NEWS in Brief

ACEI AND ARB SLOW RETINOPATHY, BUT NOT NEPHROPATHY IN TYPE 1 DIABETES.

The authors from the University of Minnesota (Mauer et al.) reported that patients with type 1 diabetes who start on renin-angiotensin blockers (angiotensin-receptor blocker or ACE inhibitor) early may slow development of retinopathy by up to 70%. But there was no significant slowing of the progression of nephropathy over 5 years.

An accompanying editorial (Perkins et al., from Harvard) noted that the finding challenges the widely-accepted belief that inhibition of the renin-angiotensin system in diabetic patients counteracts development of nephropathy. The editorial noted that numerous studies suggesting renal benefits were of short duration and focused primarily on urinary albumin excretion as a surrogate for kidney function.

The editorial also noted that finding was not unexpected. The Collaborative Study Group captopril trial showed an effect on creatinine doubling time in advanced nephropathy, but not in those with creatinine levels of less than 1.5 mg/dL.

The Minnesota group conducted the Renin-Angiotensin System Study (RASS), which followed patients for progression of the early histological lesions of diabetic nephropathy seen on biopsy. There were 285 type 1 diabetes patients, who had normal albumin excretion and blood pressure levels. They were randomly assigned to receive losartan, enalapril, or placebo for 5 years (midway through the trial, the 50-mg daily dose of losartan and 10-mg daily dose of enalapril were doubled).

The primary endpoint (change in mesangial fractional volume from baseline to 5 years) showed no significant difference for losartan or enalapril compared to placebo (+0.026 and +0.005, vs. +0.016 units, P = 0.17 and P = 0.16, respectively). Secondary measures (for example interstitial fractional volume) also showed similar results.

There was an unexpected and unexplained increase in the 5-year cumulative incidence of micro-albuminuria with losartan than with placebo (17% vs. 6%, P = 0.01) (similar incidence between enalapril and placebo, 4% vs. 6%, P = 0.96). The authors warned that this finding required further confirmation in a randomised controlled trial, but they recommended careful monitoring of the albumin excretion rate with ARB use.

There was no difference in kidney function between groups as assessed by the glomerular filtration rate over the 5 years (reduction of 6.6 to 8.9 ml per minute, P < 0.002 for all, versus baseline).

For retinopathy, a 15-step diabetic retinopathy severity scale was used. Progression of 2 or more steps on occurred in only 25% of patients who received enalapril, 21% who received losartan, and 38% who received placebo (P = 0.02, and P = 0.008). There was thus a risk reduction with enalapril (65% RR, OR 0.35 vs placebo, 95% CI 0.14 - 0.85) and losartan (70% RR, OR 0.30 vs placebo, 95% CI 0.12 - 0.73), and this seemed to be independent of glycaemia and blood pressure effects (although the authors did not rule out BP effect). The effect on retinopathy is inconsistent with the placebo-controlled DIRECT trial using the ARB candesartan, which showed a non-significant 18% reduction in the development of retinopathy in patients with type 1 diabetes compared with placebo (HR 0.82, 95% CI 0.67 to 1.00, P = 0.0508). [Chaturvedi N, et al. Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials. Lancet 2008; DOI: 10.31016/S0140-6736(08)61412-9.] The editorial (Perkins et al.) suggested that this might be due to differences in sample size, and in the drugs and doses.

The authors (Mauer et al.) cautioned: (1) about extrapolating between early and advanced stages of diabetic nephropathy, and between types 1 and 2 diabetes, and (2) that further work is required before a strategy is used for retinopathy prevention in clinical practice, particularly determining the subgroups that might not benefit, and the duration of therapy needed. The editorial (Perkins et al.) noted that: (1) inhibition of the renin-angiotensin system should not be considered for normo-tensive patients with type 1 diabetes and normo-albuminuria, (2) use of ACEIs and ARBs was questionable for micro-albuminuria in patients with type 1 or type 2 diabetes, since evidence of prevention of early decline in renal function is limited, and (3) there was little chance of retinopathy benefit for patients with type 1 diabetes who have established retinopathy or for those with type 2 diabetes regardless of retinopathy status. SMA

Source: (1) Mauer M, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. NEJM 2009; 361: 40-51. (2) Perkins BA, et al. Diabetes complications and the renin-angiotensin system. NEJM 2009; 361: 83-85.