

Trials With ACE-Inhibitors In Renal Disease

The effects of drugs including ACE-inhibitors and angiotensin-II receptor blockers on the progression of renal disease have been examined in two broad patient populations: those with diabetes and those with other disease states associated with renal injury. Included in this section are reprints from controlled trials examining the effects of ACE-inhibitors in patients with renal disease that measured clinical endpoints years (*e.g.*, incidence of end-stage renal disease, change in serum creatinine) and lasted at least 2 years. The trials include the following:

Trials in Patients with Diabetic Renal Disease

1. The Collaborative Study Group trial, comparing captopril and placebo in 409 subjects with insulin-dependent diabetes and ≥ 500 mg of proteinuria per day for a median duration of three years. The primary endpoint was a doubling of serum creatinine to at least 2.0 mg/dl. An additional endpoint was the combination of death, dialysis or renal transplantation.

2. A trial by Ravid and colleagues, comparing enalapril and placebo in 94 subjects with non-insulin-dependent diabetes and 30 to 300 mg of proteinuria per day followed for 5 years. No primary endpoint is specified in the publication, but endpoints measured include change in the reciprocal of serum creatinine and change in proteinuria.

3. The EUCLID study, comparing lisinopril and placebo in 143 subjects with insulin-dependent diabetes and urinary albumin excretion rate of 20 to 200 $\mu\text{g}/\text{min}$ followed for 2 years. The primary endpoint was progression to 'clinical proteinuria.'

4. A trial by Lebovitz and colleagues, comparing enalapril and placebo in 121 (of 165 enrolled) subjects with non-insulin-dependent diabetes and hypertension followed for up to 3 years. No primary endpoint is specified, but endpoints measured include change in GFR (measured using ^{131}I -Iothalamate clearance) and change in proteinuria.

5. A trial by the North American Microalbuminuria Study Group, comparing captopril with placebo in subjects with insulin-dependent diabetes and proteinuria followed for 2 years. No primary endpoint was specified, but endpoints measured include progression to clinical proteinuria and change in creatinine clearance (measured using 24-hour urine collection).

6. A trial by the Diabiopsies Group, comparing perindopril and placebo in 22 subjects with non-insulin-dependent diabetes followed for 2 years. The primary endpoint was histologic, but other measurements included changes in serum creatinine and proteinuria.

7 and 8. The Irbesartan Diabetic Nephropathy Trial (IDNT) and the trial conducted for 'The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group.'. These trials are the subject of today's deliberations.

9. The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study, comparing losartan with placebo in 1513 subjects with type 2 diabetes and diabetic nephropathy. The primary outcome is the time to the first event of the composite endpoint: doubling of serum creatinine concentration, end-stage renal disease, or death.

Trials in Patients with Non-Diabetic Renal Disease

1. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group trial, which compared benazapril and placebo in 583 subjects with renal insufficiency caused by several disease other than diabetes followed for 3 years. The primary endpoint was the time to a doubling of serum creatinine or the need for dialysis. Other endpoints measured included change in serum creatinine and proteinuria.

2. The GISEN Group trial (Gruppo Italiano di Studi Epidemiologici in Nefrologia), which compared ramipril to placebo in 352 subjects with proteinuria (non-diabetic), stratified by the amount of proteinuria present at baseline. The duration of follow-up varied among the strata. The primary endpoint was the rate of change of GFR, measured using ⁵¹Cr-EDTA. The results have been published in three separate articles (all included).

3. A trial by Ihle and colleagues, comparing enalapril and placebo in 70 hypertensive subjects with advanced renal insufficiency followed for up to 2 years. No primary endpoint is specified in the publication, but endpoints measured include change in GFR (measured by ⁵¹Cr-EDTA and serum creatinine) and proteinuria.

4. The African American Study of Kidney Disease and Hypertension (AASK) trial substudy results, comparing ramipril and amlodipine in 653 subjects with hypertensive renal disease. The 'primary analysis' was the rate of change in GFR, and the trial included a 'secondary clinical-outcome analysis' of time to any of the following: confirmed reduction in GFR by 50% or by 25 ml/min per 1.73 m², end-stage renal disease or death.