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Renoprotection in Type 2 diabetes: blockade of the renin-angiotensin system with angiotensin II receptor blockers

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Introduction

Diabetic nephropathy accounts for the largest number of patients with end-stage renal disease (ESRD) in the UK, Europe, Japan and the United States.¹ Despite growing evidence for the importance of blood pressure (BP) and glycaemic control in disease progression, the incidence of ESRD secondary to diabetic nephropathy continues to rise.

The worldwide prevalence of diabetes is increasing steadily and the majority, in the developed world, have Type 2 diabetes. Hypertension and microalbuminuria (30–300 mg albumin/24 hours) are frequently present, even from the time of diagnosis. Microalbuminuria progresses over 5–10 years to proteinuria (>300 mg of protein/24 hours) in 20–40% of patients.² Persistent proteinuria is the hallmark of diabetic nephropathy and is accompanied by a progressive decline in glomerular filtration rate (GFR). Heavy proteinuria and co-existing hypertension both accelerate the rate of progression to ESRD.

Microalbuminuria is a strong predictor of cardiovascular morbidity and mortality in Type 2 diabetics.³ Indeed, the leading cause of death in diabetics is cardiovascular disease.⁴ Type 2 diabetics have the same excess risk of myocardial infarction (MI) as non-diabetics who have previously had a myocardial infarct.⁵ Furthermore, the combination of diabetes and hypertension is associated with an approximately 4-fold increase in cardiovascular risk when compared with the non-diabetic normotensive population.⁶

Treatment strategies in diabetics aim to slow the onset and progression of renal disease and other microvascular complications and to reduce the associated excess cardiovascular risk. In Type 1 diabetics with proteinuria or microalbuminuria, blockade of the renin-angiotensin system (RAS) with angiotensin-converting enzyme inhibitors (ACE-I) improves renal outcome.^{7,9} ACE-I are renoprotective, in that they afford protection against progressive proteinuria and renal insufficiency, which is independent of, and probably additive to, their BP-lowering effect. There is now a consensus opinion that ACE-I, when well tolerated, should be used as first line therapy in this group. Their role in Type 2 diabetics, however, is not yet fully established.

In 1993, Ravid reported that the ACE-I, enalapril, stabilised plasma creatinine and urinary albumin excretion in 94 normotensive, Type 2 diabetics with microalbuminuria and normal renal function.² More

recently, the MICRO-HOPE study demonstrated that ramipril reduced cardiovascular mortality and early renal disease progression in individuals with both Type 1 and Type 2 diabetes.¹⁰ This effect appeared to be greater than might be attributable to the decrease in BP in the ramipril-treated group, although the potential contribution of BP reduction in this study remains contentious.

Other studies have compared ACE-I with other antihypertensives, with varying outcomes on the observed rates of diabetic complications and mortality.^{11–14} The UKPDS trial stratified treatment intensities in hypertensive Type 2 diabetics, specifying BP targets of below either 150/80 mmHg or 180/105 mmHg.¹⁵ These targets were achieved with either an ACE-I, captopril, or a beta-blocker, atenolol, as the main treatment. In the lower BP group, there was a reduction in the risk of death related to diabetes, progression of diabetic nephropathy and deterioration in visual acuity. However, further analysis of the outcome data in the lower blood pressure group showed no difference between those treated with the ACE inhibitor or beta blocker.¹⁶ Both of these agents inhibit the renin-angiotensin system and there was no comparison, in this study, with a regimen that did not block the renin-angiotensin system.

Despite the number of trials conducted to date, there remains controversy over which agent, if any, offers superior renal or cardiovascular protection in Type 2 diabetics. The question also remains as to whether blockade of the RAS will confer similar benefits in Type 2 as in Type 1 diabetics. Furthermore, it may be that BP reduction itself is more important than the treatment used to achieve it. These important questions and unresolved issues have provided the background for three prospective clinical trials, which evaluated the effect of angiotensin II receptor blockers (ARBs) on cardiovascular and renal outcomes, specifically in Type 2 diabetics. The results of these trials have now been published simultaneously in the *New England Journal of Medicine*.^{17–19}

Study of the effects of Irbesartan on microalbuminuria in hypertensive patients with Type 2 diabetes (IRMA 2)¹⁷

IRMA 2 was a prospective, randomised, double-blind trial in 590 hypertensive patients with Type 2 diabetes, normal renal function and microalbu-

minuria (urinary albumin excretion rate between 20 and 200 µg/min). Participants were randomised to receive either irbesartan 150 mg, irbesartan 300 mg or placebo, plus other antihypertensives (excluding ACE-I and other ARBs), to achieve a BP goal of ≤135/85 mmHg. The primary outcome measure of IRMA 2 was the time to development of overt proteinuria, defined as an overnight urinary albumin excretion rate (AER) exceeding 200 µg/min and an increase of urinary AER from baseline by at least 30%. Secondary endpoints included changes in overnight urinary AER, creatinine clearance as estimated by the Cockcroft-Gault formula, and the restoration of normoalbuminuria.

The achieved reduction in BP was reported as mean trough BPs, which were 144/83, 143/83 and 141/83 mmHg in the placebo, irbesartan 150 mg and irbesartan 300 mg groups respectively. The proportion of patients who progressed from microalbuminuria to overt proteinuria was 14.9% in the placebo control group, 9.7% in the irbesartan 150 mg group and 5.2% in the irbesartan 300 mg group. Thus, for the primary endpoint of progression to diabetic nephropathy, the hazard ratio was 0.3 (95% CI, 0.14 to 0.61; $p < 0.001$) in the group treated with irbesartan 300 mg and 0.61 (95% CI, 0.34 to 1.08; $p = 0.08$) in the group treated with irbesartan 150 mg.

The results of some of the secondary endpoints have also been reported. Over the 2-year study period the mean overnight urinary albumin excretion rate (AER) was reduced by 2% in the placebo group and 24% and 38% in the groups treated with irbesartan 150 mg and 300 mg respectively ($p < 0.001$ for the comparison of placebo *vs.* the combined irbesartan groups). There was no difference between groups in the rate of decline of the estimated creatinine clearance. The urinary AER normalised in 34% of individuals treated with irbesartan 300 mg as compared to 24% who received irbesartan 150 mg (no p value given) and 21% who received placebo ($p = 0.006$).

Irbesartan Type 2 Diabetic Nephropathy Trial (IDNT)²⁰

IDNT was a prospective, randomised, double-blind, placebo-controlled trial in 1640 Type 2 diabetics with hypertension and established diabetic nephropathy. The trial design and patient baseline characteristics have previously been published.²⁰ Patient characteristics, prior to randomisation, are summarised in Table 1. The study compared the effects of irbesartan (maximum dose 300 mg), amlodipine (maximum dose 10 mg) and placebo on the time to reach a primary composite endpoint of doubling of baseline creatinine, ESRD or death (all-cause mortality). Secondary outcome measures included the time to a composite endpoint of fatal or non-fatal cardiovascular events.

The mean BP achieved in each group fell short of the BP goal for the study, but were similar in the irbesartan and amlodipine groups at 140/77 and 141/77 mmHg, respectively. BP was higher in the placebo group at 144/80 mmHg. For the primary

Table 1 Baseline clinical features at entry to IDNT (n=1640). Adapted from Rodby *et al.* 2000.²⁰

Clinical characteristic	Mean	SD
Age (years)	59	8
BMI (kg/m ²)	31	7
SBP (mmHg)	156	18
DBP (mmHg)	85	11
Serum creatinine (mmol/L)	150	53
Proteinuria (g/24-hour)	4.0	3.5
HbA _{1c} (%)	8.1	1.7

composite endpoint of doubling of serum creatinine, ESRD or death, the irbesartan-treated group had a 20% relative risk reduction when compared with the placebo group ($p = 0.02$) and a 23% risk reduction when compared with the amlodipine-treated group ($p = 0.006$). When the results for the primary composite endpoints were adjusted for BP, however, there was a persistent significant relative risk reduction with irbesartan *vs.* the two other groups. The beneficial effect of irbesartan on the composite primary endpoint is mostly due to a difference in the doubling of serum creatinine between groups. There was a 33% relative risk reduction in time to doubling of serum creatinine in the irbesartan *vs.* the placebo treated groups ($p = 0.003$), and 37% relative risk reduction in the irbesartan *vs.* the amlodipine-treated groups ($p = 0.001$). There were no significant differences between treatment groups in the time to reach ESRD or in all-cause mortality. There was no difference in the relative risk for the combined primary endpoint between amlodipine and placebo, despite the fact that BP was lower in the amlodipine-treated group.

There was no difference between groups for the secondary composite endpoint of cardiovascular events, which included cardiovascular death, MI, hospitalisation for heart failure and stroke.

Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL)¹⁹

RENAAL was a prospective, randomised, double-blind, placebo-controlled trial in 1513 Type 2 diabetics with established diabetic nephropathy. The trial design and patient baseline characteristics have previously been published.²¹ Patient characteristics, prior to randomisation, are summarised in Table 2. Participants were randomised to receive either losartan (maximum dose 100 mg) or placebo in addition to other antihypertensives (excluding ACE-I and other ARBs), to achieve a BP goal of ≤140/90 mmHg. The primary outcome measure, as for IDNT, was a composite endpoint consisting of the time to the first event of doubling of serum cre-

Table 2 Baseline clinical features at entry to RENAAL (n=1512). Adapted from Brenner *et al.* 2000.²¹

Clinical characteristic	Mean	SD
Age (years)	59.6	7.4
BMI (kg/m ²)	29.7	6.3
SBP (mmHg)	153	19
DBP (mmHg)	82	10
Serum creatinine (mmol/L)	168	44
Urinary alb:creat (mg/g)	1867	2699
HbA _{1c} (%)	8.5	1.6

atnine, ESRD or death. Secondary endpoints included cardiovascular events, the progression of renal disease and changes in proteinuria.

The study was designed to continue for 3.5 years of follow-up after the last patient was enrolled, but was stopped 13 months early by the trial Steering Committee due to ethical concerns of withholding inhibitors of the renin-angiotensin system from diabetics with renal impairment. The mean follow-up time was 3.4 years.

The composite primary endpoint of doubling of serum creatinine, ESRD or death was reached by significantly fewer individuals in the losartan group than in the placebo group (relative risk reduction 16%, p=0.024). When the outcome components were analysed separately, there was a significant relative risk reduction in time to doubling of serum creatinine (25%, p=0.006) and time to ESRD (28%, p=0.002) in the losartan *vs.* the placebo group. There was no significant difference between groups in all-cause mortality. The BPs achieved throughout the study in the losartan and placebo groups are summarised in Table 3. After the first year there was no statistically significant difference between the groups, although the BP remained lower in the losartan group at the end of the study. The risk reduction for the primary composite endpoint and for ESRD was maintained (15%), after adjustment for achieved mean arterial pressure (p=0.03).

There was no difference between the losartan- and placebo-treated groups in the secondary composite endpoint of cardiovascular morbidity and mortality. However, hospitalisation for heart failure, one of the secondary endpoint components, was significantly reduced (32% risk reduction, p=0.005) in the losartan-treated group.

Discussion

The incidence of Type 2 diabetes is predicted to increase rapidly, with a projected worldwide prevalence of 210 million people by 2010.²² Between 25–40% of all diabetics will develop nephropathy, which is now the leading cause of end-stage renal disease (ESRD), necessitating chronic dialysis or

Table 3 RENAAL. Mean trough blood pressures measured throughout the trial.¹⁹

	Mean blood pressures in mmHg	
	Losartan	Placebo
Year one	146/78	150/80
Year two	143/77	144/77
End of study	140/74	142/74

renal transplantation. ESRD, as a consequence of diabetic nephropathy, thus represents an increasingly large economic burden. In addition, the outlook for diabetic patients on dialysis is very poor, as approximately one third will be dead within two years of commencing dialysis.²³ Cardiovascular disease accounts for the majority of these deaths.

Blockade of the RAS with ACE-I has been shown to postpone both the development and progression of nephropathy in Type 1 diabetes.⁷⁻⁹ ACE-I are also renoprotective in a wide range of other chronic nephropathies, including non-diabetic proteinuric nephropathies^{24,25} and hypertensive nephrosclerosis in African Americans.²⁶

There is now some evidence that ARBs might also provide renoprotection in Type 1 diabetics with established diabetic nephropathy.²⁷ The studies, recently published in the *New England Journal of Medicine*,¹⁷⁻¹⁹ have evaluated the role of angiotensin II (Ang II) receptor blockade in preventing the onset (IRMA 2), and progression (IDNT, RENAAL) of diabetic nephropathy in Type 2 diabetics. Unfortunately, there was no comparison made with an ACE-I in any of these studies. The results, however, do corroborate the growing evidence that RAS blockade provides renoprotection in Type 2 diabetics. Treatment with an ARB delays the progression of renal disease at all stages, from the point of development of microalbuminuria through to established diabetic nephropathy and ESRD. In each of the studies, renoprotection was demonstrated with the maximum approved dose of the ARB, and there was also a suggestion of a dose response in the IRMA 2 study.

The majority of Type 2 diabetics are more likely to die from cardiovascular disease than from renal disease. Unfortunately, from the results presented to date, neither the IDNT nor RENAAL studies have demonstrated a mortality benefit with ARB treatment. In addition, there did not appear to be a consistent reduction in cardiovascular risk. In the MICRO-HOPE study, which included 3496 patients with Type 2 diabetes, ramipril reduced mortality and cardiovascular risk. In a smaller sub-set of the same study population, a significant reduction in progression from microalbuminuria to overt nephropathy was also demonstrated with ramipril treatment.¹⁰ As there was no comparison made with ACE-I in the IRMA 2, IDNT or RENAAL studies, the question remains whether ARBs or ACE-I should be used as first line therapy in Type 2 diabetics with evidence of pro-

Trial acronyms used

UKPDS	United Kingdom Prospective Diabetes Study
IDNT	Irbesartan Type 2 Diabetic Nephropathy Trial
IRMA 2	Irbesartan on microalbuminuria in hypertensive patients with Type 2 diabetes trial
RENAAL	Reduction of endpoints in NIDDM with the angiotensin II antagonist losartan
MICRO-HOPE	Microalbuminuria, Cardiovascular and Renal Outcomes - Heart Outcomes Prevention Evaluation

teinuria or microalbuminuria. Similarly, none of the above studies have shown any data on subgroup analyses, where beta blockers were used to achieve BP targets. It would be interesting to see how these agents, which also inhibit the renin-angiotensin system, compared with the ARBs in type 2 diabetics.

The IRMA 2, IDNT and RENAAL studies collectively demonstrate that Ang II receptor blockade slows the progression of Type 2 diabetic renal disease, and as such they represent an important step forward in the management of Type 2 diabetes. It is not clear how ARBs might compare with ACE-I for this indication. At the very least ARBs can now be used, as an alternative to ACE-I, particularly when there are side-effects, for renoprotection in Type 2 diabetics with microalbuminuria or overt nephropathy.

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