt of oral hypoglycaemics for ≥1 year before being treated with insulin and had a body mass index >25 kg/m^2. In addition, to be included patients had to have mild-to-moderate hypertension (resting systolic/diastolic blood pressures <180/95 mmHg) while receiving an ACE inhibitor for ≥3 months before entering the study. (Previous receipt of an ACE inhibitor ensured that a patient could tolerate this class of antihypertensive drug.) Gross renal morphology, usually assessed by ultrasound, was required to be normal for ≥12 months. The urinary albumin excretion rate was to be in the range 11–999 μg/min (mean of three consecutive overnight values), with two values >10 μg/min;

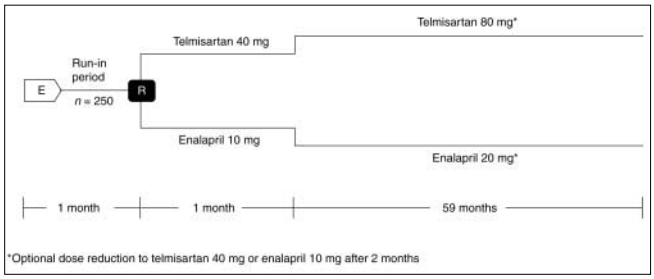

Fig. 2 Design of the DETAIL study [31]
E, enrolment; *R*, randomisation

this meant that patients with either incipient or overt nephropathy were eligible. Patients with a serum creatinine of >140 µmol/l and/or a glomerular filtration rate of <70 ml/min/1.73 m^2 were excluded. Any subject with renal dysfunction not due to diabetes, a single kidney or known renal artery stenosis, New York Heart Association class II–IV congestive heart failure, hypersensitivity to study drug, or a history of angioedema was excluded. In total, 250 patients were enrolled and randomised.

Upon enrolment, patients received their current antihypertensive medication for 1 month (Fig. 2). Thereafter, that medication was stopped and they were randomised to receive either telmisartan 40 mg or enalapril 10 mg for the next month, followed by a mandatory increase of the dose to telmisartan 80 mg or enalapril 20 mg. After a further 3 months, the protocol allowed for the dose to be reduced to either telmisartan 40 mg or enalapril 10 mg if the subject became hypotensive. In reality, this rarely occurred. Additional antihypertensive treatment (not an ACE inhibitor or an ARB) could be given if blood pressure remained elevated.

The primary endpoint was the change in the glomerular filtration rate from baseline after 5 years of study treatment. This was determined using the plasma clearance of iohexol [40]. This technique provides accurate measurements for patients with rates as low as 2–3 ml/min and is less time-consuming and cumbersome than the alternative technique of inulin clearance.

In addition to the primary endpoint, there were a number of secondary endpoints: annual changes in glomerular filtration rate, urinary albumin excretion and serum creatinine, the emergence of end-stage renal disease, incidences of cardiovascular events, and all-cause mortality.

Treatment differences were statistically analysed using analysis of covariance, with country as fixed effect and baseline value fitted as covariate. The purpose of the study was to demonstrate that telmisartan is at least as effective as enalapril, by formally showing that telmisartan is not inferior to enalapril. Non-inferiority was established if the upper bound of the 95% confidence interval for the difference between telmisartan and enalapril in the 5-year cumulative reduction in glomerular filtration rate was less than the pre-defined margin of 10 ml/min/1.73 m^2.

Effect of telmisartan and enalapril on renal function

After 5 years' treatment with telmisartan or enalapril, there was no significant difference in the glomerular filtration rate or in the change in glomerular filtration rate (Fig. 3) [41]. The difference between telmisartan and enalapril in glomerular filtration rate was –3.0 ml/min/1.73 m^2, with 95% confidence intervals –7.6 to +1.6. As the 95% confidence interval of the difference in the primary endpoint between treatments was less than –10 ml/min/1.73 m^2, statistical analysis revealed that telmisartan was non-inferior to enalapril in managing renal function. The steepest decline in GFR was seen after the first year of treatment (Fig. 4). This was probably a haemodynamic effect, associated with the lowering of systemic blood pressure, that results in reduced intraglomerular pressure [42]. In subsequent years, the rate of decline was markedly reduced with a consistent, year-on-year effect. The mean annual decline in glomerular filtration rate for patients treated with telmisartan was 3.7 ml/min/1.73 m^2 in those who completed the study and 3.6 ml/min/1.73 m^2 in the last observation carried forward dataset. In the enalapril group, the mean annual rate of decline in glomerular filtration rate was 3.3 ml/min/1.73 m^2 in those who completed the study and 3.1 ml/min/1.73 m^2 in the last observation carried forward dataset. It is also noteworthy that no patient required

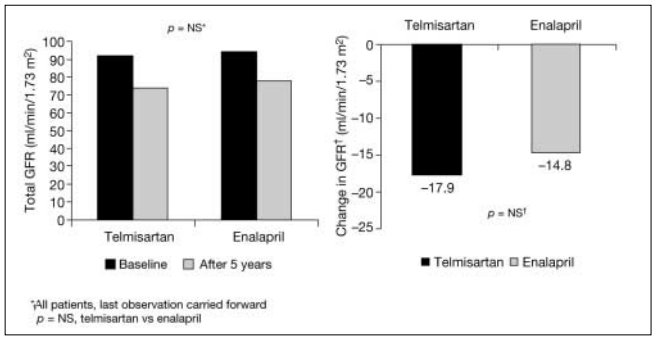

Fig. 3 Comparison of telmisartan and enalapril on glomerular filtration rate (GFR) after 5 years' treatment [41]

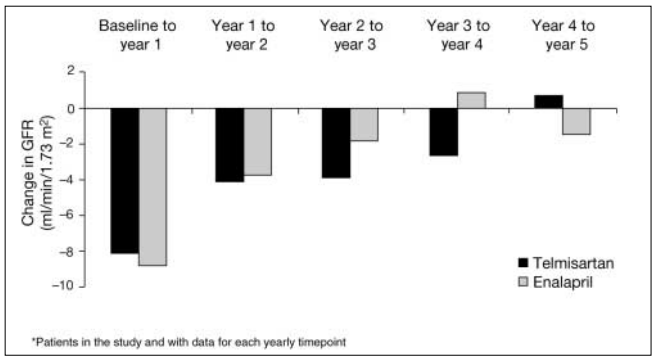

Fig. 4 Annual changes in glomerular filtration rates in patients treated with telmisartan or enalapril [41]

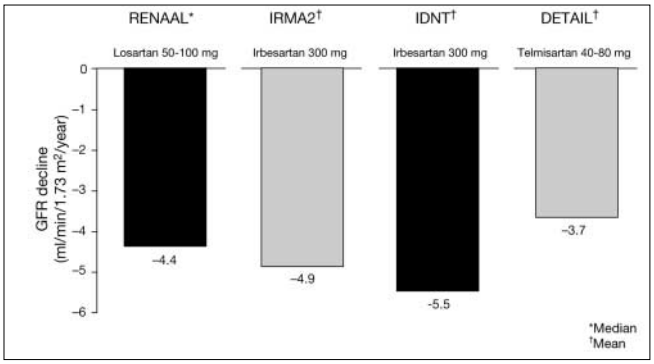

Fig. 5 Annual declines in glomerular filtration rate reported in Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) [32], IRbesartan in patients with type 2 diabetes and MicroalbuminuriA (IRMA 2) [28], Irbesartan in Diabetic Nephropathy Trial (IDNT) [33] and DETAIL [41]

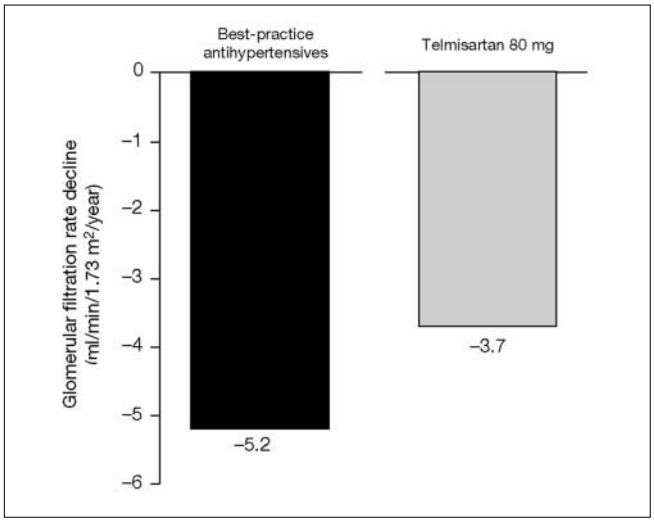

Fig. 6 Rate of decline in glomerular filtration rate in early-stage diabetic nephropathy in patients receiving best-practice antihypertensive treatment care [46] or telmisartan [41]

dialysis or had serum creatinine levels exceeding 200 mmol/l during the course of the study.

Using data from the third US National Health and Nutrition Examination Survey (NHANES III), the National Kidney Foundation has estimated that the normal age-related annual decline in glomerular filtration rate is about 1 ml/min/1.73 m^2 [43]. If a patient with type 2 diabetes and nephropathy goes untreated, there is a steady annual decline in glomerular filtration rate of about 10–12 ml/min/1.73 m^2 [44]. The aim of treatment with an ARB or an ACE inhibitor should be to reduce proteinuria to <0.05 g/24 h and the annual decline in glomerular filtration rate to <2 ml/min/1.73 m^2 [45]. In DETAIL, the initial steep decline stabilised after year 3 with telmisartan and enalapril treatment resulting in an annual decline in glomerular filtration rate of about 2 ml/min/1.73 m^2.

The renoprotective potential, measured in terms of the annual decline in glomerular filtration rate, of telmisartan demonstrated in the DETAIL study is comparable to that achieved with other ARBs in three long-term studies: IRMA 2 [28], RENAAL [32] and IDNT [33] (Fig. 5). IRMA 2 was conducted in patients with baseline characteristics (glomerular filtration rate and urinary albumin excretion) similar to those of the patients in DETAIL. Rather than direct measurement of glomerular filtration rate, as in DETAIL, it was calculated from the patients' serum creatinine concentrations. Patients in RENAAL and IDNT had more severe nephropathy at baseline than patients in DETAIL. Again, in both these studies, determination of glomerular filtration rates was based on serum creatinine concentration. The decline of glomerular filtration with telmisartan in DETAIL was lower than that achieved by using best-practice standard care (after 2001 this consisted of an ACE inhibitor or an ARB, but between 1983 and 2001 no specific antihypertensive treatment was recommended) with early antihypertensive treatment and multifactorial intervention in patients with early diabetic nephropathy followed up over a mean period of 6.5 years (Fig. 6) [46].

Effect of telmisartan and enalapril on mortality

Type 2 diabetes is a significant risk factor for premature mortality. Results from a population-based study strongly suggest that both microalbuminuria and gross proteinuria are significantly associated with subsequent mortality from all causes and from cardiovascular, cerebrovascular and coronary heart diseases [47]. Based on this population study, over a 5-year period, the expected mortality rate in older type 2 diabetics would be about 35% for those with microalbuminuria and about 50% for those with macroalbuminuria. In DETAIL, there were only six deaths in each treatment group over the 5-year duration of the study, representing a mortality rate of about 5% [41]. Only half of these deaths were due to cardiovascular events.

The ARBs have been shown previously to significantly reduce end-stage renal disease, which is an important risk factor for cardiovascular disease [31, 32]. However, they have not yet been shown to significantly reduce mortality in patients with type 2 diabetes with nephropathy. In the case of ACE inhibitors, the Heart Outcomes Prevention Evaluation (HOPE) study demonstrated that ramipril brought about a significant reduction in mortality due to cardiovascular disease and a reduction in total mortality in patients with type 2 diabetes [16].

Conclusions

Targeting the RAS using ACE inhibitors and ARBs has proved an effective therapeutic option for slowing renal disease progression. Their use is recommended in type 1

and type 2 diabetic nephropathy based on comparisons with placebo and with antihypertensive classes that do not block the RAS. However, prior to DETAIL, no truly long-term clinical trial had directly compared members of the two classes of antihypertensive agents. Therefore, it has not been possible to make an evidence-based judgement on which, if either, drug class is preferable. DETAIL sought to address this gap in therapeutic decision-making.

DETAIL is a groundbreaking study, being the first long-term one conducted in patients with hypertension and early-stage type 2 diabetic nephropathy to compare head to head an ARB and an ACE inhibitor. Another unique feature of DETAIL is the use of iohexol to determine glomerular filtration rate, the most reliable indicator of renal function. Without therapeutic intervention, a relentless decline in renal function is inevitable, with the possibility of end-stage renal disease and need for dialysis. Furthermore, there is the prospect of premature death, most likely from cardiovascular disease. DETAIL has shown that telmisartan is comparable to enalapril in reducing the decline in glomerular filtration rate and providing renoprotection in patients with type 2 diabetes and nephropathy. In addition, incidence of all-cause mortality was markedly reduced with the pharmacological intervention.

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