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RESEARCH LETTER

Baseline blood pressure modifies the role of blood pressure variability in mortality: Results from the ACCORD trial

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1 | INTRODUCTION

Previous studies indicate that visit-to-visit blood pressure variability (BPv), independent of mean blood pressure level, is associated with adverse cardiovascular outcomes and mortality.[1-3] These findings have included cohorts both with and without diabetes. In a recent meta-analysis of patients with type 2 diabetes (T2D), a significant 12% increase in all-cause mortality was linked to systolic BPv.[4]

A more recent body of literature suggests that associations between BPv and risk of nonfatal cardiovascular outcomes may be influenced by baseline blood pressure level. For example, those with blood pressure below the study median were more susceptible to risk due to BPv in several clinical trials,[3,5,6] and more recently, we noted that a U-shaped association for BPv by baseline blood pressure levels with cardiovascular disease (CVD) may exist.[7] Whether these more complex risk patterns are also pertinent to mortality is an important, and underexplored, question.

To address these gaps in the literature, we examined in post-hoc analyses the relationship between systolic and diastolic BPv and risk of all-cause and cardiovascular mortality in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Importantly, we examined these associations by clinically relevant categories of baseline blood pressure, and we also compared the association between BPv in cardiovascular and noncardiovascular mortality. With frequent visits and carefully measured blood pressure assessments, ACCORD is an exemplary cohort in which to assess this research question.

2 | METHODS

This post hoc analysis drew on data from the ACCORD trial, the design and principal results of which have been documented previously.[8] Briefly, participants were enrolled beginning in 2001 to a double two-by-two factorial, parallel treatment trial in which patients were randomly assigned to intensive glucose-lowering, as well as to distinct lipid and blood pressure intervention arms.

At each visit, participants had their blood pressure measured by certified ACCORD staff with an automated oscillometric device (OMRON Healthcare HEM-907) that records to the nearest digit. After sitting quietly for 5 minutes, three measurements of systolic (SBP) and diastolic blood pressure (DBP) were taken at 1-minute intervals, and the average of these three readings was the reported blood pressure for a visit.[8]

For this analysis, we included longitudinal data from the standard 4-month visits for all participants enrolled in all arms of the trial.[7] To account for rapid reduction in blood pressure at the early phase of the trial, the baseline visit was excluded from the BPv calculation. Those with two or fewer blood pressure measures were also excluded. We assessed BPv by coefficient of variation of SBP (CV-SBP) and DBP (CV-DBP).

Our outcomes of interest were all-cause mortality and cardiovascular mortality. We used a time-dependent Cox proportional hazards model to assess the relationship between BPv and these endpoints, the method of which we have documented in several prior analyses.[7,9] Three models for variability were reported. Model

1 adjusted for age. Model 2 adjusted for age and those covariates which differed between those who did and did not develop a fatal event. Model 3 additionally adjusted for cumulative mean blood pressure over study follow-up. We also assessed the relationship between BPv and mortality risk by clinically relevant strata of baseline SBP (>140, 120-139 and < 120 mmHg) and DBP (>80, 70-79 and < 70 mmHg). Statistical analysis was conducted using R software version 4.1.1. A two-sided *P* value < 0.05 was considered statistically significant.

3 | RESULTS

Baseline characteristics of the cohort are shown in Table S1 by subsequent total and cardiovascular mortality. After a median follow-up of 4.7 years, 623 deaths, including 280 cardiovascular deaths, were recorded. For all-cause mortality, age, sex, race/ethnicity, diabetes duration, CVD history, lifetime smoking, SBP, DBP, HDL cholesterol, glycated haemoglobin, urine albumin-to-creatinine ratio, and estimated glomerular filtration rate significantly differed between those

TABLE 1 Hazard ratios for the association of blood pressure variability with all-cause and cardiovascular mortality

	Model 1, age adjustment		Model 2, multivariate adjustment		Model 3, model 2 + cumulative mean blood pressure	
Total mortality (n = 623)						
CV-SBP	1.15 (1.12-1.19)	**<0.001**	1.13 (1.09-1.18)	**<0.001**	1.13 (1.07-1.18)	**<0.001**
CV-DBP	1.29 (1.22-1.36)	**<0.001**	1.31 (1.22-1.42)	**<0.001**	1.31 (1.21-1.42)	**<0.001**
CVD death (n = 280)						
CV-SBP	1.15 (1.11-1-20)	**<0.001**	1.13 (1.08-1.19)	**<0.001**	1.13 (1.07-1.20)	**<0.001**
CV-DBP	1.29 (1.20-1.40)	**<0.001**	1.37 (1.23-1.53)	**<0.001**	1.37 (1.23-1.53)	**<0.001**

Note: Hazard ratios (HRs), 95% confidence intervals (CIs) and *P* values estimated by Cox proportional hazards model. Blood pressure variables were adjusted for age (Model 1), baseline factors that differed significantly between those who did and did not develop each event (Model 2; see Table S1) and additionally for cumulative mean of blood pressure excluding the baseline blood pressure. *P* values <0.05 (bold font) are considered significant.
Abbreviations: CV, coefficient of variation; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

TABLE 2 Hazard ratios for the association of blood pressure variability with mortality by baseline blood pressure levels

		Model 1, age adjustment		Model 2, multivariate adjustment		Model 3, model 2 + cumulative mean blood pressure	
Total mortality	**No. of events**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
CV-SBP							
SBP > 140 mmHg	*n* = 249	1.26 (1.16-1.38)	**<0.001**	1.32 (1.16-1.51)	**<0.001**	1.37 (1.19-1.56)	**<0.001**
SBP 120-139 mmHg	*n* = 254	1.11 (1.08-1.15)	**<0.001**	1.08 (1.04-1.12)	**<0.001**	1.12 (1.07-1.18)	**<0.001**
SBP < 120 mmHg	*n* = 96	1.32 (1.13-1.55)	**<0.001**	1.31 (1.10-1.55)	**0.003**	1.33 (1.11-1.59)	**0.001**
CV-DBP							
DBP > 80 mmHg	*n* = 110	1.36 (1.20-1.55)	**<0.001**	1.32 (1.13-1.54)	**<0.001**	1.41 (1.20-1.66)	**<0.001**
DBP 70-79 mmHg	*n* = 170	1.19 (1.07-1.33)	**<0.001**	1.15 (1.02-1.30)	**0.03**	1.19 (1.06-1.33)	**0.003**
DBP <70 mmHg	*n* = 253	1.30 (1.19-1.41)	**<0.001**	1.32 (1.18-1.49)	**<0.001**	1.32 (1.17-1.49)	**<0.001**
CVD death							
CV-SBP							
SBP > 140 mmHg	*n* = 114	1.16 (1.01-1.33)	**0.01**	1.14 (0.96-1.36)	0.14	1.26 (1.06-1.50)	**0.01**
SBP 120-139 mmHg	*n* = 111	1.12 (1.07-1.17)	**<0.001**	1.08 (1.03-1.13)	**0.002**	1.10 (1.04-1.17)	**0.002**
SBP < 120 mmHg	*n* = 42	1.45 (1.17-1.80)	**<0.001**	1.37 (1.06-1.78)	**0.02**	1.35 (1.04-1.77)	**0.03**
CV-DBP							
DBP > 80 mmHg	*n* = 75	1.31 (1.10-1.57)	**0.003**	1.28 (1.07-1.53)	**0.008**	1.34 (1.10-1.64)	**0.004**
DBP 70-79 mmHg	*n* = 61	1.01 (0.82-1.24)	0.94	0.92 (0.73-1.17)	0.51	0.97 (0.77-1.23)	0.83
DBP <70 mmHg	*n* = 118	1.40 (1.25-1.54)	**<0.001**	1.38 (1.21-1.57)	**<0.001**	1.38 (1.21-1.57)	**<0.001**

Note: Hazard ratios (HRs), 95% confidence intervals (CIs), and *P* values estimated by Cox proportional hazards model. Blood pressure variables were adjusted for age (Model 1), baseline factors that differed significantly between those who did and did not develop each event (Model 2) and additionally for cumulative mean of blood pressure excluding the baseline blood pressure. *P* values <0.05 (bold font) are considered significant.
Abbreviations: CV, coefficient of variation; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

who did or did not die during trial follow-up. For cardiovascular mortality, these same risk factors and blood pressure treatment significantly differed between those who did or did not die from cardiovascular causes during the trial follow-up (Table S1). Systolic and diastolic BPv were significantly associated with risk of both all-cause and cardiovascular mortality (Table 1). This association remained significant even after adjustment for covariates that differed (Table S1) between those who did and did not develop a fatal event as well as cumulative mean blood pressure during the follow-up. There were no significant differences in the mortality outcomes for use of statins, insulin, meglitinides, sulphonylureas, or platelet aggregation inhibitors. Adjustment for total number of antihypertensive agents, use of beta-blockers, or use of loop diuretics did not appreciably influence the variability model. Adjustment for ACCORD glucose-lowering arm randomization assignments did not alter the associations. We did observe a significant interaction ($P = 0.002$) between BPv and the blood pressure randomization arm for cardiovascular deaths. The overall hazard for cardiovascular death due to BPv in the intensively treated group (hazard ratio [HR] 1.48, $P = 0.003$) was greater than in the standard treatment group (HR 1.12, $P = 0.008$). Accounting for competing mortality risk[10] did not appreciably influence the variability model results.

As we observed a statistically significant interaction between blood pressure level and BPv ($P < 0.001$), we further examined the relationship between BPv and mortality by clinically relevant categories of baseline blood pressure. We observed that the strongest associations between CV-SBP and all-cause mortality were in those with either baseline SBP > 140 mmHg (HR 1.37) or baseline SBP < 120 mmHg (HR 1.33); weaker associations were noted in those with baseline SBP of 120 to 139 mmHg (Table 2). A similar pattern was seen for CV-DBP and all-cause mortality. These patterns of excess risk in the high and low categories were also observed in the analysis of cardiovascular mortality. When cardiovascular deaths were excluded from the analysis for all-cause mortality, this pattern was mitigated; in particular, the HRs for BPv and mortality were now attenuated in the low DBP stratum (Table S2).

4 | DISCUSSION

Using data from the ACCORD trial, we report that BPv (both CV-SBP and CV-DBP) was significantly associated with all-cause and cardiovascular mortality. Notably, in stratified analyses, risk was exacerbated in both high and low strata of baseline SBP and DBP. The difference in the association by baseline pressure level was particularly striking for CV-DBP and cardiovascular death, where risk was at least 34% higher in high and low DBP strata compared with participants who entered the trial with DBP 70 to 79 mmHg.

Since Rothwell et al[1] and Muntner et al[2] first provided convincing evidence in the first half of the last decade in large prospective cohort studies that BPv is linked to risk of mortality and CVD, several refinements in the literature have emerged. One such advance shown in a variety of cohorts was that either blood pressure level or baseline cardiovascular risk modifies the overall association with cardiovascular events. For instance, in the PROSPER trial, diastolic BPv was more robustly associated with coronary events in those with SBP below the median, although this population was markedly hypertensive.[11] Similarly, VALUE trial analyses reported strong associations between BPv and cardiovascular events, but the association was stronger in those with blood pressure below the median of 137.8 mmHg.[3] In patients with established coronary heart disease from the STABILITY trial, a robust risk of the major adverse cardiovascular event outcome ($P = 0.008$) due to BPv was noted in those with low levels of diastolic function (<67 mmHg).[5] Our own prior analyses using the ACCORD trial revealed several interesting findings: heart failure risk due to BPv increased only in lower categories of baseline blood pressure,[12] while for coronary heart disease and the primary CVD outcome, BPv indicated risk exclusively in both high and low strata of blood pressure.[7]

The present analysis highlights for the first time the relevance of ambient blood pressure when considering the potential impact of BPv on mortality in a purely diabetes cohort. Moreover, we provide an assessment of this association across a wide spectrum of baseline blood pressure, leading to the identification of stronger relationships with mortality in those with high or low blood pressure, and in particular with cardiovascular death. These data support the notion that the nonlinear influences of BPv on risk of cardiovascular outcomes reported by us[7,12] and others may extend to fatal endpoints. Although it can be challenging to draw clinical implications from epidemiological data, these data are consistent with a recent position statement by the American Diabetes Association that warns of the dangers of reducing blood pressure below 70 mmHg DBP, especially in older individuals with reduced vascular compliance.[13] Our data in this study suggest that excessive BPv in those with high or low blood pressure could contribute to mortality risk. The recommendation to ensure SBP-lowering efforts do not drop DBP too low was strengthened further by a study by McEvoy et al, which showed increases in high-sensitivity troponin T, a marker of myocardial injury, as DBP decreased.[14] Whether BPv directly induces myocardial injury leading to increased troponin levels[15] merits further investigation. As ACCORD participants had T2D and were at high risk for CVD, it is possible that they may be more susceptible to this pathway of injury.

We observed in this study that the association between BPv and cardiovascular mortality was exacerbated in the intensively treated blood pressure group. Insofar as the extent of BPv is similar in both blood pressure treatment arms, this finding raises the possibility that participants undergoing intensive blood pressure treatment may be more susceptible to the adverse effects of BPv. In a previous investigation of glucose variability in the Veterans Affairs' Diabetes Trial, we observed that glucose variability posed a greater risk for cardiovascular events in the intensive glucose-lowering arm of the trial.[9] The possibility that those undergoing intensive glucose- or blood pressure-lowering may be more sensitive to the effects of metabolic risk factor variation merits exploration in large trials of glucose- or blood pressure-lowering.

Several mechanisms have been posited to account for associations between BPv and risk of CVD, including arterial stiffness, endothelial dysfunction, or accelerated atherosclerosis; these disturbances are themselves linked to mortality risk.[16-19] In an early experimental study of 73 patients with essential hypertension of varying severity, Frattola et al showed that end organ damage due to BPv increased as mean arterial pressure in the subjects was increased.[20] Our findings on BPv and mortality in ACCORD participants at the high end of baseline blood pressure are consistent with their findings. Moreover, because interactions between low baseline blood pressure and BPv were found for diastolic heart failure and coronary events,[3,7,12] we hypothesized previously that coronary hypoperfusion due to transient declines in blood pressure[12] may lead to these adverse outcomes. Our present findings that in those with lower DBP, only the association between BPv and cardiovascular mortality (and not with non-cardiovascular mortality) was increased support this concept. Although our epidemiological analysis precludes our ability to tease this out further, several of the mechanisms proposed above to link BPv to adverse endpoints are indeed modified by baseline CVD risk or blood pressure level.

The present analysis has several strengths. The ACCORD study was a large, carefully conducted clinical trial with frequent blood pressure measurements. Our use of time-dependent Cox regression models allowed us to assess BPv until the time of a death, which is advantageous compared to some other approaches used in this field. We also note a few limitations. The T2D population in ACCORD was at high risk of dying from a cardiovascular cause; it will be important to examine the role of baseline blood pressure in the influence of BPv in cohorts at lower underlying CVD risk. Moreover, limited sample size precluded our ability to examine more extensive categories of baseline blood pressure.

In conclusion, using data from a large cohort of T2D patients, we report that the association between BPv and risk of all-cause and cardiovascular mortality is greater in those with low and high baseline blood pressures. This pattern appeared to be driven by cardiovascular deaths. Although confirmation in other cohorts is needed, these findings shed new light on the dependence of risk due to BPv on overall blood pressure level and could have implications for blood pressure treatment and management.

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AUTHOR CONTRIBUTIONS

D.S.N. and P.D.R. contributed to the conception and design of the work. D.S.N. conducted the data analysis. J.J.Z. acquired the dataset. D.S.N., M.S.N., J.K. and P.D.R. wrote the manuscript. All authors contributed to the interpretation of the data, made edits to the text, and approved the final version.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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