Candesartan Does Not Prevent Microalbuminuria

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PHILADELPHIA — Nearly 5 years of treatment with the angiotensin type 1 receptor blocker candesartan did not provide statistical benefit in the prevention of microalbuminuria in patients with diabetes, according to a new post hoc analysis.

The Diabetic Retinopathy Candesartan Trials (DIRECT) program consisted of three randomized, double-blind, placebo-controlled trials that took place in 309 centers in 30 countries worldwide. These trials were primarily intended to assess whether candesartan could reduce the incidence and progression of diabetic retinopathy. The program was sponsored by AstraZeneca and Takeda, which jointly developed the drug.

In type 1 diabetes, the drug reduced the incidence of retinopathy but did not hinder its progression (Lancet 2008;372:1394-402). In type 2 diabetes, there was a nonsignificant reduction in progression of retinopathy and a significant regression of retinopathy in patients with mild to moderate ocular involvement (Lancet 2008;372:1385-93).

"Agents that block the renin-angiotensin system [RAS] also reduce albuminuria and progression of established diabetic nephropathy, but their role in the primary prevention of microalbuminuria remains to be established," Dr. Rudy W. Bilous said in a late-breaking abstract session at the annual meeting of the American Society of Nephrology.

Accordingly, he and his colleagues undertook an analysis of data from the retinopathy trials, using prespecified renal end points of the development of microalbuminuria, defined by the presence of at least three out of four consecutive overnight albumin excretion rates over 20 mcg/min, and the annual rate of change in excretion rates.

A total of 5,231 patients, whose average age was 40 years and whose mean duration of diabetes was 9 years, were randomized to placebo or candesartan at an initial dose of 16 mg/day. The dose was increased to 32 mg/day after 1 month.

At baseline, none of the patients had microalbuminuria. For inclusion in the study, blood pressure in the type 1 diabetes patients had to be less than 130/85 mm Hg, and in type 2 patients it had to be less than 160/90 mm Hg with antihypertensive treatment. The mean baseline blood pressure was 118/74 mm Hg among the normotensive patients and 139/79 mm Hg among the treated hypertensives.

Diabetes control at baseline was modest, with a mean hemoglobin A_{1c} of 8.3%, said Dr. Bilous of Newcastle University, Newcastle upon Tyne (England).

During the first month of the study there were significant reductions in blood pressure of 3 mm Hg systolic and 2 mm Hg diastolic; this was maintained throughout the study, with patients being followed for a median of 4.7 years.

The 401 patients who developed microalbuminuria during the study were more likely to be male, to be older, and to have higher baseline HbA_{1c} and systolic blood pressures.

"These findings were in accordance with previously published data on risk factors for the development of incident microalbuminuria in diabetes. But when we looked at the microalbuminuria incidence in the two treatment arms, there was absolutely no difference," Dr. Bilous said.

Furthermore, after adjustment for baseline HbA_{1c}, albumin excretion rate, systolic blood pressure, and antihypertensive therapy; and after further adjustment for achieved systolic blood pressure, there were no differences in hazard ratios for the two arms, he said.

The secondary renal end point of rate of change in overnight albumin excretion showed a statistically significant 5.7% annual decrease. "However, this represented only a difference of 0.11 mcg/min, and the clinical significance is uncertain over the long term," Dr. Bilous said.

"In conclusion … we found no statistical benefit to candesartan in prevention of microalbuminuria over a median follow-up of 4.7 years, although there was a modest reduction in the annualized rate of change. So we cannot conclude that candesartan is of benefit in preventing diabetic nephropathy in patients with normal albuminuria over this short period of time," he said.

Dr. Bilous disclosed that he and his coinvestigators have acted as consultants to Takeda and AstraZeneca; were on the steering committee of this investigator-initiated study; and received fees for attendance at meetings of the steering committee. ■