

REFERENCES

1. Wilke WS, Mackenzie AH. Methotrexate therapy in rheumatoid arthritis. Current status. *Drugs* 1986; 32:103-113.
2. Furst DE. Proposition: methotrexate should not be the first second-line agent to be used in rheumatoid arthritis if NSAIDs fail. *Semin Arthritis Rheum* 1990; 20:69-75.
3. Alarcon GS, Lopez-Mendez A, Walter J, et al. Radiographic evidence for disease progression in methotrexate treated and non-methotrexate disease modifying antirheumatic drug treated rheumatoid arthritis patients: a meta-analysis. *J Rheumatol* 1992; 19:1868-1873.
4. Drosos AA, Tsiptaki N, Tsiakou K, et al. Influence of methotrexate on radiographic progression in rheumatoid arthritis: a 60-month prospective study. *Clin Exp Rheumatol* 1997; 15:263-267.
5. Bologna C, Jorgensen C, Sany J. Methotrexate as the initial second-line disease modifying agent in the treatment of rheumatoid arthritis patients. *Clin Exp Rheumatol* 1997; 15:597-607.
6. Felson DT, Anderson JJ, Meenan RF. Use of short-term efficacy/toxicity trade-offs to select second-line drugs in rheumatoid arthritis: a meta-analysis of published clinical trials. *Arthritis Rheum* 1992; 35:1117-1125.
7. Fries JF, Williams CA, Ramey D, Bloch DA. The relative toxicity of disease-modifying antirheumatic drugs. *Arthritis Rheum* 1993; 36:297-306.
8. Wolfe F, Hawley DJ, Kathey MA. Termination of slow-acting anti-rheumatic therapy in rheumatoid arthritis: a 14-year prospective evaluation of 1017 consecutive starts. *J Rheumatol* 1990; 17:994-1002.
9. Pincus TE, Marcum SV, Callahan LF. Long-term drug therapy for rheumatoid arthritis in 7 rheumatology private practices: 2. Second-line drugs and prednisone. *J Rheumatol* 1992; 19:1885-1894.
10. Kremer JM, Lee RG, Tolman KG. Liver histology in rheumatoid arthritis patients receiving long-term methotrexate therapy: a prospective study of baseline and sequential biopsy samples. *Arthritis Rheum* 1989; 32:121-127.
11. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for monitoring drug therapy in rheumatoid arthritis. *Arthritis Rheum* 1996; 39:723-731.
12. Wilke WS, Cash JM. The use of slow-acting (Class III) symptom-modifying anti-rheumatic drugs in rheumatoid arthritis. *Clin Immunother* 1996; 5:309-325.
13. O'Dell JR. Methotrexate use in rheumatoid arthritis. *Rheum Dis Clin North Am* 1997; 23(4):779-796.
14. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998; 41:1552-1563.
15. Weinblatt ME, Kremer JM, Coblyn JS, et al. Leflunomide plus methotrexate in refractory rheumatoid arthritis: a pilot study [abstract]. *Arthritis Rheum* 1997; 40(suppl):S193.
16. Morgan S, Baggott JE, Vaughn WH, et al. Supplementation with folic acid during methotrexate therapy for rheumatoid arthritis. Double-blind, placebo-controlled trial. *Ann Intern Med* 1994; 121:833-841.

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 al¹ and Mogensen² 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,

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 al⁵ 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-HOPE¹⁰ 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

REFERENCES

1. Parving HH, Andersen AR, et al. Diabetic nephropathy and arterial hypertension. The effect of antihypertensive treatment. *Diabetes* 1983; 32(Suppl 2):83–87.
2. Mogensen CE. Antihypertensive treatment inhibiting the progression of diabetic nephropathy. *Acta Endocrinol* 1980; 238(Suppl):103–108.
3. Kasiske BL, Kalil RSN, Ma JZ, Liao M, Keane WG. Effect of antihypertensive therapy on the kidney in patients with diabetes: a metaregression analysis. *Ann Intern Med* 1993; 118:129–138.
4. Salem JK, Hoogwerf BJ. Diabetic nephropathy: strategies for preventing renal failure. *Cleve Clin J Med* 1996; 63:331–338.
5. Lewis IF, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993; 329:1456–1462.
6. Ravid M, Savin H, et al. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. *Ann Intern Med* 1993; 118:577–581.
7. UK Prospective Diabetes Study (UKPDS) Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* 1998; 317:713–720.
8. Estacio RO, Jeffers BW, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998; 338:645–652.
9. The HOPE Study Investigators. The HOPE (Heart Outcomes Prevention Evaluation) Study: the design of a large, simple randomized trial of an angiotensin-converting enzyme inhibitor (ramipril) and vitamin E in patients at high risk of cardiovascular events. *Can J Cardiol* 1996; 12:127–137.
10. Gerstein HC, Bosch J, et al. Rationale and design of a large study to evaluate the renal and cardiovascular effects of an ACE inhibitor and vitamin E in high-risk patients with diabetes. The MICRO-HOPE Study. *Heart Outcomes Prevention Evaluation. Diabetes Care* 1996; 19:1225–1228.