

CLINICAL INQUIRIES

From the Family Practice Inquiries Network

For those intolerant to ACE inhibitors and ARBs, what is the best therapy for reducing the risk of diabetic nephropathy?

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EVIDENCE-BASED ANSWER

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) are the first-line agents for reducing the risk of diabetic nephropathy. For patients intolerant to these agents, non-dihydropyridine calcium antagonists (NDCAs), such as verapamil and diltiazem, are preferred agents to treat hypertension in those with diabetes who have proteinuria (strength of recommendation [SOR]: **A**, based on a systematic review). Diuretics are effective in treating hypertension in patients with diabetes

who are at high risk for cardiovascular disease. One study suggests sustained-release indapamide (a diuretic) is effective as first-line treatment in hypertensive patients with diabetes and proteinuria (SOR: **B**, based on a randomized controlled trial [RCT]). Atenolol was as effective as the ACE inhibitor captopril in lowering the risk of diabetic microvascular and macrovascular complications, according to a substudy of the United Kingdom Prospective Diabetic Study (UKPDS) (SOR: **B**, based on RCT).

CLINICAL COMMENTARY

Controlling blood pressure in diabetes is more important than what agents we use

Diabetic renal insufficiency and failure is unfortunately very common, and a significant cause of death and disability in our patients. We have been taught from good evidence to start with ACE inhibitors or ARBs when treating hypertension in those with diabetes. However, it appears from this article that controlling blood pressure in diabetes is more important than what agents we use.

We often are not aggressive enough in controlling blood pressure for those with diabetes, despite evidence that it impacts outcomes more than glycemic control. Though there does not appear to be direct evidence that other blood pressure agents prevent renal failure in those with diabetes, it is reassuring that BP control, even when we are unable to use ACE inhibitors or ARBs, is a worthy goal.

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■ Evidence summary

Diabetic nephropathy is the leading cause of end-stage renal disease, and it occurs in 20% to 40% of patients with diabetes. Optimal glycemic (glycosylated hemoglobin [HbA_{1c}] level <7%) and

hypertension control (<130/80 mm Hg) can prevent or slow the progression of diabetic nephropathy.¹⁻³

An average of 3 antihypertensive medications are needed to achieve currently recommended blood pressure

FAST TRACK

Diuretics are effective for treating hypertension in patients with diabetes at high risk for cardiovascular disease

goals in those with diabetes.² In hypertensive and normotensive patients with type 2 diabetes and microalbuminuria, ACE inhibitors have been well studied and found to reduce the risk of mortality, major cardiovascular events, and slow the progression to overt nephropathy, in patients with diabetes and at least 1 other risk factor.⁴ In patients with type 2 diabetes and hypertension, macroalbuminuria, and serum creatinine >1.5 mg/dL, ARBs are effective in slowing the progression of diabetic nephropathy.⁵

Some patients, however, are intolerant to ACE inhibitors and ARBs. When patients are intolerant to these medications, diuretics, NDCAs, or beta-blockers are recommended agents for the treatment of hypertension.

According to a systematic review, NDCAs cause a greater reduction in proteinuria compared with DCAs (dihydropyridine calcium antagonists, such as nifedipine and amlodipine), although there was no significant differences in lowering blood pressure.⁶ Mean change in proteinuria was +2% for DCAs and -30% for NDCAs (95% confidence interval [CI], 10%–54%; $P=.01$). In another RCT, amlodipine was no more effective than placebo in reducing proteinuria, while irbesartan effectively reduced end-stage renal disease (number needed to treat [NNT]=25 over 2.6 years).⁵

In the UKPDS-Hypertension in Diabetes study (a multicenter randomized study in patients with type 2 diabetes that evaluated the effects of different levels of blood pressure control on diabetic complications), researchers found that patients assigned to the tight-control group (blood pressure goal <150/85 mm Hg) had 37% risk reduction in microvascular endpoints (nephropathy and advanced retinopathy).⁷ There was no difference in study endpoints between the ACE inhibitor captopril and the beta-blocker atenolol. Selective beta-blockers like carvedilol appear to have

fewer adverse metabolic effects, although the clinical significance of this difference is unclear.⁸ In insulin-dependent patients and patients with hypoglycemic episodes, peripheral vascular disease, and bronchospastic disease, beta-blockers should be used with caution.

The NESTOR study—a multinational, multicenter, double-blind, randomized controlled, 2-parallel-groups study over 1 year—found that indapamide SR (a thiazide-type diuretic) treatment is as efficacious as enalapril in reducing proteinuria and lowering blood pressure.⁹

A meta-analysis of RCTs in patients with non-diabetic renal disease and RCTs or time-controlled studies with nonrandomized crossover design in patients with diabetic nephropathy revealed that dietary protein restriction effectively slows the progression of both diabetic and non-diabetic renal disease.¹⁰ In small studies, weight loss, use of lipid-lowering agents, and smoking cessation all revealed reduction in proteinuria.^{11,12}

Recommendations from others

From the American Diabetes Association's "Standards of Medical Care in Diabetes"¹² (position statement): to reduce the risk or slow the progression of nephropathy, optimize glucose and blood pressure control.

- Patients with diabetes should be treated to a blood pressure <130/80 mm Hg
- For patients with diabetes and albuminuria or nephropathy who are intolerant to ACE inhibitors or ARBs, NDCAs, diuretics, or beta blockers are recommended for treating hypertension. NDCA use may reduce albuminuria in patients with diabetes, including during pregnancy.

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