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CLINICAL UPDATE

Combination treatment effective option for hypertensive, diabetic patients with microalbuminuria

Morgensen CE, Neldam S, Tikkanen I, Oren S, Viskoper R, Watts RW, et al, for the CALM study group. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ* 2000;321:1440-4.

Background: Inhibition of the renin-angiotensin system (RAS) reduces microvascular complications in patients with diabetic nephropathy. However, existing drugs only partially block the RAS: angiotensin-converting-enzyme (ACE) inhibitors do not prevent the synthesis of angiotensin II by other enzymes, and current angiotensin II type 1 (AT_1) receptor blockers block only the type 1 subtype of the receptor. Combination treatment with an ACE inhibitor and an AT_1 receptor blocker may achieve more complete blockade of the RAS.

Question: Is dual blockade of the RAS with lisinopril (an ACE inhibitor) and candesartan (an AT_1 receptor blocker) superior to either drug alone in lowering blood pressure and the albumin:creatinine ratio in hypertensive patients with diabetes and microalbuminuria?

Design: This randomized, double-blind, double-dummy trial was conducted at 37 centres in Australia, Denmark, Finland and Israel. Patients aged 30–75 years with hypertension (diastolic pressure 90–110 mm Hg), diabetes mellitus type 2 and microalbuminuria (urinary albumin:creatinine ratio 2.5–25 mg/mmol) were eligible. Exclusion criteria included severe obesity (body mass index > 40), moderate systolic hypertension (systolic pressure > 200 mm Hg), secondary causes of hypertension, renal impairment (serum creatinine level > 130 μmol/L in women and > 150 μmol/L in men), poor glycemic control (glycated hemoglobin concentration > 10%), pregnancy or potential pregnancy, and breast-feeding. After 4 weeks of placebo treatment, patients were randomly assigned to receive monotherapy with either lisinopril (20 mg/d) or candesartan (16 mg/d) for 12 weeks. From weeks 12 to 24, one-third of the patients were randomly assigned to receive both drugs; the remaining patients continued to receive monotherapy. The primary outcome measures were reductions in blood pressure and the urinary albumin:creatinine ratio; secondary outcome measures included calculated creatinine clearance and tolerability of the treatments.

Results: During the first 12 weeks of treatment 98 patients received lisinopril, and 99 received candesartan. From weeks 12 to 24, 67 patients received the combination treatment, 64 continued to receive lisinopril and 66 continued with candesartan. The 3 groups were similar in baseline characteristics. Monotherapy with either drug was similarly effective in lowering blood pressure and the urinary albumin:creatinine ratio from baseline to 24 weeks (mean reduction in blood pressure 16.7/10.7 mm Hg and urinary albumin:creatinine ratio 39% with lisinopril; 14.1/10.4 mm Hg and 24%, respectively, with candesartan). The combination treatment was more effective than either monotherapy (mean reduction in blood pressure 25.3/16.3 mm Hg and urinary albumin:creatinine ratio 50%). The superiority of the combination treatment over monotherapy was statistically significant in all comparisons except when compared with lisinopril in reducing the urinary albumin:creatinine ratio (p > 0.20). The 3 treatment regimens were generally well tolerated. The combination treatment was associated with a negligible increase in serum levels of potassium (0.3 mmol/L) and creatinine (8.1 μmol/L); creatinine clearance was reduced slightly with the combination treatment (4.4 mL/min) and with the lisinopril therapy (5.0 mL/min).

Commentary: Combination treatment with an ACE inhibitor and an AT_1 receptor blocker appears to achieve better blockade of the RAS than monotherapy with either drug at the dosages described. The combination treatment resulted in better control of hypertension and microalbuminuria among diabetic patients. Since the maximum dose of either drug as monotherapy was not used in this study, it is unknown whether higher doses of monotherapy with either drug would be as effective as combination treatment. The tolerability of combination treatment is reassuring and consistent with another recent study of dual blockade of the RAS.[1]

Practice implications: ACE inhibitors remain the drugs of first choice for hypertensive patients with diabetes and microalbuminuria.[2] When blood pressure goals cannot be achieved with monotherapy, combination treatment with an ACE inhibitor and an AT_1 receptor blocker is a safe and effective option. — *Benjamin H. Chen*

The Clinical Update section is edited by Dr. Donald Farquhar, head of the Division of Internal Medicine, Queen's University, Kingston, Ont. The updates are written by members of the division.

References

1. Ruilope LM, Aldigier JC, Ponticelli C, Oddou-Stock P, Botteri F, Mann JF, et al. Safety of the combination of valsartan and benazepril in patients with chronic renal disease. *J Hypertens* 2000;18:89-95.
2. Feldman RD, Campbell N, Larochelle P, Bolli P, Burgess E, Carruthers SG, et al. 1999 Canadian recommendations for the management of hypertension. *CMAJ* 1999;161(12 Suppl):S1-S17. Available: www.cma.ca/cmaj/vol-161/issue-12/hypertension/hyper-e.htm