Hypertension is a major determinant of the progression of diabetic renal disease. Despite effective conventional anti-hypertensive therapy, the incidence of diabetic nephropathy as a cause of end stage renal disease (ESRD) is continuing to rise. This rise is more pronounced in certain ethnic groups such as Indo-Asians and Chinese.

Racial differences in diabetic nephropathy

Several studies have shown marked racial variation in the progression of diabetic renal disease. Compared to Caucasians, subjects of Asian, Indo-Asian and African-Caribbean origin have considerably greater risk of developing ESRD. Hence postponing the progression of renal disease in Type 2 diabetic patients of these racial origins represents a major pharmacological challenge.

RENAAL Asian data

Results from two landmark trials, RENAAL (Reduction in Endpoints in Non-Insulin-Dependent Diabetes Mellitus) and the IDNT (Irbesartan Diabetic Nephropathy Trial) provided solid evidence that treatment with an angiotensin receptor blocker (ARB) (losartan and irbesartan in respective studies) in addition to conventional anti-hypertensive therapy slowed down progression to ESRD in Type 2 diabetic patients with nephropathy compared to placebo group. This was achieved despite similar blood pressure reduction between groups. These remarkable pharmacological effects appear to confer even greater benefits for Asians with diabetic nephropathy as revealed in a recent publication of Asians subgroup analysis. In the RENAAL study, Asian accounted for 17% (n=252) of the total population (n=1513). After a mean follow up period of 3.2 years, losartan (50 mg titrated up to 100 mg daily) reduced the risk of the primary composite endpoint (doubling of serum creatinine, ESRD, or all cause mortality) in Asian patients by 35%. In addition, losartan reduced the level of proteinuria by 47% (Figure 1) and rate of renal function decline by 31% in Asian patients. Compared to the level of risk reduction in ESRD (28%) and doubling of serum creatinine (25%) in the total population in RENAAL study, it would appear that the renoprotective effect of losartan is more pronounced in Asian patients (38% and 36% respectively). In this Asian sub-population, baseline proteinuria and haemoglobin were significant predictors of risk for the renal endpoints.

Similar Asian data are unavailable from the IDNT study. It remains unclear whether the renoproteective effect of losartan observed in the Asian Type 2 diabetic patients can be replicated using other ARBs.

ARB and renoprotection: drug or class effect?

Several studies of other ARBs showed beneficial effects on microalbuminuria in Type 2 diabetic patients and it has generally been accepted that renoprotection in Type 2 diabetes by ARBs is a class effect. This is further supported by results of MARVAL (Microalbuminuria Reduction with Valsartan) study as well as IRMA2 (Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria) study. In the MARVAL study, valsartan was found to be superior in reducing urinary albumin excretion compared to amlodipine in 332 normotensive and hypertensive subjects with Type 2 diabetes, despite similar blood pressure reduction. Similarly, in IRMA2 study, high dose irbesartan (300 mg daily) reduced urinary albumin excretion compared to low dose irbesartan (150 mg daily) and compared to placebo group over a 2-year period. Although these findings are suggestive of a class effect in renoprotection, compelling evidence would need to come from large-scale studies using solid renal endpoints.

There is now a growing body of evidence to suggest that losartan may exert its renoprotection via mechanisms not mediated through AII blockade. Indeed, losartan has...
distinctive pharmacological properties not shared by other drugs of the same class. These include anti-inflammatory and anti-aggregatory effects of its metabolite, EXP3179\(^9\) and the uricosuric effects of losartan\(^10,11\). At therapeutic dose, losartan also has anti-platelet effects mediated via blockade of thromboxane A\(_2\) receptors\(^12\). This property is not shared by candesartan or valsartan, at least in animal models\(^13\). In addition, losartan has been shown to reduce the plasma concentration of pre-fibrotic transforming growth factor TGF-\(\beta\) in Type 2 diabetic patients\(^4\). Taken together, the renoprotective effect of losartan, along with its remarkable effects in Asian diabetic kidney disease would support this as the drug of choice in this therapeutic class.

**Economic implications**

It is estimated that there are 44 million people with type 2 diabetes in the Western Pacific Region and 1.8 million of them have proteinuria. Pharmacological treatment with the ARB, losartan, in additional to aggressive blood pressure control would result in a substantial reduction in the incidence of ESRD in these high-risk Asians. The findings in the RENNAL Asian subgroup have important healthcare implications\(^15\).

**References**