Angiotensin Receptor Blocker to Prevent Microalbuminuria?

Reviewed by John R. White, Jr.

STUDY

SUMMARY
Objective. Microalbuminuria is a predictor of cardiovascular disease (CVD), as well as diabetes-related nephropathy. This study was designed to determine whether the occurrence of microalbuminuria could be prevented or delayed in patients with type 2 diabetes with the angiotensin receptor blocker (ARB) olmesartan.

Design and methods. This study was a randomized, multicenter, double-blind, controlled trial of 4,447 patients with type 2 diabetes. The patients were 18–75 years of age and had normoalbuminuria at the onset of the trial. They were randomized to receive either placebo or olmesartan, 40 mg daily, for a median of 3.2 years.

During the trial, patients were treated to a blood pressure of <130/90 mmHg using conventional antihypertensive medications (excluding ACE inhibitors, ARBs, or aldosterone blockers except for the ARB olmesartan in the active treatment group). Patients who had used ACE inhibitors or ARBs during the 6-month period leading up to the study were excluded. Blood pressure was measured with an automated device at each follow-up visit. The blood pressure value used was the mean of three measurements taken at 3-minute intervals by an automated device.

The primary outcome was the elapsed time until the initial onset of microalbuminuria. Urine was tested by validated measurements of morning spot urine samples. Microalbuminuria was described in this trial as a urinary albumin (mg) to creatinine (g) ratio of >35 in women or >25 in men. Any new abnormal albumin-to-creatinine ratio was confirmed by another positive result (out of two tests) within 2 weeks of the initial abnormal finding. Patients with confirmed positive findings were assigned to an open-label arm of the study and were treated with olmesartan, 40 mg daily.

Secondary endpoints were 1) a composite of cardiovascular complications, 2) death from cardiovascular causes, and 3) renal events.

The median follow-up period in this trial was 3.2 years. The mean A1C level was 7.7%, and the mean duration of diabetes was 6.1 years. Of the patients enrolled in this trial, 67.7% had four cardiovascular risk factors, and >97% had at least two risk factors in addition to diabetes.

Results. Blood pressure: Mean blood pressure during the follow-up period was 128.7/76.2 and 125.7/74.3 mmHg in the placebo and treatment arms, respectively. Approximately 80% of the patients in the treatment arm and 71% of those in the placebo arm achieved a target blood pressure (<130/90 mmHg) at 48 months.

Primary outcome: In the olmesartan group, 178 of 2,160 patients (8.2%) developed microalbuminuria, compared to 210 of 2,139 patients (9.8%) in the placebo group during the double-blind period of the trial. Median time to onset of microalbuminuria was 722 days in the olmesartan group and 576 days in the placebo group. The time to onset of microalbuminuria (the primary endpoint) was increased by 23% in the olmesartan group (hazard ratio [HR] of onset of microalbuminuria 0.77, 95% confidence interval [CI] 0.63–0.94, P=0.01). The HR after adjustment for small baseline differences in BMI, systolic blood pressure, and levels of HDL cholesterol and triglycerides was similar at 0.75 (95% CI 0.62–0.92, P=0.006).

Secondary endpoints: A slightly greater reduction in mean glomerular filtration rate was reported in the olmesartan group (from 85 to 80.1 ml/min/1.73 m²) versus the placebo group (from 84.7 to 83.7 ml/min/1.73 m²). This difference was statistically significant (P<0.001 for between-group change from baseline). A doubling of serum creatinine was reported in 23 patients (~1%) in each group. End-stage renal disease (ESRD) did not develop in any of the patients in either group.

The proportion of patients reaching the composite endpoint of death
from cardiovascular causes or cardiac complications was similar in the two groups: 4.3% in the olmesartan group and 4.2% in the placebo group. Mortality rates from any cause were 1.2% (26 deaths) in the olmesartan group and 0.7% (15 deaths) in the placebo group ($P = 0.10$). However, the number of deaths from cardiovascular causes alone was statistically significantly higher in the olmesartan group than in the placebo group (15 vs. 3 deaths in the olmesartan and placebo groups, respectively; $P = 0.01$). These deaths were primarily the result of higher rates of myocardial infarction (MI; 5 vs. 0) and sudden cardiac death (7 vs. 1) in the olmesartan group compared to the placebo group.

Adverse events: Overall, the number of adverse events was similar in the two groups. Serious events were reported in 15.2% of the placebo group and in 15% of the olmesartan group. A statistically significant difference was reported in drug-related adverse events (11.4% in the olmesartan group vs. 7.5% in the placebo group, $P < 0.001$). These differences were primarily caused by much higher rates of hypotension (58 vs. 6, $P < 0.001$) and dizziness (103 vs. 61, $P = 0.001$) in the olmesartan group compared to the placebo group. The number of withdrawals from the study because of symptomatic hypotension was greater in the olmesartan group ($n = 10$) than in the placebo group ($n = 1$).

Conclusion. The researchers concluded that this trial suggests that olmesartan increases the time to onset of microalbuminuria in patients with type 2 diabetes, even under conditions of excellent blood pressure control.

**COMMENTARY**

The question being evaluated in this study is important. Should we preemptively treat patients with type 2 diabetes with an ARB to delay the appearance of microalbuminuria? The obvious implication is that, if we can delay the initial appearance of microalbuminuria, then perhaps we can delay or circumvent the progression to ESRD.

Taking this logic a step further, perhaps this type of pharmacological modality might also be associated with an improvement in cardiovascular outcome. This second step, although seemingly logical, is based on the potentially flawed assumption that if we treat one of the markers of CVD (microalbuminuria), the complication itself will be assuaged.

Thus far in other studies, it has been quite difficult to tease out the impact of blood pressure reduction from the impact of microalbuminuria reduction from the impact of other pleiotropic effects of renin/angiotensin modulation on CVD. However, the HOPE (Heart Outcomes Prevention Evaluation) study and its Micro-HOPE substudy did demonstrate that the ACE inhibitor ramipril was associated with a reduction in CVD outcomes MI, stroke, and death in patients with diabetes.\(^1\)

Diabetes-related nephropathy occurs in 20–40% of patients with diabetes and is the leading cause of ESRD.\(^2\) Persistent microalbuminuria has been shown to be a marker for the development of nephropathy in patients with type 2 disease. Additionally, microalbuminuria is well established as a marker for CVD risk.\(^3\) It is clear that inhibition of the renin-angiotensin system (RAS) is useful in slowing down the progression of nephropathy in patients with demonstrable microalbuminuria. If fact, the American Diabetes Association (ADA) is clear in recommending the use of RAS inhibition (with converting enzyme inhibitors or ARBs) in non-pregnant type 2 diabetic patients with microalbuminuria.\(^4\)

The BENEDICT study\(^4\) reported that the use of the ACE inhibitor trandolapril in hypertensive, normoalbuminuric patients with type 2 diabetes was associated with a reduction in the development of diabetic nephropathy. The study also demonstrated that this effect was not enhanced by the addition of a non-dihydropyridine calcium channel antagonist.

It has been demonstrated that ARBs can reduce the rate of progression from microalbuminuria to macroalbuminuria and to ESRD in patients with type 2 diabetes,\(^5\)–\(^7\) hence the ADA recommendations mentioned above. However, one ARB, candesartan, was not shown to have a protective effect against the initial development of microalbuminuria in normotensive normoalbuminuric patients with type 2 diabetes.\(^8\)

Although this study did demonstrate that the use of the ARB olmesartan was associated with delay in the onset of microalbuminuria in patients with type 2 diabetes, the effect was modest (mean difference was < 5 months). Additionally, the statistically significant number of deaths from cardiovascular causes in the olmesartan arm, although possibly due to chance, is reason for concern.

At this juncture, it would be premature to recommend an ARB for prevention of microalbuminuria in normotensive patients with type 2 diabetes. The most prudent and beneficial course is to attend to patients’ glycemic and blood pressure control while continuing annual screening for microalbuminuria and treating microalbuminuria if it develops with an ACE inhibitor or an ARB.
REFERENCES


John R. White, Jr., PA, PharmD, is the interim chairman and a professor of pharmacotherapy at Washington State University in Spokane. He is a deputy editor of Clinical Diabetes.