Diastolic Blood Pressure and the J-Curve—Causal Effect or Confounding?
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The landmark Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated cardiovascular and all-cause mortality benefits with an intensive systolic blood pressure (SBP) goal of less than 120 mm Hg compared with a standard SBP goal of less than 140 mm Hg in patients with high blood pressure but without diabetes. The study by Foy and colleagues investigated whether intensive SBP lowering was associated with adverse outcomes if the baseline diastolic blood pressure (DBP) is low in a post hoc analysis combining SPRINT with the Action to Control Cardiovascular Risk in Diabetes—Blood Pressure (ACCORD-BP) trial.3

The root of the question of Foy et al harkens back to a long-observed J- or U-shaped association between DBP and risk of poor cardiovascular outcomes. In 1987, Cruickshank et al observed that DBP between 85 and 90 mm Hg was associated with the lowest risk of death from myocardial infarction (MI), whereas DBP less than or greater than this range was associated with higher risk. The question is whether this is a causal relationship or observational association reflecting confounding due to other conditions associated with both low DBP and poor outcomes, such as atherosclerosis. This question could be tested by examining whether an SBP intervention that also lowers DBP is associated with worse outcomes in those with lower baseline DBP. In other words, is low baseline DBP associated with modifying the beneficial effects of the SBP intervention?

Similar to many prior observational analyses, the study by Foy et al found in an observational analysis that lower baseline DBP was significantly associated with a higher risk of both all-cause death and a composite cardiovascular end point of cardiovascular death, nonfatal MI, and nonfatal stroke in pooled study participants. However, when Foy et al tested for a continuous interaction between SBP intervention and baseline DBP on outcomes, there was no statistically significant interaction for all-cause death or the composite cardiovascular end point. In further analysis, the SBP intervention was associated with lower risk of all-cause death (hazard ratio [HR], 0.77; 95% CI, 0.59-1.01) and the composite cardiovascular end point (HR, 0.78; 95% CI, 0.62-0.98) for baseline DBP of 80 mm Hg but higher risk of all-cause death (HR, 1.80; 95% CI, 0.95-3.39) for baseline DBP of 50 mm Hg. Of note, there was no increased risk of the composite cardiovascular end point associated with the SBP intervention for baseline DBP of 50 mm Hg (HR, 0.77; 95% CI, 0.44-1.33). Foy and colleagues inferred that “these findings cast doubt on whether blood pressure–lowering therapy should be intensified in patients whose baseline DBP is low...”

A prior analysis of SPRINT by Beddhu et al noted that despite the observational association of lower baseline DBP with higher risk of cardiovascular events and all-cause death, there was no significant interaction between SBP intervention and baseline DBP for either cardiovascular events or all-cause death. Another pooled analysis by Kalkman et al using data on achieved SBP and DBP of SPRINT and ACCORD-BP patients found that J-curves for cardiovascular events and all-cause death were similarly shaped in both treatment arms, with a nadir just below each respective goal SBP. Kalkman et al also found assessed the hazard of cardiovascular events and all-cause death associated with the amount of deviation from the intended SBP target and found lower hazard of poor outcomes among patients who were closest to their target BP. These findings suggest that the observations of increased cardiovascular events and all-cause death at lower DBP were not driven by the absolute level of attained BP but by a fundamental difference among patients who deviate from their goal BP treatment goal and achieve lower BPs.

Given the above data, how does one interpret the findings of Foy and colleagues? The major difference between the SPRINT analysis by Beddhu et al and the study by Foy et al is that Foy et al
included ACCORD-BP\textsuperscript{3} participants. When interpreting ACCORD-BP data, it is crucial to account for the 2 × 2 factorial design of ACCORD-BP that is comprised of an intensive vs standard SBP (<120 mm Hg vs ≥140 mm Hg) intervention and an intensive vs standard glycemic (hemoglobin A\textsubscript{1c}, <6\% vs 7.0\%–7.9\%) intervention. Glycemic control in ACCORD-BP was terminated early because of increased all-cause mortality.\textsuperscript{7} Subsequently, an interaction between the glycermia and SBP interventions on all-cause mortality was reported.\textsuperscript{8} Furthermore, in the standard glycemia group of ACCORD-BP, there was no evidence of interaction between baseline DBP and cardiovascular events or all-cause mortality, but in the intensive glycemia group, there was an interaction between baseline DBP and SBP intervention for all-cause mortality.\textsuperscript{9} Thus, the observed interaction between baseline DBP and SBP intervention on all-cause death in the pooled SPRINT and ACCORD-BP participants in the study by Foy and colleagues\textsuperscript{2} may reflect the interaction previously observed in the intensive glycemia arm in ACCORD.

A proposed physiological basis for the J-curve phenomenon is that myocardial blood supply occurs during diastole and lowering DBP with intensive SBP lowering could compromise myocardial oxygen balance. However, Foy and colleagues\textsuperscript{2} did not observe an elevated risk of cardiovascular events with intensive SBP lowering in those with low baseline DBP. Indeed, myocardial oxygen balance is a function of both supply and demand.\textsuperscript{10} By lowering myocardial oxygen demand, intensive SBP lowering in those with low DBP could potentially improve myocardial oxygen balance. Taken together, the current literature\textsuperscript{5,6,9} supports the notion that low baseline DBP should not be an impediment for SBP control in people without diabetes or in people with diabetes using standard glycemic control.

Nonetheless, the study by Foy et al\textsuperscript{2} renews the attention on the potential increase in all-cause mortality associated with intensive SBP lowering in patients with low baseline DBP and diabetes using strict glycemic control. It should be noted that intensive glycemic control in ACCORD-BP was achieved with insulin and other older agents.\textsuperscript{7} With the recent advances in glycemia management with sodium/glucose cotransporter 2 inhibitors and glucose-like peptide-1 analogs in type 2 diabetes, randomized clinical trials of SBP lowering in patients with type 2 diabetes and low baseline DBP are warranted.


