January 2004 (Vol. 53, No. 1)

CLINICAL INQUIRIES FROM THE FAMILY PRACTICE INQUIRIES NETWORK

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

Lisa Sferra, MD ***Gary Kelsberg, MD***
Valley Family Care Medicine Residency, Renton, Wash
Sherry Dodson, MLS
University of Washington Health Sciences Libraries, Seattle

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 heterogenous 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*=.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*=.10).

The decreased rate of developing new microalbuminuria was also not significant (relative risk reduction [RRR]=12.7%; *P*=.10).[1]

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.[2]

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).[3]

RECOMMENDATIONS FROM OTHERS

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

CLINICAL COMMENTARY

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

Joseph Saseen, PharmD, FCCP, BCPS

University of Colorado Health Sciences Center,Denver

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.[4] 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.[5] Despite not preventing the development of nephropathy, ACE inhibitors should be used for most patients with type 2 diabetes for cardiovascular risk reduction.

REFERENCES

1. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. The EUCLID Study Group. *Lancet* 1997;349:1787–1792.
2. Ravid M, Brosh D, Levi Z, Bar-Dayan Y, Ravid D, Rachmani R. Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus. A randomized, controlled trial. *Ann Intern Med* 1998;128:982–988.
3. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 2000;355:253–259.
4. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145–153.
5. Arauz-Pacheco C, Parrott MA, Raskin P. American Diabetes Association. Treatment of hypertension in adults with diabetes. *Diabetes Care* 2003;26 Suppl 1:S80–S82.