Diabetics Need Lower Blood Pressure Targets Than Guidelines Recommend

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VIENNA — Evidence is catching up with the blood pressure targets for patients with diabetes.

In 2003, the most recent update of the U.S. hypertension treatment guidelines, JNC 7, set the goal pressure for patients with diabetes at 130/80 mm Hg. But no major trial results have ever proved that a target this low helps patients. Results from the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trial took a step toward supplying the proof in a study of more than 11,000 patients with diabetes.

Treatment with an antihypertensive regimen that combined the ACE inhibitor perindopril and the diuretic indapamide produced an average systolic blood pressure of 135 mm Hg. The treatment also produced a 14% relative drop in all-cause deaths and an 18% relative fall in cardiovascular deaths, both of which were significant, compared with patients not on the tested regimen, Dr. Stephen MacMahon reported at the annual meeting of the European Society for Cardiology. The average systolic pressure among patients in the control arm was 140 mm Hg.

The findings are important because they provide evidence that patients benefit when systolic pressure is reduced to 135 mm Hg instead of 140 mm Hg, commented Dr. Sidney C. Smith Jr., director of the Center for Cardiovascular Science and Medicine at the University of North Carolina at Chapel Hill.

"The current target is 130/80 mm Hg, but we don't have good evidence supporting the systolic target. That's why this trial is important. This is further, confirmatory evidence that reducing blood pressure is important. But we need more data because we're still not at the target level," said Dr. Smith, who is also vice chairman of the task force that produces treatment guidelines for the American College of Cardiology and the American Heart Association. He cited the importance of another, large ongoing study that will compare achieved systolic blood pressures of 120 and 140 mm Hg in patients with diabetes.

The new findings "strengthen the argument" in favor of a blood pressure target of 130 mm Hg for patients with diabetes, agreed Dr. Raymond J. Gibbons, professor of medicine at the Mayo Clinic in Rochester, Minn. He voiced hope that a stronger evidence base will better motivate diabetic patients and their physicians to follow the JNC 7 blood pressure guidelines.

The ADVANCE trial was run at 215 centers in 20 countries, and was sponsored in part by Servier, which markets a formulation of perindopril and indapamide (Preterax). A formulation that combines both of these drugs has not been approved by the Food and Drug Administration. The trial included another randomization that is testing the value of glycemic control with the drug gliclazide (Diamicron), but that analysis is not completed.

The study enrolled patients with type 2 diabetes who were at least 55 years old and had at least one other cardiovascular disease risk factor. Eligible risk factors included a history of major cardiovascular disease, microalbuminuria, smoking, hypercholesterolemia, and age of 65 or older. During a run-in period, all patients were treated with a daily, fixed-dose, combination tablet of 2 mg perindopril and 0.65 mg indapamide. Other treatments could continue at the discretion of each patient's physician.

Patients who were maintained on an ACE inhibitor before entering the study were switched to either a 2- or 4-mg daily dosage of perindopril. All patients who tolerated the study drug during the run-in could participate in the main study, which randomized patients to continue on active treatment or switch to placebo. After 3 months, daily dosages were doubled to 4 mg perindopril plus 1.25 mg indapamide.

During an average follow-up of 4.3 years, the mean systolic blood pressure was 135/75 mm Hg in the active arm and 140/77 mm in the control group. Patients in both groups were taking an average of one to two antihypertensive drugs in addition to the study medications.

The study's primary end point was a composite that included cardiovascular death, nonfatal myocardial infarction or stoke, and several types of microvascular events such as macroalbuminuria or need for renal replacement therapy.

These events occurred in 15.5% of the 5,569 patients who received the combination drug, and in 16.8% of the 5,571 patients in the placebo group, a 9% relative risk reduction that just barely achieved statistical significance, reported Dr. MacMahon, professor of cardiovascular medicine and epidemiology at Australia's University of Sydney. Another benefit of treatment was a 21% relative drop in the rate of new renal disease. The results were reported in an article in The Lancet that was released online concurrent with the report at the meeting (doi:10.1016/S0140-6736[07]61303-8).

The active treatment in ADVANCE was well tolerated. By the end of the study, adherence was 73% to the study regimen and 74% to placebo.

An editorial that accompanied the article questioned whether the results were specific for treatment with the perindopril and indapamide combination used in the study, and suggested that any regimen that reduced blood pressure to the same level would probably have the same benefit. Dr. MacMahon made it clear that he agrees with using any safe and effective regimen that brings down a patient's blood pressure.

"The results suggest a broader role for blood pressure lowering. Lowering the blood pressure of everyone with diabetes is a critical component of preventing complications," he said. "The critical issue is to get as many people as possible on treatment."

The new findings "will strengthen the current guidelines, and will also push [the guidelines] forward," commented Dr. Guiseppe Mancia, head of internal medicine at San Gerardo Hospital, Milan, and a co-investigator in the study. ■

Metabolic Syndrome Tied to Mortality After CABG

Patients with metabolic syndrome are nearly three times as likely to die following coronary artery bypass graft surgery as are patients without the syndrome, according to a large study.

Patients with both metabolic syndrome and diabetes had a 2.7-fold increase in the risk of mortality, and patients with metabolic syndrome but without diabetes had a 2.4-fold increase in risk. In the multivariate analysis, there proved to be no significant increase in the risk of mortality in patients who had diabetes but not metabolic syndrome, wrote Dr. Najmeddine Echahidi of the Centre de Recherche de l'Hôpital Laval, Quebec, and colleagues (J. Am. Coll. Cardiol. 2007;50:843-51).

The retrospective analysis involved 5,304 consecutive patients who underwent an isolated coronary artery bypass graft (CABG) between 2000 and 2004 at a single institution. An analysis of prospectively collected laboratory and physical data revealed that 46% met criteria for metabolic syndrome as set out by the National Cholesterol Education Program Adult Treatment Panel III.

The study's primary end point was death from any cause, either within 30 days of surgery or after any interval if the patient was not discharged from the hospital. Results were adjusted for gender, peripheral vascular disease, chronic obstructive pulmonary disease, preoperative renal failure, preoperative myocardial infarction, and preoperative stroke.

The overall unadjusted mortality was 1.6%, but was significantly higher (2.4%) among patients with metabolic syndrome, and significantly lower (0.9%) among patients without metabolic syndrome.

In addition to metabolic syndrome, several other factors increased the risk of mortality following CABG. These included age older than 75 years (relative risk 3.4), body mass index (kg/m^2) less than 18.5 (RR 10.3), renal failure (RR 3.4), myocardial infarction within 7 days before surgery (RR 4.0), urgent surgery (RR 2.5), and emergent surgery (RR 6.4).

Considering the prevalence of metabolic syndrome, the investigators suggested that patients be assessed for metabolic syndrome before surgery, and that metabolic syndrome be incorporated into operative risk algorithms.

—Robert Finn