COMMENTARY

Diastolic Blood Pressure Does Not Influence Cardiovascular Outcomes in Type 2 Diabetes; or Does It?

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Hypertension and diabetes are prominent cardiovascular (CV) risk factors and major issues of public health (1,2). The common coexistence of hypertension and type 2 diabetes is long-established and represents a "deadly" combination: diabetes increases CV risk threefold at any level of systolic blood pressure (SBP), while the presence of hypertension in patients with diabetes increases CV risk by fourfold (3,4).

The optimal level of blood pressure (BP) in patients with diabetes has been a matter of debate for many years (5–7). Following older observational evidence and interventional data from the UK Prospective Diabetes Study (UKPDS) 38 and Hypertension Optimal Treatment (HOT) study, which showed CV benefits with diastolic blood pressure (DBP) of <85 mmHg and <80 mmHg, hypertension and diabetes guidelines from the late 1990s suggested a BP target of <130/80 mmHg in diabetes (8,9). However, until the Action to Control Cardiovascular Risk in Diabetes blood pressure trial (ACCORD BP) (10) was performed, the bulk of the data regarding the SBP target were derived from observational studies. ACCORD BP aimed to identify the optimal SBP goal by randomizing 4,733 high-risk patients (i.e., >15% 10-year CV risk) with type 2 diabetes to a target SBP of <120 mmHg or <140 mmHg. After 4.7 years of follow-up, the two groups had no differences in the primary outcome (nonfatal myocardial infarction, nonfatal stroke, death from CV causes) (hazard ratio [HR] 0.88, 95% CI 0.73–1.06; $P = 0.20$), CV mortality, and all-cause mortality; those in the intensive group had fewer stroke events (HR 0.59, 95% CI 0.39–0.89) but a higher incidence of serious adverse events (3.3% vs. 1.3%, $P < 0.001$), including hypotension, syncope, arrhythmias, hyperkalemia, angioedema, and renal failure.

The ACCORD BP findings were considered by many as conclusive evidence against the <130 mmHg SBP target and favoring the <140 mmHg target in diabetes and led to changes in relevant recommendations (11,12). However, this interpretation met criticism for several reasons (6,7). ACCORD was a 2 × 2 factorial design trial, where the initially well-powered group for target BP assessment lost power following the premature termination of the ACCORD glycemia study (due to high mortality in the intensive glycemia group) (13). The intensive SBP target of <120 mmHg and the method of measurement, which were similar to those in the Systolic Blood Pressure Intervention Trial (SPRINT), did not follow clinical practice or existing guidelines recommending a target of <130 mmHg (14). Moreover, from 1 year to the study end, the mean SBPs were 119.3 and 133.5 mmHg, respectively, i.e., the low actual BPs achieved in the "conservative" target may have diluted any between-group differences in outcome. A higher event rate could have favored the "intensive" target group, as relative risks of most outcomes in ACCORD BP pointed toward benefit with the "intensive" target. Hence, no firm answer was achieved by ACCORD BP.

A previous post hoc analysis explored the combined effects of BP and glycemia regimes in ACCORD by allocating patients into four groups and yielded results contrasting the main ACCORD BP analysis (15). Patients in the intensive BP/intensive glycemia (HR 0.71, 95% CI 0.52–0.96), intensive BP/standard glycemia (HR 0.74, 95% CI 0.55–1.00), and standard BP/intensive glycemia groups (HR 0.67, 95% CI 0.50–0.91) all had reduced risk of the primary outcome when compared with the standard BP/standard glycemia group. All secondary outcomes were neutral or favored the intensive treatment groups. Another post hoc analysis of ACCORD BP (16) investigated the effect of intensive SBP control in patients with >9 years of follow-up. They included participants in the standard glycemia arm who had established CV disease, had chronic kidney disease (CKD), were aged ≥75 years, or had a 10-year coronary heart risk ≥15%. Intensive SBP control reduced

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the composite outcome by 25% (HR 0.75, 95% CI 0.60–0.95), with the benefit driven mostly by a reduction in nonfatal myocardial infarction.

Since the original analyses by Franklin (17) showing that SBP largely determines CV outcomes in people over age 50 years, there has been less attention paid to DBP. There continues to be a controversy, however, regarding the J-curve phenomenon, i.e., the concern whether intensive SBP lowering could result in increased CV events due to an extreme decrease in DBP (18). This question is particularly relevant in individuals with increased arterial stiffness and high pulse pressure (i.e., the elderly, those with CKD or diabetes). In this issue of *Diabetes Care*, Ilkun et al. (19) present a post hoc analysis of 4,731 ACCORD BP patients, examining whether baseline DBP modifies the effects of intensive SBP control on outcomes. The analysis was performed separately for patients in the standard and intensive glycemia arms, and the study population was categorized into three groups by baseline DBP (≤70, 71–79, or ≥80 mmHg). Those with DBP ≤70 mmHg were older and had a higher prevalence of heart failure, CKD, history of stroke or myocardial infarction, and a longer duration of diabetes. Within each tertile of baseline DBP, the mean achieved DBP during follow-up was lower for the intensive SBP group (i.e., for baseline DBP ≤70, achieved mean DBPs were 60 ± 6 vs. 65 ± 6 mmHg for intensive and standard SBP groups, respectively).

In the standard glycemic arm, intensive SBP lowering decreased the risk of the ACCORD BP primary composite outcome (HR 0.76, 95% CI 0.59–0.98). As indicated by spline regression analysis, this effect of low SBP was not related to baseline DBP (linear interaction term for baseline DBP as a continuous variable $P = 0.67$). With DBP considered a dichotomous variable, the risk for the primary outcome with intensive SBP lowering was similar for those with DBP ≤70 mmHg (HR 0.76, 95% CI 0.50–1.17) and DBP >70 mmHg (HR 0.78, 95% CI 0.56–1.07), interaction $P = 0.96$. Conversely, in the intensive glycemic arm, intensive SBP lowering did not reduce the composite outcome risk (HR 1.06, 95% CI 0.81–1.40); again, this outcome was not affected by baseline DBP as a linear (interaction $P = 0.85$) or dichotomous (interaction $P = 0.92$) variable. Moreover, intensive SBP lowering did not affect all-cause mortality in any glycemic arm. No interactions with baseline DBP were noted in the standard glycemic arm. However, in the intensive glycemia arm, intensive SBP lowering signified a risk for participants with DBP ≤70 mmHg (HR 1.93, 95% CI 1.18–3.14), interaction $P = 0.04$ (19).

The strengths of this study include the large original sample and a thorough statistical analysis employing Cox regression, cubic spline models, and a large set of sensitivity analyses. Examining the impact of baseline DBP both as a continuous and a dichotomous variable adds to the validity of the conclusions. However, the study is limited by its post hoc nature and the low power for included subgroup analyses, resulting in progressively wider confidence intervals.

These data are of interest when placed in the context of other analyses. Unlike the current study that chose a cut point of <70 mmHg for DBP, much of the concern relates to DBP levels <60 mmHg where coronary autoregulatory flow reserve may be compromised in advanced atherosclerosis and contribute to acute flow obstruction. Data from an Atherosclerosis Risk in Communities (ARIC) study cohort of 11,565 adults (31% with prediabetes or diabetes) evaluated associations between DBP and outcomes over 6 years (20). DBP <60 mmHg at baseline was independently associated with progressive myocardial damage based on the annual change in hs-cTnT. Additionally, compared with a DBP of 80–89 mm Hg, a DBP <60 mmHg was associated with incident coronary heart disease and mortality but not with stroke. A separate post hoc analysis of the SPRINT trial, including participants without diabetes, demonstrated a U-shaped association between baseline DBP and the risk of the primary CV outcome (21). However, the effects of intensive SBP intervention on the primary outcome were not influenced by baseline DBP (P for interaction = 0.83). The primary outcome HR in the intensive versus standard SBP group was 0.78 (95% CI 0.57–1.07) in the lowest DBP quintile (mean baseline DBP 61 ± 5 mmHg) with an interaction P value of 0.78. Results were similar for all-cause death and renal events. The authors concluded that low baseline DBP was associated with increased risk of CV disease events, but the benefit of the intensive SBP lowering did not differ by baseline DBP.

Ilkun et al. (19) suggest that in patients with diabetes and standard glycemic control, there was no effect of baseline DBP on the ability of low SBP to reduce CV risk. While this may be true, it appears from older data that those at highest risk of having DBP <60 mmHg are those with higher magnitudes of atherosclerosis (22). Thus, the existence of a J- or U-shaped curve between the achieved levels of DBP and CV events, while highly debated, may depend more on the preexisting state of atherosclerosis and a magnitude of DBP drop below 60 mmHg (18,22). A relevant open discussion regards the possibility that the J- or U-curve is not a result of purely low DBP but rather of increased pulse pressure reflecting high arterial stiffness and, therefore, increased CV risk (23). Given the fact that the vast majority of existing literature on the J-curve phenomenon derives also from observational studies or post hoc analyses of outcome trials, the current study, taken together with data from SPRINT in individuals without diabetes, provides important evidence against the interference of low baseline DBP (at levels <70 mmHg and not <60 mmHg) on the CV benefits of low SBP. These promising observations call for confirmation in future trials.

Duality of Interest. P.S. is an advisor/speaker to Amgen, Bayer, Boehringer Ingelheim, Elpen Pharmaceuticals, Genesis Pharma, Menarini, Innovis Pharma, and Winmedica and has received research support for an Investigator-Initiated Study from AstraZeneca. G.B. serves on the 2020–2021 American Diabetes Association Clinical Practice Guideline committee and is a consultant for Merck, Novo Nordisk, Bayer, Janssen, AstraZeneca, Relypsa, and Vascular Dynamics.

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