Do ACE inhibitors prevent nephropathy in type 2 diabetes without proteinuria?

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EVIDENCE-BASED ANSWER

Angiotensin-converting enzyme (ACE) inhibitors make a significant difference for patients with diabetes as a whole. If patients both with and without microalbuminuria are included together, ACE inhibitors significantly reduce the progression of the albumin excretion rate (strength of recommendation [SOR]: A, based on multiple randomized controlled trials) and the development of overt nephropathy (SOR: A, based on 1 randomized controlled trial).

However, studying diabetes without microalbuminuria separately, the effect of ACE inhibitors on progression to nephropathy does not reach statistical significance. This applies to both type 1 and 2 diabetes (SOR: A, based on randomized controlled trials with heterogeneous results). Results are contradictory regarding whether ACE inhibition delays new onset of diabetic microalbuminuria.

EVIDENCE SUMMARY

There are 3 prospective randomized controlled trials studying the effect of ACE inhibitors on albumin excretion for patients with diabetes who do not have microalbuminuria. A 2-year randomized controlled trial compared lisinopril (Prinivil; Zestril) 10 mg/d with placebo in 530 normotensive adults (aged 20–59 years) with insulin-dependent diabetes, defined as those diagnosed with diabetes before age 36 and using continuous insulin therapy within 1 year of diagnosis. At the beginning of the study, 90 patients had microalbuminuria—defined as an albumin excretion rate (AER) >29 mg/24 hr—and 440 patients did not. When the results for all patients who had and did not have microalbuminuria were combined, there was a significantly smaller rise in the AER for the lisinopril group vs the placebo group (3.2 mg/24 hr lower; \( P=0.03 \)). However, for the patients without initial microalbuminuria, the reduction in the rise of AER with lisinopril was not significant (1.4 mg/24 hr lower; \( P=0.10 \)).
The decreased rate of developing new microalbuminuria was also not significant (relative risk reduction [RRR]=12.7%; \( P = .10 \)).

A subsequent trial compared enalapril (Vasotec) 10 mg/d with placebo in 194 normotensive patients (aged 40–60) with type 2 diabetes and without microalbuminuria, defined as AER >30 mg/24 hr. Over the 6-year course of the study, the AER in the placebo group rose from 10.8 mg/24 hr to 26.5 mg/24 hr. The AER of the treatment group dropped from 11.6 mg/24 hr initially to 9.7 mg/24 hr at 2 years, then rose to 15.8 mg/24 hr at 6 years. Enalapril significantly slowed the rise in AER (RRR=0.4; \( P = .001 \)). Nineteen percent of the placebo group developed microalbuminuria, compared with 6.5% of those taking enalapril (absolute risk reduction [ARR]=12.5%; number needed to treat=8; \( P = .042 \)). While this study described a modest and statistically significant renal protective effect of enalapril, it did not use an intention-to-treat analysis.

MICRO-HOPE, a subset of the HOPE trial, studied ramipril (Altace) 10 mg/d vs placebo in 2437 patients with diabetes who did not have clinical proteinuria. Patients were aged 55 years or older and had either a previous cardiovascular event or at least 1 other cardiovascular risk factor. There were 1140 patients with microalbuminuria, defined as an albumin/creatinine ratio 2 mg/mmol, and 2437 patients without. After 4.5 years, 10% of patients had developed overt nephropathy, defined as albumin/creatinine >36 mg/mmol.

When all patients in the study were examined together, ramipril provided significant renal protection over placebo (RRR=24%; ARR=1%; \( P = .027 \)). It also lowered the risk of MI by 22%, stroke by 33%, and cardiovascular death by 37%. But in a separate analysis of the patients without microalbuminuria, ramipril did not significantly reduce overt nephropathy \( (P = .50) \). Ramipril also did not significantly reduce the risk of developing new microalbuminuria in this group (RRR=9%; \( P = .17 \)). Further, for patients without microalbuminuria, ramipril did not reduce the combined outcomes of myocardial infarction, stroke, or cardiovascular death (odds ratio=0.85; 95% CI, 0.70–1.02).

**RECOMMENDATIONS FROM OTHERS**

We could find no guidelines recommending for or against the use of ACE inhibitors for patients with diabetes without microalbuminuria.

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**CLINICAL COMMENTARY**

**ACE inhibitors should still be used in most patients with type 2 diabetes**

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ACE inhibitors do not prevent the development of type 2 diabetic nephropathy. In contrast to type 1 diabetes, cardiovascular disease is the primary cause of death in type 2. The HOPE study demonstrated that ACE inhibitor therapy significantly reduces cardiovascular events in type 2 diabetes independent of hypertension status. These benefits are so
compelling that the American Diabetes Association strongly recommends ACE inhibitor therapy for type 2 diabetics aged ≥55 years with 1 additional risk factor. Despite not preventing the development of nephropathy, ACE inhibitors should be used for most patients with type 2 diabetes for cardiovascular risk reduction.

REFERENCES


