Reevaluating the Evidence for Blood Pressure Targets in Type 2 Diabetes

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There is general consensus that treating adults with type 2 diabetes mellitus (T2DM) and hypertension to a target blood pressure (BP) of <140/90 mmHg helps prevent cardiovascular disease (CVD). Whether more intensive BP control should be routinely targeted remains a matter of debate. While the American Diabetes Association (ADA) BP guidelines recommend an individualized assessment to consider different treatment goals, the American College of Cardiology/American Heart Association BP guidelines recommend a BP target of <130/80 mmHg for most individuals with hypertension, including those with T2DM (1–3).

In large part, these discrepant recommendations reflect the divergent results of the Action to Control Cardiovascular Risk in Diabetes-BP trial (ACCORD-BP) among people with T2DM and the Systolic Blood Pressure Intervention Trial (SPRINT), which excluded people with diabetes (4,5). Both trials evaluated the effect of intensive compared with standard BP treatment targets (<120 vs. <140 mmHg systolic) on a composite CVD end point of nonfatal myocardial infarction or stroke or death from cardiovascular causes. SPRINT also included unstable angina and acute heart failure in its composite end point. While ACCORD-BP did not show a significant benefit from the intervention (hazard ratio [HR] 0.88; 95% CI 0.73–1.06), SPRINT found a significant 25% relative risk reduction on the primary end point favoring intensive therapy (0.75; 0.64–0.89).

Why did ACCORD-BP and SPRINT arrive at divergent conclusions? Recent secondary analyses provide new insights into potential reasons, including differences in trial design, populations studied, approach to BP lowering, trial end points, and statistical power or chance findings.

While SPRINT used a parallel group study design, ACCORD-BP used a complex 2-by-2 factorial design with concurrent evaluation of intensive BP and glucose lowering. In a post hoc subgroup analysis of ACCORD-BP, Margolis et al. (6) found a significant benefit from intensive BP lowering in the standard glycemic control group but not in the intensive glycemic control group. However, the biological plausibility for this interaction is weak, and this interaction was not statistically significant. It is therefore unlikely that the divergent results between the trials are explained by a true interaction between intensive BP and glycemic control.

Differences in population characteristics of ACCORD-BP and SPRINT (other than T2DM) are also unlikely to account for the divergent results. This is supported by findings published in this issue of *Diabetes Care* by Mi and Mukamal (7), who found significant differences in the effects of intensive BP control on all-cause mortality comparing ACCORD-BP (HR 1.02; 95% CI 0.81–1.39) and SPRINT (0.71; 0.58–0.88; *P* for interaction = 0.02) after balancing population characteristics in both trials. This contrasts with an earlier report from Buckley et al. (8), which found a significant 31% relative risk reduction in the composite CVD end point favoring intensive BP control in a subset of "SPRINT-eligible" ACCORD-BP participants. However, Buckley et al. restricted their analysis to participants in the standard glycemic control arm of ACCORD-BP, artificially favoring the effect of intensive BP control by focusing on a subgroup already known to have more favorable outcomes but not likely providing the most representative overall effect of ACCORD-BP.

ACCORD-BP and SPRINT attained strikingly similar BPs, used very similar classes and numbers of antihypertensive agents, and used automated devices to measure blood pressure. It is therefore unlikely that any of these intervention features contributed substantially to the divergent findings. Furthermore, although SPRINT measured BP in the absence of an observer for the majority of participants (as opposed to ACCORD-BP), similar results were found when analyses were performed separately in observed or unobserved participants (9).

Differences in trial end points and the effects of intensive BP control on these end points may partially explain the

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divergent results of ACCORD-BP and SPRINT. The primary end point in ACCORD-BP was more heavily weighted toward CVD death than in SPRINT (27 vs. 18% of events, respectively). However, CVD death was not significantly reduced by intensive BP control in ACCORD-BP (HR 1.06; 95% CI 0.74–1.52), while it was reduced in SPRINT (0.57; 0.38–0.85). These findings are consistent with the results of a study reported in this issue of *Diabetes Care* by Wan et al. (10). In this observational study of patients with T2DM, there was no benefit from intensification of BP therapy to achieve systolic BP <130 mmHg compared with <140 mmHg. Interestingly, the precise cause of CVD death was determined in only 56% of cases in ACCORD-BP compared with 95% of CVD deaths in SPRINT. Together, these results imply that the underlying causes of CVD death may have differed between the trials, with ACCORD-BP fatal events possibly less amenable to intensive BP control (11). Similarly, intensive BP control did not reduce heart failure in ACCORD-BP (0.94; 0.70–1.26), while it did in SPRINT (0.62; 0.45–0.84), again suggesting potential differential effects in the two populations.

It is possible that differences in statistical power or chance findings between ACCORD-BP and SPRINT may have contributed to the divergent results. In this issue of *Diabetes Care*, Brouwer et al. (12) pooled individual-level data from ACCORD-BP and SPRINT and report a significant 18% relative risk reduction in a harmonized composite CVD end point favoring intensive BP control, with no evidence of statistically significant interaction by the presence of diabetes (P = 0.13), suggesting a similar effect of intensive BP control in patients with and without T2DM. These results should, however, be interpreted with caution since these trials were not designed and therefore powered to test for interactions. Furthermore, although the play of chance alone may be a plausible explanation for the small differences in some of the nonfatal CVD outcomes between the trials, and perhaps the primary composite outcomes, it is harder to argue that chance findings were solely responsible for the marked qualitative differences in heart failure and CVD and all-cause mortality.

To some extent, CVD mechanisms and causes of death differ in T2DM patients compared with the general population. Microvascular disease (particularly kidney disease), accelerated vascular calcification, and diabetic cardiomyopathy are common in T2DM (13–15). Moreover, the rate of sudden cardiac arrest is markedly increased in T2DM and related, in part, to diabetes-specific factors other than ischemic heart disease (16). Hypoglycemia is a potential cause of CVD mortality that is specific to diabetes (17). In addition, polypharmacy is common and may increase CVD risk (18). Furthermore, nonvascular causes of death account for approximately 40% of the premature mortality burden experienced by T2DM patients (19). Whether these disease processes may render patients with T2DM less amenable to derive a mortality benefit from intensive BP control, however, is not known and should be the focus of future research.

In conclusion, the divergent results between ACCORD-BP and SPRINT are most readily explained by the apparent lack of benefit of intensive BP control on CVD and all-cause mortality in ACCORD-BP, rather than differences in the design, population characteristics, or interventions between the trials. This difference in effects on mortality may be attributable to differential mechanisms underlying CVD mortality in T2DM, to chance, or to both. These observations suggest that caution should be exercised extrapolating the results of SPRINT to patients with T2DM and support current ADA recommendations to individualize BP targets, targeting a BP of <140/90 mmHg in the majority of patients with T2DM and considering lower BP targets when it is anticipated that individual benefits outweigh risks.

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References

1. de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. Diabetes Care 2017;40:1273–1284
2. American Diabetes Association. 9. Cardiovascular disease and risk management: *Standards of Medical Care in Diabetes—2018*. Diabetes Care 2018;41(Suppl. 1):S86–S104
3. Whelton PK, Karey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 7 November 2017 [Epub ahead of print]. DOI: 10.1016/j.jacc.2017.11.006
4. SPRINT Research Group, Wright JT Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103–2116
5. Cushman WC, Evans GW, Byington RP, et al.; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–1585
6. Margolis KL, O'Connor PJ, Morgan TM, et al. Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: the ACCORD randomized trial. Diabetes Care 2014;37:1721–1728
7. Mi MY, Mukamal KJ. Comment on Buckley et al. Intensive versus standard blood pressure control in SPRINT-eligible participants of ACCORD-BP. Diabetes Care 2017;40:1733–1738 (Letter). Diabetes Care 2018;41:e84–e85
8. Buckley LF, Dixon DL, Wohlford GF IV, Wijesinghe DS, Baker WL, Van Tassell BW. Intensive versus standard blood pressure control in SPRINT-eligible participants of ACCORD-BP. Diabetes Care 2017;40:1733–1738
9. Johnson KC, Whelton PK, Cushman WC, et al.; SPRINT Research Group. Blood pressure measurement in SPRINT (Systolic Blood Pressure Intervention Trial). Hypertension. 12 March 2018 [Epub ahead of print]. DOI: 10.1161/HYPERTENSIONAHA.117.10479
10. Wan EYF, Yu EYT, Chin WY, et al. Effect of achieved systolic blood pressure on cardiovascular outcomes in patients with type 2 diabetes: a population-based retrospective cohort study. Diabetes Care 2018;41:1134–1141
11. Perkovic V, Rodgers A. Redefining blood-pressure targets–SPRINT starts the marathon. N Engl J Med 2015;373:2175–2178
12. Brouwer TF, Vehmeijer JT, Kalkman DN, et al. Intensive blood pressure lowering in patients with and patients without type 2 diabetes: a pooled analysis from two randomized trials. Diabetes Care 2018;41:1142–1148
13. Boudina S, Abel ED. Diabetic cardiomyopathy, causes and effects. Rev Endocr Metab Disord 2010;11:31–39
14. Chen NX, Moe SM. Arterial calcification in diabetes. Curr Diab Rep 2003;3:28–32
15. Fowler MJ. Microvascular and macrovascular complications of diabetes. Clin Diabetes 2008;26:77–82
16. Siscovick DS, Sotoodehnia N, Rea TD, Raghunathan TE, Jouven X, Lemaitre RN. Type 2 diabetes mellitus and the risk of sudden cardiac arrest in the community. Rev Endocr Metab Disord 2010;11:53–59
17. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Increased mortality of patients with diabetes reporting severe hypoglycemia. Diabetes Care 2012;35:1897–1901
18. Peron EP, Ogbonna KC, Donohoe KL. Antidiabetic medications and polypharmacy. Clin Geriatr Med 2015;31:17–27, vii
19. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829–841