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Q: Should all diabetic patients take ACE inhibitors, even those without proteinuria?

ACE inhibitors are not yet recommended for all diabetic patients

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A: RECENT STUDIES have shown that angiotensin-converting enzyme (ACE) inhibitors can slow the progression to diabetic nephropathy in patients with type 1 or type 2 diabetes with microalbuminuria or macroalbuminuria.

Should we extend this reasoning, and give all patients with diabetes ACE inhibitors, even if they have no proteinuria?

I believe it is premature to recommend using ACE inhibitors in *all* patients with diabetes mellitus. We do, however, have good evidence that ACE inhibitors are beneficial in *specific* groups of diabetic patients, eg, those with microalbuminuria or frank proteinuria. There is also accumulating evidence of benefit in patients with congestive heart failure and myocardial infarction. Whether these indications should be expanded awaits the results of further study.

Blood pressure and the kidney

A major principle to protect the kidney from the complications of diabetes is to treat high blood pressure aggressively, no matter what type of antihypertensive drug is used. In early studies in patients with type 1 diabetes, Parving et al[1] and Mogensen[2] used antihypertensive drugs such as diuretics, beta-blockers, and hydralazine; they demonstrated that lowering blood pressure reduces proteinuria and slows the decline of renal function.

Current guidelines suggest that a value less than 130/85 mm Hg is a reasonable target. Whether lower blood pressures will accrue greater benefits is not yet firmly established.

ACE inhibitors and renal disease in diabetes

Although the primary goal in protecting the kidney is to reduce the blood pressure, a preponderance of current evidence indicates that ACE inhibitors protect the kidney better than other blood-pressure-lowering medications,

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probably because ACE inhibitors specifically lower the intrarenal pressure.

After animal studies demonstrated a renal protective effect of ACE inhibitors, a number of human trials followed.[3,4] Lewis et al[5] performed a landmark study in patients with type 1 diabetes, albuminuria, and mildly impaired creatinine clearance—ie, patients who were just beginning to develop renal failure. The ACE inhibitor captopril reduced the risk for a decline in renal function compared with other antihypertensive regimens (not including calcium channel blockers).

Additional data indicate that ACE inhibitors may slow the progression of microalbuminuria to macroalbuminuria even in normotensive patients.[6] An increasing urine albumin excretion rate is a surrogate for end-stage renal disease, and is the basis for the current recommendations for use of ACE inhibitors and blood pressure regimens in diabetic patients who have microalbuminuria or macroalbuminuria.

Enthusiasm for ACE inhibitors may be tempered by the findings of the United Kingdom Prospective Diabetes Study (UKPDS), in which atenolol (a beta-blocker) and captopril were equally effective in reducing the risk for albuminuria in hypertensive type 2 diabetic subjects.[7] Since proteinuria in type 2 diabetic patients may not necessarily be related to diabetic nephropathy, other methods of managing hypertension may be equally efficacious in protecting type 2 diabetic patients from adverse medical outcomes—including renal disease and atherothrombotic events.

ACE inhibitors and coronary heart disease

Because angiotensin has potential adverse effects on the heart, use of ACE inhibitors in diabetic patients may help to reduce the risk for coronary heart disease events. In the Appropriate Blood Pressure Control in Diabetes (ABCD) trial,[8] the risk of fatal and nonfatal myocardial infarction was higher in patients receiving a calcium channel blocker (nisoldipine) than with an ACE inhibitor (enalapril).

Although this finding was interpreted as an adverse effect of the calcium channel blocker, it may have been a beneficial effect of the ACE inhibitor.

A major trial is underway to assess the effects of ACE inhibitors in patients at high risk of atherosclerotic events. This trial, called the HOPE (Heart Outcomes Prevention Evaluation) study, has two components: the main HOPE study (in patients at high risk for coronary heart disease events, with or without diabetes)[9] and a substudy called MICRO-HOPE[10] in diabetic patients only. The latter should be able to demonstrate whether ACE inhibitor therapy will prevent new-onset albuminuria as well as reduce the risk for coronary heart disease events.

Results of this study should be available in early 2000. Positive results would lend support to the notion that high-risk type 2 diabetic patients, even those without proteinuria, might benefit from routine use of ACE inhibitors.

Several studies with angiotensin II receptor blockers are also underway.

Antihypertensive treatment per se slows renal decline

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