Very Intensive Blood Pressure Control Does Not Clearly Reduce Combined Incidence of Cardiovascular Events

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STUDY

ACCORD Study Group: Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F: Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 362:1575–1585, 2010

SUMMARY

Design. A randomized, controlled trial within a factorial trial that also compared intensive versus conventional glycemic control.

Subjects. Subjects included a total of 4,733 participants with type 2 diabetes who were either older than 40 years of age with a history of cardiovascular disease (CVD) or older than 55 years of age with no history of cardiovascular events but increased CVD risk. Participants had systolic blood pressure readings at entry between 130 and 180 mmHg and were on three or fewer antihypertensive medications. Patient had a mean age of 62 years; 48% were female, 60% were white, 24% were African American, and 34% had a history of CVD. The mean systolic blood pressure at entry was 139 mmHg in each group.

Methods. Participants were randomized to either intensive (target systolic blood pressure < 120 mmHg) or standard (target systolic blood pressure < 140 mmHg) blood pressure control. Treatment was conducted in a non-blinded manner: intensive-group patients were seen monthly for 4 months and every 2 months thereafter; standard-therapy patients were seen at 1 and 4 months every 4 months thereafter. Intensive therapy involved increasing the medication dosage or adding new medications when systolic blood pressure was > 120 mmHg at a visit. In the standard therapy group, therapy was augmented (increased dosage or addition of new medication) if systolic blood pressure was > 160 mmHg at one visit or > 140 mmHg at two consecutive visits and was down-titrated if systolic blood pressure was < 135 mmHg on two consecutive visits or < 130 mmHg on a single visit. The trial was designed to have > 90% power to detect a 20% difference in the primary study outcome of the incidence of first myocardial infarction, stroke, or cardiovascular death.

Results. Within the first year, the intensive-therapy group achieved a mean systolic blood pressure of 119.3 mmHg compared to 133.5 mmHg in the standard-therapy group, an average difference of 14.2 mmHg. This difference was achieved through more intensive use of medications: those in the intensive-therapy group used a mean of 3.4 medications versus 2.1 in the standard-therapy group.

Despite the difference in blood pressure, the incidence of the main outcome did not differ significantly between the two groups (1.87% annual incidence in the intensive group vs. 2.09% incidence in the standard group, hazard ratio [HR] 0.88, 95% CI 0.73–1.06, $P = 0.20$). Secondary outcomes included reduction in stroke (annual incidence 0.32 vs. 0.53%, HR 0.59, 95% CI 0.39–0.89) and an increase in serious adverse effects (3.3 vs. 1.3%, $P < 0.001$).

Mortality was slightly higher in the intensive-therapy group (relative risk 1.07, 95% CI 0.85–1.35), but this result was not statistically significant. There were no statistically significant interactions between demographic or clinical characteristics and the efficacy of intensive therapy; however, those who were in the standard glycemic control arm or who had an A1C of < 8.0 % on entry appeared to have somewhat more benefit with intensive blood pressure control than those who were assigned to intensive glycemic control or had an A1C of > 8.0% ($P = 0.08$ and 0.11, respectively, for interaction).

Conclusion. Intensive therapy with a target systolic blood pressure of < 120 mmHg did not reduce cardiovascular events compared to standard therapy with a goal systolic blood pressure of < 140 mmHg.

COMMENTARY

Before the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, only limited evidence was available to help guide decision-making about the intensity

of blood pressure control in patients with type 2 diabetes. Epidemiological evidence shows a continuous and graded relationship between increasing blood pressure and increasing risk of cardiovascular events.[1] The U.K. Prospective Diabetes Study found that treating patients with diabetes and a systolic blood pressure > 150 mmHg (mean achieved systolic blood pressure: 144 mmHg) reduced CVD events by 34% compared to a less aggressive policy of only treating systolic blood pressure > 180 mmHg (mean achieved systolic blood pressure: 154 mmHg).[2] A subgroup analysis of the Hypertension Optimal Treatment trial found a 51% reduction in CVD events for patients with diabetes who were allocated to a goal diastolic blood pressure of 80 mmHg versus a goal of 90 mmHg.[3]

Many guideline-issuing organizations had adopted lower blood pressure goals (systolic blood pressure < 130 mmHg and diastolic blood pressure < 80 mmHg) on the basis of the epidemiological evidence and limited trial data.[4] Whether aiming for a lower systolic blood pressure goal would be associated with sufficient clinical benefit to warrant the additional effort and increased risk of adverse events required to achieve such a level was not clear. Therefore, the ACCORD trial is particularly important for guiding the care of patients with type 2 diabetes.

The findings of the ACCORD blood pressure trial, although not definitive, suggest that intensive blood pressure control with a goal of achieving a systolic blood pressure of < 120 mmHg is not clearly superior to a less intensive goal of achieving a systolic blood pressure of < 140 mmHg. More intensive therapy was associated with a reduction in stroke (a secondary outcome), but not with an overall reduction in the primary outcome of incidence of important cardiovascular events (myocardial infarction, stroke, and CVD death). More intensive therapy was also associated with an increased risk of adverse events related to the intensive blood pressure control.

There are several potential explanations for why more intensive control did not improve the primary outcome. First, it is possible that adverse effects related to lowering blood pressure canceled out its beneficial effects, leading to no overall reduction.

Second, it is possible that more intensive control does produce modest benefits, but that the investigators did not observe a statistically significant result because the trial was not powered to detect smaller effect sizes. Testing for a true risk reduction of 10% would require a much larger trial or higher event rates among participants. Whether a 10% relative reduction in events would produce sufficient absolute benefits in practice to justify the additional expense and effort (for both patients and the health care system) required to achieve intensive control will require additional modeling.

Third, it is possible that more intensive blood pressure lowering may be beneficial for some, but not for others.

Interpretation of subgroup effects within a trial should always be performed with caution. In this trial, the lack of effect seemed to be relatively consistent across subgroups, except that those who were randomized to intensive blood glucose control seemed to have less effect from blood pressure lowering than those randomized to standard blood glucose control. One could postulate that the combination of intensive glucose and blood pressure control could exacerbate the risk of adverse effects and cancel out any benefits from lower blood pressure. Similarly, those with initial A1C levels < 8% appear to have derived more benefit from blood pressure lowering than those with higher initial A1C levels.

Should the results of ACCORD change our approach to blood pressure control in diabetes? Several guideline-issuing organizations have recommended that patients with diabetes have their systolic blood pressure lowered to < 130 mmHg, based mainly on the epidemiological relationship between blood pressure and CVD events and the high absolute CVD risk of patients with diabetes.[4] Other organizations have used these recommendations to develop quality measures. (See, for example, http://www.ncqa.org/tabid/139/Default.aspx.)

ACCORD suggests that there is little net benefit from very intensive blood pressure control (systolic blood pressure goal of < 120 mmHg; actual mean systolic blood pressure of 119 mmHg), compared with moderate control (goal of < 140 mmHg and actual mean of 133.5 mmHg). Achieving even moderate blood pressure control can be very difficult and resource intensive. Based on the large unmet need for better CVD risk factor control among patients with diabetes, it would seem prudent at this time to focus on achieving moderate blood pressure control (along with appropriate use of other effective CVD risk–reducing therapies such as statins and smoking cessation) across the population of patients with diabetes.

Moderate control could be implemented by following the "standard care" algorithm from ACCORD (i.e., increased dosage or addition of new medication if systolic blood pressure is > 160 mmHg at one visit or > 140 mmHg at two consecutive visits). Clinical prudence would suggest reduction in blood pressure medication for patients who are experiencing any adverse effects

from low blood pressure. Whether blood pressure medication should be reduced in asymptomatic patients with a systolic blood pressure of < 130 mmHg is not clear.

Achieving moderately intensive control will require practices to develop and implement systems to ensure that all patients have sufficient access and training to be full partners in their care. Few practices have achieved this level of performance across their populations of patients with diabetes. Participation in organized efforts to improve collaboratively may be helpful in this regard, although previous evaluations have not found consistent improvements in blood pressure control.[5]

By helping to define the limited net benefit from more intensive control and allowing us to focus on achieving moderately intensive control, ACCORD has provided important guidance for practice. It serves as an important model for how comparative effectiveness research can be used to help guide clinical care.

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