

Intensive versus moderate blood-pressure control in normotensive patients with type 2 diabetes

Original article Estacio RO *et al.* (2006) Effect of intensive blood pressure control with valsartan on urinary albumin excretion in normotensive patients with type 2 diabetes. *Am J Hypertens* 19: 1241–1248

SYNOPSIS

KEYWORDS albuminuria, angiotensin receptor blocker, blood pressure, type 2 diabetes, valsartan

BACKGROUND

Studies of the beneficial effects of anti-hypertensive therapy in diabetic nephropathy have largely focused on hypertensive patients with microalbuminuria or overt albuminuria.

OBJECTIVE

To establish whether intensive blood-pressure control retards the progression of diabetic nephropathy more than moderate blood-pressure control in patients with type 2 diabetes who do not have hypertension or overt albuminuria.

DESIGN

For this single-center, randomized US trial, adults aged 40–81 years who had type 2 diabetes, systolic blood pressure <140 mmHg, diastolic blood pressure 80–90 mmHg and albuminuria <200 µg/min were prospectively recruited over a 4-year period. Patients who had experienced a myocardial infarction or cerebrovascular accident during the previous 6 months were among those excluded.

INTERVENTION

After stratification on the basis of gender and baseline serum creatinine level, participants were randomized to receive valsartan at a starting dose of 80 mg/day (intensive blood-pressure control) or placebo (moderate blood-pressure control). To maintain the respective diastolic blood-pressure targets of 75 mmHg and 80–90 mmHg, the valsartan dose could be increased, and agents such as hydrochlorothiazide and metoprolol could be prescribed. The 5-week placebo run-in phase

was preceded by a 4-week washout period for patients who were on antihypertensive therapy at the time of screening. Urine albumin excretion (UAE), creatinine clearance (both calculated from 24 h urine collections) and serum creatinine level were recorded every 6 months.

OUTCOME MEASURE

Following early termination of the trial because of funding constraints, the primary end point was redefined as change in UAE (<20 µg/min = normoalbuminuria; 20–200 µg/min = microalbuminuria).

RESULTS

Of the 129 patients randomized, 66 were assigned to intensive blood-pressure control (mean age 56.7 years) and 63 to moderate blood-pressure control (mean age 55.5 years). The mean baseline blood pressure was 126/84 mmHg in both groups, but the moderate blood-pressure control group had a higher baseline prevalence of microalbuminuria (27% vs 14%). Mean follow-up was 1.9 years and 5 patients discontinued in each group. Average blood pressure during the study was 118/75 mmHg in the intensive-control group and 124/80 mmHg in the moderate-control group ($P < 0.001$). Creatinine clearance and serum creatinine level remained stable in both groups during the study. Analysis of covariance, with adjustment for factors including age, gender and glycated hemoglobin level, revealed that $\log(\text{UAE} + 1)$ had decreased by 0.76 after 2 years in the intensive blood-pressure control group ($n = 32$) compared with the moderate-control group ($n = 33$; $P = 0.007$). More patients regressed from microalbuminuria to normoalbuminuria in the intensive-control group than in the moderate-control group (7/9 [78%] vs 6/18 [33%]; $P = 0.046$).

CONCLUSION

Lowering blood pressure to 120/75 mmHg seems to reduce UAE in patients with type 2 diabetes even in the absence of hypertension.

COMMENTARY

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Treatment of progressive diabetic renal disease has three key components: control of blood pressure, control of glycemia, and blockade of the renin-angiotensin system (RAS). The evidence for the benefits of blood-pressure control is very strong. As nephrologists know, some argument persists about the renoprotective mechanism of RAS blockade,^{1,2} but the major progression trials—the Collaborative Study Group's captopril trial, IDNT, IRMA2, RENAAL, ABCD and MICRO-HOPE—have provided clear evidence that patients with type 1 or type 2 diabetes accompanied by persistent albuminuria and/or hypertension benefit from this intervention.³

Can we extend these data and start treating diabetic patients with RAS blockers before the development of overt hypertension or albuminuria? If so, given that hypertension and albuminuria are both continuous variables, where should we draw the line? The Cochrane Renal Group has reviewed the evidence for the use of angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in the prevention of diabetic nephropathy. On the basis of a meta-analysis of 43 trials comprising more than 7,000 participants, the authors concluded that ACEIs reduced all-cause mortality and ameliorated renal injury (as assessed by progression from microalbuminuria to macroalbuminuria, or regression from microalbuminuria to normoalbuminuria) in patients without overt nephropathy. ARBs also showed a beneficial effect on renal outcomes, but had no significant effects on mortality.⁴

The authors of the Cochrane Review note, however, that few of the ACEI studies and none of the ARB studies enrolled patients without hypertension. The study by Estacio and co-workers is one modest step toward remedying our uncertainty about treating the nonhypertensive, nonalbuminuric patient with type 2 diabetes. The authors randomized 129 normotensive patients with type 2 diabetes to either moderate or intensive blood-pressure control with placebo or valsartan, respectively (target diastolic blood pressure levels of 80–90 mmHg and 75 mmHg, respectively), and followed them for a mean of 1.9 years. Intensive treatment was apparently

well tolerated, because the drop-out rates were the same in the two groups. UAE stabilized in the moderate-control group, and actually fell significantly in the intensively treated group.

The study has a number of limitations, and needs to be interpreted with caution. It lacks a placebo control arm, the sample size is modest, and the duration of follow-up is short. Nevertheless, the study provides some evidence that targeting a diastolic blood pressure of 75 mmHg is practical in normotensive normoalbuminuric patients with type 2 diabetes. It also offers some hints that such a target might actually prevent renal damage, and is a useful reminder of the important unanswered questions highlighted above. We all await results from larger, randomized, placebo-controlled trials in this setting, such as the ROADMAP trial of olmesartan.

What should we do in the meantime? The Estacio *et al.* study is one additional piece of evidence to weigh during the risk and cost-benefit assessments we make before recommending treatment for normotensive diabetic patients. As practitioners we can and should offer our patients an individualized judgment, based on their actual risk profile. There have been several excellent recent discussions of such risk assessment (e.g. by Caramori *et al.*⁵). The key elements are the familiar measures: frequent assessment of UAE and careful attention to blood pressure (including home values, and in selected cases—e.g. if office and home values are not consistent—ambulatory blood pressure recordings).

References

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Competing interests

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PRACTICE POINT

Control of blood pressure in diabetic patients really matters; intensive blood-pressure control might even benefit those who do not have hypertension, but it cannot yet be uniformly recommended