Intensive Blood Pressure Control Does Not Reduce Cardiovascular Events in Type 2 Diabetics

Cushman W, Evans G, Byington R, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–85.

Study Overview

Objective. To determine whether therapy targeting systolic blood pressure (SBP) less than 120 mm Hg reduces major cardiovascular events in high-risk patients with type 2 diabetes.

Design. Multicenter, nonblinded, randomized controlled trial.

Setting and participants. 4733 patients aged 40 to 79 years with type 2 diabetes and hemoglobin A1C of 7.5 or above. Patients were a subset of the ACCORD glycemia trial, which enrolled 10,251 high-risk diabetic patients who received care at 77 clinical sites in the United States and Canada. The participants of the blood pressure trial were recruited in 2 periods, the vanguard phase from January 2001 to June 2001, and then subsequently from January 2003 to October 2005. "High-risk" patients were considered those aged 40 to 54 years with a history of cardiovascular disease and those aged 55 to 79 with evidence of end-organ disease such as anatomical evidence of atherosclerosis, albuminuria, left ventricular hypertrophy, or 2 additional risk factors such as dyslipidemia, hypertension, smoking, or obesity. Patients were also eligible if they had SBP between 130 and 180 mm Hg on a maximum of 3 medications and had 24-hour urine protein less than 1 g. Patients were excluded if they had body mass index greater than 45, serum creatinine above 1.5 mg/dL, or another serious illness. Patients were randomly assigned to intensive therapy that targeted SBP of less than 120 mm Hg or standard therapy that targeted SBP of less than 140 mm Hg.

Main outcome measures. The primary outcome measure was the first major cardiovascular event, defined as the composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. Secondary outcome measures included revascularization, hospitalization, or death due to congestive heart failure, fatal coronary event, fatal or nonfatal stroke, death from any cause, and death from cardiovascular causes.

Main results. The patients in the intensive therapy and standard therapy groups were similar in baseline characteristics, with a mean age of 62.2 years, almost half (47.7%) women, and about one-third (33.7%) with cardiovascular disease. Mean baseline SBP was 139.2/76.0 mm Hg. The mean SBP attained was 119.3 mm Hg in the intensive therapy group and 133.5 mm Hg in the standard therapy group, resulting in a difference of 14.2 mm Hg between the groups. The intensive therapy group took about 1 additional blood pressure medication, with a mean of 3.4 medications, compared with 2.1 medications in the standard therapy group.

There was no significant difference in the primary outcome of major cardiovascular events over the mean follow-up period of 4.7 years. The main outcome occurred at a rate of 1.87% per year in the intensive therapy group compared with 2.09% per year in the standard therapy group (hazard ratio, 0.88 [95% confidence interval {CI}, 0.73–1.06]; $P = 0.20$). The annual rate of death from any cause was 1.28% per year in the intensive therapy group and 1.19% in the standard therapy group (hazard ratio, 1.07 [CI, 0.85–1.35]; $P = 0.55$). The annual rate of cardiovascular death was 0.52% in the intensive therapy group and 0.49% in the standard therapy group (hazard ratio, 1.06 [CI, 0.74–1.52]; $P = 0.74$).

There were statistically significant differences in the rates of the secondary outcome of stroke. The annual rate of total stroke was 0.32% in the intensive therapy group and 0.53% in the standard therapy group (hazard ratio, 0.59 [CI, 0.39–0.89]; $P = 0.01$). The annual rate of nonfatal stroke was 0.30% in the intensive therapy group and 0.47% in the standard therapy group (hazard ratio, 0.63 [CI, 0.41–0.96]; $P = 0.03$).

The rates of serious adverse events were higher in the intensive therapy group. The significant adverse events attributed to blood pressure medication were hypotension (0.7% intensive therapy vs. 0.04% standard therapy; $P < 0.001$), bradycardia or arrhythmia (0.5 vs. 0.13; $P = 0.02$), and hyperkalemia (0.4% vs. 0.04%; $P = 0.01$). The adverse laboratory measures included hypokalemia (2.1% intensive therapy vs. 1.1% standard therapy; $P = 0.01$) and elevations in serum creatinine > 1.5 mg/dL in men (12.9% vs. 8.4%; $P < 0.001$) and > 1.3 mg/dL in women (10.9% vs. 7.1%; $P < 0.001$).

Conclusion. The lowering of SBP to below 120 mm Hg versus below 140 mm Hg did not decrease the rate of major cardiovascular events in this group of high-risk type 2 diabetic patients.

Commentary

The current study (ACCORD BP trial) examines the issue of the optimal blood pressure goal for type 2 diabetes patients. The effects of blood pressure lowering on diabetes-related morbidity and mortality have been previously established by the UKPDS trial [1]. Compared with the ACCORD BP trial, the blood pressures studied in the UKPDS trial were higher (baseline blood pressure, 160/94 mm Hg). The blood pressure attained in the tight control group was 144/82 mm Hg versus 154/87 mm Hg in the less tight control group, and there was a 24% risk reduction in diabetes-related endpoints for the tight control group [1].

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) states that the risk of cardiovascular disease increases twofold for all patients with every increment of 20/10 mm Hg above 115/75 mm Hg [2]. The JNC-7 recommendation of a blood pressure goal less than 130/80 mm Hg for diabetic patients was made after the initiation of the ACCORD BP trial, so this specific goal was not tested [2]. ACCORD BP did not find benefit in the intensive lowering of SBP below 120 mm Hg, which is 10 mm Hg lower than the currently recommended goal for diabetic patients. The standard therapy group in ACCORD BP attained a blood pressure of 133.5 mm Hg, which is close to the current JNC-7 recommendation. The ACCORD BP trial population had a baseline blood pressure of 139.2/76.0 mm Hg, so this population did not reflect diabetic patients with comorbid uncontrolled hypertension. Such higher-risk patients will require more intensive treatment to achieve and sustain larger reductions in blood pressure to attain their goals.

The limitation of the ACCORD BP trial was the power calculation, based on a primary outcome rate of 4% per year in the standard therapy. There was reduced power in the study, since the actual event rate (2.09%) was about half the predicted rate of cardiovascular events. Patients were also receiving treatments for multiple areas of risk factor modification, including statins and aspirin. A follow-up period longer than 4.7 years may be necessary to see significant effects of intensive BP therapy.

The study does suggest that there may be benefit in reducing the rate of stroke among high-risk type 2 diabetes by lowering blood pressure below 120 mm Hg. The number needed to treat with intensive therapy over 5 years to prevent 1 stroke was 89. The main adverse events from intensive blood pressure lowering below 120 mm Hg include hypotension, bradycardia, and laboratory abnormalities of potassium and creatinine.

Applications for Clinical Practice

Intensive control of SBP to less than 120 mm Hg compared with less than 140 mm Hg may not reduce cardiovascular events in type 2 diabetes. The study findings do not conflict with current guidelines because the recommended goal of 130 mm Hg was not tested. There may be additional benefit of blood pressure lowering below 120 mm Hg for stroke prevention in type 2 diabetic patients. The adverse events associated should not deter intensification of blood pressure medication regimens but instead, they should reinforce the need for close clinical monitoring during and after medication titration.

—Review by Sherley Abraham, MD, NYU School of Medicine, New York, NY, and Nirav R. Shah, MD, MPH

References

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