Does Intensive Glucose Control Cancel Out Benefits of Systolic Blood Pressure Target <120 mm Hg in Patients With Diabetes Mellitus Participating in ACCORD?

Sverre E. Kjeldsen, Ingrid Os, Peter M. Nilsson

See related article, pp 323–330

The relationship between BP and blood glucose has been known for >40 years when Leren et al[1] reported positive correlations between blood glucose and systolic (r=0.21) and diastolic BP (r=0.11) in apparently healthy white men (n=14 816) between 40 and 49 years of age. However, the associations between BP and glucose received little attention until 1998. Then, results from the HOT study (Hypertension Optimal Treatment)[2] and from the UKPDS (United Kingdom Prospective Diabetes Study)[3] appeared addressing treatment of hypertension in patients with diabetes mellitus. Randomization was stratified for diabetes mellitus status in the HOT study with 500 patients with diabetes mellitus and hypertension in 3 treatment arms. The trend for reduction in the primary cardiovascular end point, composite cardiovascular mortality, stroke, and myocardial infarction was reduced with 50% (P=0.005) favoring a diastolic BP target of 80 mm Hg. Although this was a subgroup analysis in a randomized clinical mega trial that overall failed on the primary end point,[2] the interest and awareness for hypertension in patients with diabetes mellitus escalated. Large outcome trials have subsequently been performed in patients with diabetes mellitus and hypertension.[4,5] Other hypertension outcome trials comparing different drug regimens[6,7] have been enriched with subgroups of many thousand patients with diabetes mellitus, though not showing that patients with hypertension and diabetes mellitus have different benefits compared with people with hypertension and no diabetes mellitus. Today, the question is mostly how aggressively BP should be treated in patients with diabetes mellitus to protect against cardiovascular and renal disease,[4,5] as the BP target below 130/80 mm Hg recommended in guidelines has been questioned.

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) analysis published in this issue of *Hypertension*[8] assessed whether intensive systolic BP treatment (<120 mm Hg) in patients with diabetes mellitus is associated with reduction in cardiovascular events in patients receiving standard (n=2362) versus intensive glycemic control (n=2371). The mean follow-up averaged 4.5 years, and 528 patients experienced cardiovascular events. The cardiovascular event rate in patients receiving standard glycemic control (hemoglobin A_{1c} [HbA_{1c}], >7%) was 30% (P=0.005) lower in the intensive BP treatment arm than in the standard BP treatment arm, whereas in the patients receiving intensive glycemic control (HbA_{1c}, <6%), the outcomes did not differ between the 2 BP study arms. There was also a statistically significant interaction between the BP treatment and the glycemic control strategies. The secondary end point of stroke risk in patients receiving standard glycemic control was also significantly lower in the intensive BP treatment arm but not in patients receiving intensive glycemic control. All-cause mortality tended to be higher in patients receiving intensive glycemic control and intensive BP treatment compared with standard BP treatment (P=0.05). Thus, the overall benefits of intensive BP treatment <120 mm Hg were only seen in ACCORD BP study participants receiving standard glycemic control.

The new data[8] suggest that episodes of severe hypoglycemia have interfered with the intensive BP treatment and probably cancelled out potential benefits of lowering systolic BP <120 mm Hg in patients with both diabetes mellitus and hypertension. This may be a severe limitation with intensive glycemic control also discussed in another randomized clinical trial.[4] Intensive glycemic control in patients with long-standing diabetes mellitus may be dangerous, especially in susceptible patients on older antidiabetes mellitus drugs, thereby increasing cardiovascular mortality as discussed in the new article[8] and should be avoided.

This discussion of the new ACCORD findings[8] should at this stage clearly be separated from reduction of total and cardiovascular mortality and the prevention of heart failure in patients with diabetes mellitus treated with some new classes of antidiabetic drugs (eg, empagliflozin and liraglutide type of drugs)[9] that carry multiple apparently beneficial effects in patients with diabetes mellitus including that they improve glycemic control, although not to extremely low values, they lower BP and also lower body weight. However, the empagliflozin and liraglutide type of drugs[9] and potential interactions with first-line antihypertensive drugs[6,7] would be highly interesting to investigate. We would be tempted to hypothesize a positive interaction in the sense of further cardiovascular prevention in the diabetic patients.

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Hypertension and diabetes mellitus have through decades been ranked by the World Health Organization as major causes of morbidity and mortality in the world. Glycemic control provides no great cardiovascular benefits, at least not with older drugs, including metformin, and should be critically evaluated[4,8] at least in the majority of patients with combined diabetes mellitus and hypertension. The hallmark of hypertension is increased total peripheral resistance caused by structural vascular changes in the small precapillary arterioles. This is most favorably treated with BP-lowering drugs that normalize the structure of the arterioles and subsequently lower BP and prevent cardiovascular complications.[6,7] The pathophysiological marker of diabetes mellitus, usually much more advanced than in essential hypertension, is the extensive damage of the arterioles and the microcirculation, in all organs, including the retina, the nervous system, the kidneys, and in the heart, and this explains why the majority of people with diabetes mellitus die from cardiovascular diseases in developed countries. Time has come to reconsider the resources in diabetes mellitus research and aim toward getting more knowledge and insight into the mechanism explaining the breakdown of the microvascular system, and potential early protection, beyond the demands by the American Food and Drug Administration for showing cardiovascular safety: any new drug approved to treat diabetes mellitus should also show prevention of cardiovascular disease.

The ACCORD study originally randomized hypertensive patients with type 2 diabetes mellitus to systolic BP targets <120 versus <140 mm Hg and came out without statistically significant benefit for the primary composite end point in the intensive treatment group.[5] ACCORD enrolled 4733 patients with normal renal function into a factorial design that included lipid- and glucose-lowering treatments, as well as BP reduction. However, possibly because of this multi-intervention, ACCORD achieved only ≈50% of the expected end points and was thus underpowered. ACCORD did show a 11% reduction favoring the target systolic BP <120 mm Hg compared with <140 mm Hg for the primary end point, a composite of cardiovascular mortality, stroke, and myocardial infarction, and a significant 48% reduction of stroke, which was a secondary end point. Many patients in the intensive BP treatment arm experienced adverse events, including syncope—a well-known clinical problem most likely because of overtreatment in patients with diabetes mellitus. Measurement of BP should include orthostatic test in patients with diabetes mellitus, as well as use of 24-hour ambulatory BP to detect and avoid too low BP.

In an already published post hoc analysis of ACCORD, attaining a usual systolic BP target between 120 and 140 mm Hg demonstrated a clear benefit for lowering cardiovascular risk.[10] Intensive systolic BP target <120 mm Hg did not attenuate the risk but rather increased the risk of severe adverse events. These findings support the contention of a wide range for targeting systolic BP between 120 and 140 mm Hg, which may be appealing to clinicians. It is noteworthy that also this ACCORD analysis maintained the randomization and assessed cardiovascular disease prevention in relation to whether study participants had achieved the systolic BP targets in their respective target group <120 versus <140 mm Hg.[10] The new ACCORD analysis in this issue of *Hypertension*[8] is bouncing back on the group randomized to systolic BP target <120 mm Hg and is reactualizing the question of cardiovascular prevention also in this group of study participants by avoiding intensive glucose control.

However, the new analysis[8] also suffers from a post hoc approach and being as statistically underpowered as the main ACCORD analysis.[5] These are weaknesses that open for chance findings, which is apparent when scrutinizing the key data in the report. In a snapshot of the findings of the new ACCORD analysis (Table), it is apparent that the intensive and the standard BP groups under standard glucose control are the 2 extremes of the 4 subgroups, while the 2 BP groups without difference but under intensive glucose control are centered in between. Statistical analyses have honored the factorial design and are correctly performed, but nevertheless, a play of chance may be involved when study groups become small like here and when they contain 50% only of the expected number of end points.

The new ACCORD analysis[8] is another strong argument for launching one or more interventional trial with appropriate study design and sufficient statistical power that may convincingly clarify whether a systolic BP target <120 mm Hg prevents cardiovascular complications in patients with diabetes mellitus. Until such data appear from the ACCORD study organization, or from others, the target systolic BP in patients with diabetes mellitus remains 130/80 mm Hg as now stated in both the American and European hypertension guidelines.

Disclosures

S.E. Kjeldsen has received honoraria for lecturing from Bayer, Merck & Co, Sanofi, and Takeda and for study committee work

Table. Primary End Point in the ACCORD Study (Composite of Cardiovascular Death, Stroke, and Myocardial Infarction) in Relation to Standard and Intensive Glycemic Control and in Relation to Standard (<140 mm Hg) and Intensive (<120 mm Hg) Systolic BP Target

	Standard Glycemic Control		Intensive Glycemic Control	
	Standard BP (<140 mm Hg)	Intensive BP (<120 mm Hg)	Standard BP (<140 mm Hg)	Intensive BP (<120 mm Hg)
Parameters	n=1178	n=1184	n=1193	n=1178
Event rate (per 1000 person-years)	29.7	21.1	23.2	24.9
Hazard ratio (95% CI)	1.00 (ref)	0.71 (0.56–0.90)	1.00 (ref)	1.06 (0.83–1.36)
P value	0.005		0.61	

Statistical comparisons are done according to the factorial design for study randomization.[8] ACCORD indicates Action to Control Cardiovascular Risk in Diabetes; BP, blood pressure; and CI, confidence interval.

from Takeda. P.M. Nilsson has received honoraria from Amgen, AstraZeneca, Boehringer-Ingelheim, Merck & Co, and Novo Nordisk. I. Os reports no conflicts.

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