New Treatment Options for Diabetic Patients with Hypertension and Microalbuminuria

Mogensen CE, Neldam S, Tikkanen I, et al. 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.

Study Overview

Objective. To evaluate and compare the effects of lisinopril, candesartan, and combination treatment on blood pressure and urinary albumin excretion in patients with type 2 diabetes, hypertension, and microalbuminuria.

Design. Randomized, double-blind, controlled trial.

Setting and participants. 199 patients aged 30 to 75 years who had type 2 diabetes and a previous diagnosis of hypertension and microalbuminuria were recruited from 37 tertiary hospitals and primary care centers in 4 countries. All subjects had a urinary albumin–creatinine ratio of 2.5 to 25 mg/mmol and diastolic blood pressure (DBP) of 90 to 110 mm Hg after 2 and 4 weeks of placebo treatment. Exclusion criteria were: body mass index (BMI) more than 40 kg/m^2; systolic blood pressure (SBP) more than 200 mm Hg; elevated serum creatinine, potassium, or glycosylated hemoglobin (HbA_{1c}) concentrations; nondiabetic cause of secondary hypertension; cardiovascular event in the past 6 months; pregnancy or potential pregnancy; and breastfeeding.

Intervention. All patients received either candesartan 16 mg daily, lisinopril 20 mg daily, or both. After a 4-week run-in period of placebo treatment, subjects were randomized to 4 groups: (1) candesartan alone for 24 weeks (n = 66), (2) lisinopril alone for 24 weeks (n = 64), (3) candesartan alone for 12 weeks then combined lisinopril/candesartan for 12 weeks (n = 34), and (4) lisinopril alone for 12 weeks then combined lisinopril/candesartan for 12 weeks (n = 35). Patients who had a DBP less than 80 mm Hg after the first 12 weeks did not receive the combination regimen. A total of 9 clinic visits were scheduled; during each visit, blood pressure was measured with an automatic device. Potassium, serum creatinine, and HbA_{1c} were measured at different intervals throughout the study. Using the urinary albumin–creatinine ratio, microalbuminuria was determined at baseline and at weeks 0 (ie, at randomization), 12, and 24. Creatinine clearance was calculated with the Cockroft-Gault formula, and the angiotensin-converting enzyme (ACE) genotype was determined for each patient.

Main outcome measures. Blood pressure and urinary albumin–creatinine ratio.

Main results. Only 2 randomized patients could not be evaluated. At 12 weeks, members of the candesartan and lisinopril groups showed reductions from baseline in DBP (mean, 9.5 mm Hg and 9.7 mm Hg, respectively) and SBP (mean, 12.4 mm Hg and 15.7 mm Hg). For both measures, the mean difference between treatments were not statistically significant. Mean urinary albumin–creatinine ratios also were reduced by 30% in the candesartan groups and by 45% in the lisinopril groups (P = 0.058). From baseline to 24 weeks, all 3 treatments (candesartan, lisinopril, and combination therapy) improved both blood pressure and urinary albumin–creatinine ratio, with the combination showing the greatest efficacy. Mean reductions of DBP, SBP, and urinary albumin–creatinine ratio were: 10.4 mm Hg, 14.1 mm Hg, and 24%, respectively, in the candesartan group; 10.7 mm Hg, 16.7 mm Hg, and 39% in the lisinopril group; and 16.3 mm Hg, 25.3 mm Hg, and 50% in the combination therapy group. Although candesartan-group patients showed a 24% mean reduction in urinary albumin–creatinine ratio, the P value for these findings was 0.05, with a wide confidence interval (between 0% and 43%). No significant difference in HbA_{1c} was observed from baseline to 12 or 24 weeks, and the ACE genotype did not significantly influence the response of blood pressure or albuminuria to any of the study treatments. Side effects (most commonly respiratory infection, cough, and headache) were reported in less than 10% of patients.

Conclusion

Candesartan 16 mg daily is as effective as lisinopril 20 mg once daily in reducing blood pressure and microalbuminuria in hypertensive patients with type 2 diabetes. A regimen combining these agents is well tolerated and more effective in reducing blood pressure.

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Commentary

Numerous large studies have shown that ACE inhibitors can prevent diabetic nephropathy [1]. However, studies of patients with hypertension have shown that monotherapy with ACE inhibitors very often fails to achieve blood pressure goals. Angiotensin II–receptor antagonists are a new and promising class of antihypertensive agents. These agents have different physiologic effects than ACE inhibitors as well as fewer side effects—in particular, cough, which is a common problem with ACE inhibitors. Experience with angiotensin II–receptor antagonists in patients with diabetic nephropathy is limited. A recent study showed that losartan can reduce albuminuria in such patients; however, this study was small (only 16 patients) and did not include a combination regimen [2].

This study by Morgensen et al was well conducted, with good follow-up and a low patient drop-out rate. Treatment groups had similar baseline characteristics. Researchers may have introduced some bias when they compared baseline results with those at week 24. The patient groups at week 24 were different than at baseline, as 53 patients were withdrawn from the study at week 12 because their DBP was less than 80 mm Hg. To avoid any bias, the authors should have compared the same patients at week 12 and week 24.

Further studies should be conducted to determine which of the angiotensin II–receptor antagonists is most effective. Their effects on normotensive patients with microalbuminuria or type 1 diabetes should be researched as well. We also need to know which combination therapy can achieve the greatest reduction in blood pressure and improvement in proteinuria (for example, ACE inhibitors and angiotensin II–receptor antagonists, ACE inhibitors and calcium channel blockers, ACE inhibitors and diuretics, and so on).

Applications for Clinical Practice

ACE inhibitors should remain first-line therapy in diabetic patients with hypertension and microalbuminuria / proteinuria. However, if blood pressure control cannot be achieved with monotherapy, a combination of ACE inhibitors and angiotensin II–receptor antagonists should be considered.

References

1. Mogensen CE, Keane WF, Bennett PH, et al. Prevention of diabetic renal disease with special reference to microalbuminuria. Lancet 1995;346:1080–4.
2. Andersen S, Tarnow L, Rossing P, et al. Renoprotective effects of angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. Kidney Int 2000;57:601–6.