

Refining determinants of associations of visit-to-visit blood pressure variability with cardiovascular risk: results from the Action to Control Cardiovascular Risk in Diabetes Trial

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Objectives: As there is uncertainty about the extent to which baseline blood pressure level or cardiovascular risk modifies the relationship between blood pressure variability (BPv) and cardiovascular disease, we comprehensively examined the role of BPv in cardiovascular disease risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial.

Methods: Using data from ACCORD, we examined the relationship of BPv with development of the primary CVD outcome, major coronary heart disease (CHD), and total stroke using time-dependent Cox proportional hazards models.

Results: BPv was associated with the primary CVD outcome and major CHD but not stroke. The positive association with the primary CVD outcome and major CHD was more pronounced in low and high strata of baseline SBP (<120 and >140 mmHg) and DBP (<70 and >80 mmHg). The effect of BPv on CVD and CHD was more pronounced in those with both prior CVD history and low blood pressure. Dips, not elevations, in blood pressure appeared to drive these associations. The relationships were generally not attenuated by adjustment for mean blood pressure, medication adherence, or baseline comorbidities. A sensitivity analysis using CVD events from the long-term posttrial follow-up (ACCORDION) was consistent with the results from ACCORD.

Conclusion: In ACCORD, the effect of BPv on adverse cardiovascular (but not cerebrovascular) outcomes is modified by baseline blood pressure and prior CVD. Recognizing these more nuanced relationships may help improve risk stratification and blood pressure management decisions as well as provide insight into potential underlying mechanisms.

Keywords: blood pressure, cardiovascular disease, coronary hypoperfusion, type 2 diabetes, variability

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes Trial; ARV, average real variability; CV, coefficient of variation

INTRODUCTION

A large body of epidemiologic evidence indicates that visit-to-visit blood pressure variability is associated with cardiovascular risk [1–4], including among individuals with type 2 diabetes (T2D) [5]. Such associations have been reported to be independent of average blood pressure level [1,2,6] and may be explained by several putative mechanisms, such as reductions in aortic distensibility [7], increased arterial stiffness [8], impaired endothelial function [9], or increasing global longitudinal strain [10].

Recent studies indicate that the association between blood pressure variability and cardiovascular disease (CVD) may be modified by baseline cardiovascular history or blood pressure level. In post hoc analyses of three studies – the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial, the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), and the Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy (STABILITY) trial – it was observed that the association between SBP or DBP (SBP or DBP) variability and CVD was strongest in those with blood pressure levels below the median or in the lowest tertile [11–13]. Furthermore, dips rather than peaks in blood pressure in the STABILITY trial were shown to be more closely associated with cardiovascular mortality [13].

Although these new findings are noteworthy, there are some limitations to the work previously described. Although several of these studies examined the relationship between blood pressure variability and CVD outcomes in groups stratified by median blood pressure, rigorous examination by finer baseline blood pressure categories could help provide a clearer understanding of the risk associated

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with variability across the spectrum of blood pressure. It may also provide additional insight into the underlying mechanisms of cardiovascular risk because of blood pressure variability. Moreover, previous studies did not systematically explore the relationship between blood pressure categories and blood pressure variability on different cardiovascular outcomes.

One potential pathway proposed to account for heightened cardiovascular risk [13,14] in those with increased blood pressure variability is an increased occurrence of coronary hypoperfusion. As coronary perfusion is dependent on diastolic blood flow in epicardial vessels, factors, such as low blood pressure or restrictions in blood flow would be expected to exacerbate the effects of blood pressure variability. In addition, one would anticipate cardiac outcomes to be particularly sensitive to blood pressure variability.

To address several of these limitations and unanswered questions in this area, we performed a comprehensive post hoc assessment of blood pressure variability and cardiovascular risk outcome measures in participants of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. This included among other approaches a more focused examination of background blood pressure levels, relevant patterns of blood pressure variability, prior CVD history, and type of incident CVD outcomes affected. With a large sample size, detailed medical history, frequent blood pressure measurements, and a broad group of adjudicated outcomes, ACCORD provides an ideal cohort to use to explore this research question.

METHODS

Study design, participants, and variability measures

The ACCORD trial was a double two-by-two factorial, parallel treatment trial in which patients were randomly assigned to receive intensive glucose lowering targeting an HbA1c concentration of less than 6% or standard treatment targeting HbA1c of 7–7.9%. Participant recruitment began in 2001, and the goal of at least 10 000 participants recruited was reached in September 2005. The trial also included randomization to distinct blood pressure and lipid intervention arms. ACCORD included participants with T2D, HbA1c concentrations at least 7.5%, and who were aged 40–79 years with a history of CVD or 55–79 years with evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two risk factors for CVD (dyslipidemia, hypertension, obesity, or smoking). Of the 10 251 participants in the entire ACCORD population, 4733 were randomized to two blood pressure intervention arms: an intensive blood pressure arm with a goal of reducing SBP to less than 120 mmHg or a standard blood pressure arm with a goal of reducing SBP to less than 140 mmHg. Blood pressure measurements were available at baseline and 4-month intervals for all participants. After participants sat quietly for 5 min, blood pressures were measured by certified staff. Using the Omron Healthcare HEM-907 (Omron Healthcare, Kyoto, Japan), an automated oscillometric device, three SBP and DBP measurements were taken automatically at 1 min intervals. Blood pressure readings were recorded to the nearest digit,

and the average of the three readings was the blood pressure value reported for a visit [15,16]. Details of the overall design of the ACCORD trial [17], as well as the rationale and treatment protocol for the blood pressure intervention [18], have been reported previously.

This post hoc analysis included those who did and did not participate in the blood pressure-lowering intervention arms of the trial. We included longitudinal data from the standard 4-month visits in the current analysis for all participants. The baseline visit was excluded from the analysis to reduce the effect of rapid reduction in blood pressure at the early phase of the trial. Those who had two or fewer blood pressure measurements were also excluded. We report coefficient of variation of SBP (CV-SBP) and DBP (CV-DBP) in this analysis. Analyses of average real variability (ARV) of SBP and DBP were also conducted and are presented in supplemental tables.

Outcomes

The primary outcome in ACCORD, and this analysis, was a composite of first occurrence of a major cardiovascular event – cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke. Secondary outcomes evaluated were major coronary heart disease (CHD), (a composite of fatal coronary artery disease events, nonfatal MI, or unstable angina) and total stroke. As described previously [17], diagnosis of MI in ACCORD was based on occurrence of a clinical syndrome associated with diagnostic elevation in cardiac enzymes (e.g. troponin I or troponin T to a level indicative of myonecrosis). Total stroke (fatal and nonfatal) was diagnosed by autopsy, MRI, evidence of hemorrhage or brain infarction by CT, or a focal neurologic deficit lasting greater than 24 h [17].

Statistical analysis

Data are expressed as means \pm SD or means and standard deviations for continuous variables or as numbers and percentages for categorical variables. Differences between participants who did and did not develop an event were analyzed using the Wilcoxon test for continuous variables and chi-square test or Fisher's exact test, as appropriate, for categorical variables. We display age-adjusted hazard ratios for CVD outcomes across quartiles of CV-SBP and CV-DBP.

We used a time-dependent approach for assessing the effect of risk factor variability on cardiovascular outcomes that has been described in detail in previous post hoc analyses of several clinical trials [6,19–21]. Briefly, Cox proportional hazards models were fitted to evaluate time-dependent effects of blood pressure measures on CVD outcomes. Hazard ratios for all variables were standardized to a change of 1 SD. Three models for variability were reported. Model 1 adjusted for age only. Model 2 adjusted for age and those covariates reflecting significant baseline differences between those who did and did not develop the event in question. Model 3 adjusted for model 2 covariates and added cumulative mean of blood pressure; this model tests whether variability measures provide additional information beyond overall blood pressure control. We tested the Cox model of SBP and DBP variability metrics and determined that there was no violation of the proportional hazards assumption.

Several subgroup analyses and sensitivity analyses were performed. To test, as previously hypothesized, whether risk of adverse events due to blood pressure variability depends on level of baseline blood pressure, we tested these associations across strata of baseline SBP (>140 , 120 – 139 , <120 mmHg) and baseline DBP (>80 , 70 – 79 , <70 mmHg). To determine whether variability above the mean blood pressure ('elevations') or variability below the mean blood pressure ('dips') conferred risk, we estimated this blood pressure area as trapezoids based on consecutive visits ('variability area') and tested for associations of this area with the cardiovascular outcomes. We examined the role of blood pressure variability by presence or absence of CVD history in development of the primary CVD outcome and of the secondary major CHD outcome. For the primary CVD outcome, we ran several additional sensitivity analyses: we checked for consistency of results with prior blood pressure variability studies [11,12] by examining whether the variability of SBP or DBP below the median (in ACCORD, 126 and 68 mmHg at baseline, respectively) was more strongly associated with risk; we adjusted the effect of variability for use of blood pressure medications to assess the influence of adherence; we adjusted for a modified Charlson Comorbidity Index to assess the effect of baseline comorbidities on risk because of blood pressure variability (point assignment in this index is described in Supplementary Table 1, <http://links.lww.com/HJH/B697>); we used an alternative landmark period approach [2] that captured variability during the ACCORD trial, and reported continuous CV-SBP and CV-DBP hazard ratios for risk of the primary CVD outcome during the long-term observational follow-up study (ACCORDION, 2005–2009) [22], to provide evidence that the associations reported within ACCORD are unlikely to be artifacts of reverse causality; using the added number of events from both ACCORD and ACCORDION we tested effects of blood pressure variability on the primary CVD outcome using more granular subsets of baseline DBP and SBP; we tested the role of variability in a subset of participants with no evidence of atrial fibrillation; we assessed how limiting the time-dependent analysis to those with four or more visits with blood pressure measures, a more restrictive condition, may influence the coefficient of variance result.

All statistical analyses were performed using R software 4.0.2 (<http://www.r-project.com>). A two-sided P less than 0.05 was considered statistically significant.

RESULTS

After exclusion of those with two or fewer eligible visits, 9856 participants were included in this post hoc analysis. During the median 4.7-year ACCORD study period, a primary CVD outcome occurred in 879 individuals, a major CHD event occurred in 985 individuals, and a stroke occurred in 167 individuals. Our analysis included a mean of 12.7 (median of 13) blood pressure visit measures ($SD = 3.8$) and the cohort included a maximum of 21 visit measures per participant. Baseline characteristics among those who did or did not experience adverse events are presented in Table 1. Supplementary Figure 1, <http://links.lww.com/HJH/B696> shows

the mean SBP and DBP during the ACCORD study, depicting the protocol-driven initial drop in blood pressures during the early phase of the trial.

Blood pressure variability and cardiovascular outcomes

To assess the relationship between blood pressure variability and outcomes, we determined age-adjusted hazard ratios across quartiles of CV-SBP and CV-DBP. For the primary CVD outcome and major CHD (Fig. 1), but not stroke, we observed a pattern of increasing risk with increasing quartiles of both CV-SBP and CV-DBP (P for trend <0.001 for the primary CVD outcome and major CHD).

After adjustment for age, variability of both SBP and DBP (as continuous variables) were significantly associated with the primary CVD outcome (Table 2) (CV-SBP: hazard ratio = 1.13; CV-DBP: hazard ratio = 1.19, $P < 0.001$ for both). This association remained significant after adjusting for baseline covariates that differed between those who did and did not develop a primary outcome event (model 2), as well as cumulative mean blood pressure (model 3: CV-SBP, hazard ratio = 1.07, $P = 0.002$; CV-DBP, hazard ratio = 1.13, $P < 0.001$). A very similar pattern was observed in the analysis for major CHD (model 3: CV-SBP hazard ratio = 1.07, $P = 0.001$; CV-DBP hazard ratio = 1.13, $P < 0.001$). In contrast, neither CV-SBP or CV-DBP were associated with risk of total stroke in adjusted models (Table 2). These major findings were consistent in the analyses using ARV-SBP and ARV-DBP (Supplementary Table 2, <http://links.lww.com/HJH/B697>). There were no significant differences by primary CVD event status for use of statins, sulfonylureas, or meglitinides. Adjustment for total number of antihypertensive medications, or use of beta-blockers or loop diuretics that differed between event groups, did not appreciably influence the hazard ratios for variability. This was also true for adjustment for biguanides and platelet aggregation inhibitors. Associations between baseline covariates and SBP variability (CV-SBP) are presented in Supplementary Table 3, <http://links.lww.com/HJH/B697>.

In a sensitivity analysis using blood pressure variability during ACCORD, we tested for associations with primary CVD outcomes ($n = 671$) that developed during the subsequent ACCORDION follow-up study (2005–2009). In this landmark period approach, both SBP and DBP variability were again associated with risk of the primary CVD outcome in a fully adjusted model that included cumulative mean blood pressure (CV-SBP: hazard ratio = 1.17; CV-DBP: hazard ratio = 1.15, $P < 0.001$ for both).

Blood pressure variability by strata of baseline blood pressure

To examine whether blood pressure levels might modify effects of blood pressure variability, we first tested for, and found, an interaction between baseline SBP and DBP blood pressure (above vs. below the median) and blood pressure variability for the primary CVD outcome (CV-SBP P for interaction = 0.0013; CV-DBP P -for-interaction = 0.021). We noted very similar contrasts in effects of blood pressure variability when we used median 'on-study' blood pressure

TABLE 1. Baseline characteristics in the Action to Control Cardiovascular Risk in Diabetes by primary outcome, major coronary heart disease, and total stroke

	Primary CVD outcome ^a			Major CHD ^b			Total stroke ^c		
	No (n = 8902)	Yes (n = 879)	P value	No (n = 8722)	Yes (n = 985)	P value	No (n = 9689)	Yes (n = 167)	P value
Age (years)	62.6 (6.5)	64.6 (7.1)	<0.001	62.6 (6.5)	63.9 (7.2)	<0.001	62.7 (6.6)	64.8 (7.0)	<0.001
Intensive BP treatment (n, %)	2083 (23.4)	175 (19.9)	0.02	2033 (23.3)	225 (21.2)	0.14	2235 (23.1)	31 (18.6)	0.20
Female (n, %)	3494 (39.2)	265 (30.1)	<0.001	3430 (39.3)	329 (31.1)	<0.001	3720 (38.4)	58 (34.7)	0.38
Race (n, %)			0.02			<0.001			0.21
Black	1693 (19.0)	151 (17.2)		1686 (19.3)	158 (14.9)		1813 (18.7)	40 (24.0)	
Hispanic	639 (7.2)	54 (6.1)		626 (7.2)	67 (6.3)		687 (7.1)	12 (7.2)	
White	5523 (62.0)	591 (67.2)		5378 (61.7)	736 (69.5)		6070 (62.6)	102 (61.1)	
Other	1047 (11.8)	83 (9.4)		1032 (11.2)	98 (9.3)		1120 (11.6)	13 (7.8)	
Diabetes duration (years)	10.6 (7.5)	12.5 (8.4)	<0.001	10.6 (7.5)	12.1 (8.3)	<0.001	10.8 (7.6)	12.8 (8.1)	0.001
CVD history (n, %)	2914 (32.7)	479 (54.5)	<0.001	2771 (31.8)	622 (58.7)	<0.001	3361 (34.7)	78 (46.7)	0.002
Smoker ^d (n, %)	3980 (51.2)	437 (57.7)	0.001	3887 (51.0)	530 (57.8)	<0.001	4368 (51.7)	79 (54.5)	0.56
BMI (kg/m ²)	32.3 (5.4)	32.0 (5.4)	0.001	32.2 (5.4)	32.4 (5.3)	0.33	32.3 (5.4)	31.2 (5.4)	0.01
DBP (mmHg)	75 (10)	73 (11)	<0.001	75 (10.5)	73 (11.4)	<0.001	75 (10)	75 (11)	0.95
SBP (mmHg)	136 (17)	138 (18)	0.005	136 (16.9)	137 (17.6)	0.24	136 (17)	141 (19)	<0.001
HDL cholesterol (mg/dl)	42 (11)	40 (12.1)	<0.001	42 (11.6)	40 (11.4)	<0.001	42 (11)	41.5 (13)	0.66
LDL cholesterol (mg/dl)	105 (34)	106 (35)	0.20	105 (33)	105 (34)	0.93	105 (34)	108 (35)	0.19
Total cholesterol (mg/dl)	183 (42)	184 (44)	0.44	183 (42)	183 (42)	0.70	183 (42)	188 (49)	0.12
Triglycerides (mg/dl)	189 (150)	196 (134)	0.21	189 (150)	199 (136)	0.04	190 (149)	197 (149)	0.54
HbA1c (%)	8.3 (1.0)	8.5 (1.1)	<0.001	8.3 (1.1)	8.4 (1.1)	0.006	8.3 (1.0)	8.8 (1.3)	<0.001
Fasting glucose (mg/dl)	174 (56)	179 (58)	0.02	175 (56)	176 (57)	0.40	175 (55.8)	187 (64.8)	0.09
Albumin-to-creatinine ratio (mg/g)	85.4 (312.1)	197.3 (554.1)	<0.001	86.2 (315.0)	173.1 (510.4)	<0.001	95.2 (353.0)	239.4 (565.7)	<0.001
eGFR (ml/min per 1.73 m ²)	91.5 (27.2)	86.9 (27.6)	<0.001	91.6 (27.2)	87.5 (26.9)	<0.001	91.1 (27.2)	87.5 (28.0)	0.09
Statin [n (%)]	5566 (62.5)	515 (58.6)	0.29	5411 (62.0)	609 (61.8)	<0.001	6072 (62.7)	89 (53.3)	0.46
Sulfonylurea [n (%)]	4080 (45.8)	377 (42.9)	0.46	4004 (45.9)	412 (41.8)	0.82	4440 (45.8)	75 (44.9)	0.31
Total antihypertensives	1.68 (1.20)	1.97 (1.21)	<0.001	1.70 (1.20)	1.92 (1.13)	0.01	1.70 (1.20)	1.89 (1.16)	0.06
Beta-blocker [n (%)]	6252 (70.2)	457 (52.0)	<0.001	6205 (71.1)	481 (48.8)	<0.001	6685 (69.0)	100 (59.8)	0.50
Loop diuretic [n (%)]	8023 (90.1)	672 (76.5)	<0.001	7885 (90.4)	747 (75.8)	<0.001	8676 (89.5)	128 (76.6)	0.06

Data are means, SD or n (%). CHD, coronary heart disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate from four variable Modification of Diet in Renal Disease Study (MDRD) equation; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

^aPrimary composite CVD outcome is first occurrence of major cardiovascular event – cardiovascular death, nonfatal MI, or nonfatal stroke.

^bMajor CHD is a composite of fatal coronary artery disease events, nonfatal MI, or unstable angina.

^cTotal stroke includes both fatal and nonfatal stroke events.

^dSmoker: smoked more than 100 cigarettes during lifetime.

(CV-SBP *P*-for-interaction = 0.0008; CV-DBP *P*-for-interaction = 0.046).

We then examined effects of blood pressure variability across clinically relevant baseline blood pressure ranges. The CV-SBP was significantly associated with the primary CVD outcome in the less than 120 and more than 140 mmHg SBP strata (hazard ratios 1.24 and 1.15, *P* = 0.02 and *P* = 0.01, respectively), but not in the 120–139 mmHg SBP strata (hazard ratio = 1.06, *P* = 0.07) (Table 3). Similarly, a significant association of CV-DBP with the primary CVD outcome was found in the less than 70 mmHg and greater than 80 mmHg baseline DBP strata (respectively, hazard ratios 1.25 and 1.23, *P* = 0.002 and *P* < 0.001) but not in the 70–79 mmHg baseline DBP stratum (hazard ratio = 1.12, *P* = 0.09). Results for the major CHD outcome by strata of baseline SBP and DBP were very similar (Table 3). In contrast, the CV-SBP or CV-DBP were not associated with risk of total stroke in any of the baseline blood pressure strata (Table 3). The patterns of risk by strata described for the primary CVD outcome and major CHD were consistent in the analysis of ARV-SBP and ARV-DBP (Supplementary Table 4, <http://links.lww.com/HJH/B697>).

We also combined ACCORD and ACCORDION follow-up periods to examine the effect of baseline blood pressure categories over an extended time period. Hazard ratios for

the primary CVD outcome in those with DBP less than 70 mmHg (*n* = 596; CV-DBP hazard ratio = 1.22, *P* < 0.001) and DBP greater than 80 mmHg (*n* = 438; CV-DBP hazard ratio = 1.15, *P* = 0.002) were similar to effects observed in our primary ACCORD analysis. In this combined analysis, the association we noted in the analysis limited to ACCORD was attenuated in those with high baseline SBP. However, this analysis, which had greater power to examine a broader range of blood pressure, revealed that even more extreme low levels of baseline SBP exacerbated the relationship between CV-SBP and the primary CVD outcome (e.g. for baseline SBP < 110 mmHg, model 3 CV-SBP hazard ratio = 1.46, *P* < 0.001) (Supplementary Table 5, <http://links.lww.com/HJH/B697>).

To explore the hypothesis that effects of variability may be due in part to reduced coronary perfusion during diastole, we examined whether prior CVD history influenced CV-DBP associations, and whether this was further strengthened by low baseline blood pressure (defined as <120 mmHg SBP and <70 mmHg DBP) (Table 4). Interestingly, associations of CV-DBP with CVD risk were generally weaker in those without CVD history, even in those with low baseline blood pressures. Conversely, CV-DBP was strongly associated with risk of the primary CVD outcome or a major CHD in those with CVD history, and the

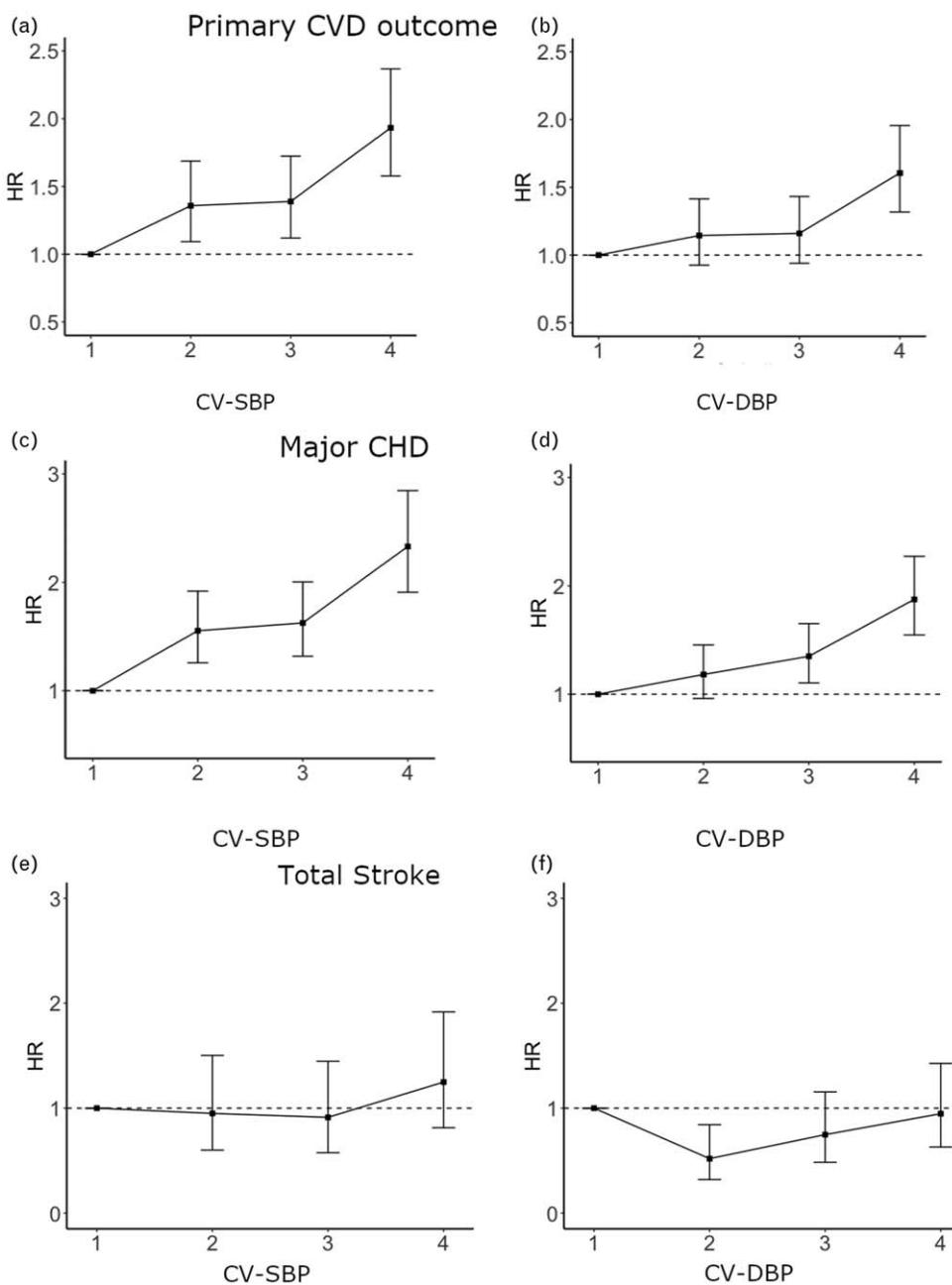


FIGURE 1 Age-adjusted hazard ratio estimates for risk of primary cardiovascular disease outcome, major coronary heart disease, and total stroke by quartiles of blood pressure variability in Action to Control Cardiovascular Risk in Diabetes. Panels a and b show quartiles of CV-SBP and CV-DBP for the primary CVD outcome, respectively. Panels c and d show quartiles of CV-SBP and CV-DBP for major CHD, respectively. Panels e and f show quartiles of CV-SBP and CV-DBP for total stroke, respectively. Results of trend tests for panels a, b, c, and d are all P less than 0.001.

association was heightened further in those with low baseline blood pressures (Table 4). The strongest association was observed between CV-DBP and major CHD in those with CVD history and low baseline blood pressure (hazard ratio = 1.40 in the fully adjusted model, $P < 0.0001$).

Sensitivity analyses

If decreased coronary perfusion was a contributor to CVD risk conveyed by blood pressure variability, 'dips' in blood pressure would be expected to be more harmful. We, therefore, calculated 'variability area' above or below participants' mean blood pressure preceding an event. For SBP,

dips in blood pressure were associated with risk of the primary CVD outcome, major CHD, and total stroke ($P < 0.001$, $P < 0.001$, and $P = 0.022$, respectively) but elevations in blood pressure were not ($P > 0.6$ for all). Dips in DBP were also related to the primary CVD outcome, major CHD, and total stroke ($P < 0.001$ for all) but we did not observe an association with elevations in DBP ($P > 0.4$ for all).

To test whether adherence to blood pressure medication might account for the relationship between blood pressure variability and CVD, we also included in fully adjusted models, the reported adherence with these medications during the ACCORD study. This adjustment had little effect

TABLE 2. Hazard ratios for the association of blood pressure variability with cardiovascular outcomes

	Model-1 Age adjustment		Model-2 Multivariate adjustment		Model-3 Model 2 with cumulative mean BP	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Primary CVD outcome (n = 879)						
CV-SBP	1.13 (1.09–1.17)	<0.001	1.08 (1.04–1.13)	<0.001	1.07 (1.03–1.11)	0.002
CV-DBP	1.19 (1.12–1.25)	<0.001	1.13 (1.05–1.20)	<0.001	1.13 (1.05–1.20)	<0.001
Major CHD (n = 985)						
CV-SBP	1.14 (1.11–1.18)	<0.001	1.08 (1.04–1.12)	<0.001	1.07 (1.03–1.12)	0.001
CV-DBP	1.22 (1.16–1.28)	<0.001	1.13 (1.06–1.20)	<0.001	1.13 (1.06–1.20)	<0.001
Total stroke (n = 167)						
CV-SBP	1.11 (1.01–1.21)	0.03	0.97 (0.85–1.10)	0.63	—	—
CV-DBP	1.05 (0.92–1.21)	0.46	1.00 (0.87–1.16)	0.99	—	—

Hazard ratios (HR), 95% confidence interval (95% CI), and P values estimated by Cox proportional hazards model. Blood pressure variables were adjusted for age (model 1), baseline factors from Table 1 that differed significantly between those who did and did not develop each distinct event (model 2) and additionally for cumulative mean of blood pressure excluding the baseline BP. Model 3 was not computed if model 2 HRs were not statistically significant. P values less than 0.05 (bold font) are considered significant. The primary outcome is a composite of CVD death, nonfatal MI and nonfatal stroke. Major CHD includes fatal coronary artery disease events, nonfatal MI, and unstable angina. CV, coefficient of variation.

on the associations of blood pressure variability with the primary CVD outcome. Similarly, when added to model 3, adjustment for various baseline comorbidities in a modified comorbidity index also had a negligible effect.

When restricting the ACCORD population to those participants who had a normal echocardiogram, and thus no evidence of atrial fibrillation or flutter, a primary CVD outcome occurred in 694 participants. Even in this subset

free of atrial fibrillation, CV-SBP and CV-DBP were significant predictors of risk of the primary CVD outcome (model 3, CV-SBP: hazard ratio = 1.08, $P < 0.001$; CV-DBP: hazard ratio = 1.12, $P = 0.002$). Finally, in a subset of the cohort that had four or more office visits of blood pressure, the significant associations we reported held (age-adjusted CV-SBP: hazard ratio = 1.14, $P < 0.001$; CV-DBP: hazard ratio = 1.25, $P < 0.001$).

TABLE 3. Hazard ratios for the association of blood pressure variability with cardiovascular outcomes by baseline blood pressure levels

	No. of events	Model 1 Age adjustment		Model 2 Multivariate adjustment		Model 3 Model 2 with cumulative mean BP	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Primary CVD outcome							
CV-SBP							
SBP >140 mmHg	n = 355	1.09 (0.99–1.19)	0.07	1.14 (1.02–1.28)	0.02	1.15 (1.02–1.29)	0.02
SBP 120–139 mmHg	n = 361	1.12 (1.07–1.16)	<0.001	1.07 (1.01–1.12)	0.01	1.06 (0.99–1.12)	0.07
SBP <120 mmHg	n = 134	1.38 (1.21–1.57)	<0.001	1.25 (1.06–1.48)	0.008	1.24 (1.05–1.46)	0.01
CV-DBP							
DBP >80 mmHg	n = 230	1.20 (1.07–1.35)	0.002	1.19 (1.05–1.34)	0.005	1.23 (1.08–1.40)	0.002
DBP 70–79 mmHg	n = 280	1.21 (1.10–1.33)	<0.001	1.10 (0.97–1.25)	0.13	1.12 (0.98–1.27)	0.09
DBP <70 mmHg	n = 339	1.32 (1.22–1.43)	<0.001	1.25 (1.15–1.36)	<0.001	1.25 (1.15–1.36)	<0.001
Major CHD							
CV-SBP							
SBP >140 mmHg	n = 382	1.15 (1.06–1.25)	0.001	1.12 (1.01–1.25)	0.04	1.13 (1.02–1.26)	0.03
SBP 120–139 mmHg	n = 425	1.12 (1.08–1.15)	<0.001	1.05 (0.99–1.11)	0.06	1.05 (0.99–1.11)	0.08
SBP <120 mmHg	n = 150	1.39 (1.23–1.57)	<0.001	1.22 (1.04–1.43)	0.01	1.21 (1.03–1.42)	0.02
CV-DBP							
DBP >80 mmHg	n = 236	1.26 (1.13–1.40)	<0.001	1.21 (1.08–1.34)	<0.001	1.25 (1.11–1.41)	<0.001
DBP 70–79 mmHg	n = 326	1.18 (1.09–1.29)	<0.001	1.11 (0.99–1.24)	0.06	1.10 (0.98–1.23)	0.11
DBP <70 mmHg	n = 387	1.32 (1.22–1.42)	<0.001	1.23 (1.12–1.35)	<0.001	1.23 (1.12–1.35)	<0.001
Total stroke							
CV-SBP							
SBP >140 mmHg	n = 82	0.98 (0.82–1.18)	0.86	0.94 (0.81–1.11)	0.48	0.99 (0.85–1.18)	0.99
SBP 120–139 mmHg	n = 61	1.09 (0.99–1.19)	0.07	1.08 (0.97–1.20)	0.18	1.02 (0.90–1.15)	0.78
SBP <120 mmHg	n = 24	1.32 (0.98–1.76)	0.07	1.26 (0.95–1.68)	0.11	1.05 (0.75–1.48)	0.75
CV-DBP							
DBP >80 mmHg	n = 57	1.11 (0.95–1.30)	0.18	1.11 (0.94–1.29)	0.21	1.11 (0.96–1.29)	0.17
DBP 70–79 mmHg	n = 48	1.02 (0.79–1.32)	0.86	0.95 (0.71–1.28)	0.76	1.01 (0.76–1.33)	0.93
DBP <70 mmHg	n = 57	1.13 (0.90–1.40)	0.27	1.09 (0.87–1.37)	0.46	1.12 (0.91–1.36)	0.49

Hazard ratios (HR), 95% confidence interval (95% CI), 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 less than 0.05 (bold font) are considered significant. CHD, coronary heart disease; CVD, cardiovascular disease; CV, coefficient of variation.

TABLE 4. Hazard ratios for the association of DBP variability with the primary outcome and major coronary heart disease in those with cardiovascular disease history at baseline, those with cardiovascular disease history and low baseline blood pressure (<120 mmHg SBP and <70 mmHg DBP), and those without cardiovascular disease history at baseline in each category

	Model 1 Age adjustment		Model 2 Multivariate adjustment		Model 3 Model 2 with cumulative mean BP	
Primary CVD outcome						
With CVD history						
All (n=479)	1.20 (1.12–1.28)	<0.0001	1.20 (1.11–1.30)	<0.0001	1.21 (1.12–1.30)	<0.0001
Low BP (n=73)	1.33 (1.15–1.53)	0.0001	1.33 (1.15–1.53)	0.0001	1.29 (1.13–1.48)	0.0002
No CVD history						
All (n=400)	1.07 (0.98–1.18)	0.10	1.09 (0.98–1.20)	0.11	1.09 (0.98–1.20)	0.10
Low BP (n=36)	1.22 (0.93–1.62)	0.14	1.25 (0.95–1.64)	0.12	1.19 (0.90–1.57)	0.22
Major CHD						
With CVD history						
All (n=572)	1.22 (1.14–1.29)	<0.0001	1.22 (1.14–1.30)	<0.0001	1.22 (1.13–1.31)	<0.0001
Low BP (n=86)	1.42 (1.26–1.59)	<0.0001	1.40 (1.22–1.60)	<0.0001	1.40 (1.22–1.61)	<0.0001
No CVD history						
All (n=413)	1.17 (1.07–1.27)	0.0004	1.14 (1.03–1.25)	0.01	1.14 (1.03–1.25)	0.01
Low BP (n=37)	1.06 (0.79–1.43)	0.69	1.04 (0.77–1.40)	0.79	1.02 (0.75–1.38)	0.89

Hazard ratios (HR), 95% confidence interval (95% CI), and P values estimated by Cox proportional hazards model for coefficient of variation of DBP. 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 BP. P values less than 0.05 (bold font) are considered significant. CHD, coronary heart disease; CVD, cardiovascular disease.

DISCUSSION

In this comprehensive post hoc evaluation in the ACCORD trial, blood pressure variability was significantly associated with risk for a spectrum of cardiovascular events, with an especially prominent relationship with coronary heart disease events. Consistent with reports from other large cohort studies [1,2,5], the effect was robust to adjustment for baseline risk factors and cumulative mean blood pressure. Importantly, our analysis of SBP and DBP variability by levels of baseline blood pressure provided novel evidence of more robust effects of blood pressure variability at low baseline blood pressures. These associations were independent of baseline comorbidities and blood pressure medication adherence during the trial. The significant relationships also persisted in a sensitivity analysis including long-term observational ACCORDION follow-up, reducing the likelihood that these findings are because of reverse causality.

The extent to which baseline or on-study blood pressure level modifies the association between blood pressure variability and adverse outcomes has been scrutinized in some recent studies using cohort-specific threshold values. In the VALUE trial, Mehllum *et al.* [11] report a significantly stronger association between SBP variability and cardiovascular risk in participants with treatment SBP below the median, though the same test was not performed for DBP. Moreover, in the PROSPER trial, DBP variability was more strongly associated with vascular mortality among those with SBP below the median [12]. However, these trials did not address whether the relationship between blood pressure variability and CVD risk differs in clinically defined blood pressure categories, nor explore potential mechanisms underlying these findings. In our prior analysis using ACCORD data, we observed a stepwise increase in risk of heart failure for both SBP and DBP variability in those with lower SBP and DBP levels [6]. The present finding that variability in ACCORD participants with lower DBP or SBP was associated with elevated risk of the primary CVD outcome and CHD events compared with

those in the higher but normal blood pressure stratum provides novel evidence for the dependence of this association on absolute blood pressure level categories.

Insofar as risk from increased blood pressure variability was also elevated in participants with high SBP and DBP, our study appears to be the first to report a potential U-shaped pattern for variability effects by baseline blood pressure level. As this may have implications for both understanding mechanisms of blood pressure variability risk and treatment approaches, these results should be confirmed in other populations. However, in a recent investigation by Ferreira *et al.* [23] of patients in the Eplerenone Post-Acute Myocardial Infarction with Heart Failure Efficacy and Survival Study (EPHESUS), both low and high levels of blood pressure variability appeared to be linked to increased risk of cardiovascular mortality. These data, along with our current and prior findings [6] of a blood pressure level and blood pressure variability interaction, suggest that the relationship of visit-to-visit blood pressure variability with cardiovascular risk is more complex than previously reported and possibly nonlinear [23,24]. Developing clinical strategies for evaluating blood pressure variability, if proven to be causally linked with CVD, will depend on a clearer understanding of these more nuanced risk patterns.

Our finding that dips, rather than elevations, in SBP and DBP appear to be driving the association between variability and CVD is consistent with patterns observed previously in two clinical trials. In the STABILITY trial, dips in blood pressure appeared to be driving the effect on adverse cardiovascular outcomes. Also, DBP variability in the STABILITY trial was most potent in those in the lowest tertile of DBP [13]. Our findings also echo data on blood pressure instability in the Health, Aging, and Body Composition Study, where episodes of decreased DBP were associated with a 30% increase in cardiovascular mortality [25].

Reductions in aortic distensibility [7], increased arterial stiffness [26], autonomic dysfunction [27], impaired endothelial function [9], and aggravation of atherosclerosis [28,29] have been posited as potential explanations for

increased cardiovascular risk in those with increased blood pressure variability. The enhancing effect of low blood pressure levels on this association suggests other mechanisms. One possibility is that blood pressure variability – particularly transient decreases in DBP – may put cardiac tissue at increased risk of coronary hypoperfusion [13] and exacerbate myocardial ischemia. Notably, in the Atherosclerosis Risk in Communities (ARIC) Study, McEvoy *et al.* [14] reported that low DBP in healthy individuals was associated with damage to myocardium as estimated by increased levels of high-sensitivity cardiac troponin-T. In a recent investigation from the SPRINT group, DBP variability was specifically linked to potential hypoperfusion-related adverse events, including acute kidney injury [30]. This hypoperfusion hypothesis is further supported by the fact that in the present study, the effects of blood pressure variability were greatest at low levels of blood pressure; the risk was enhanced in those with low DBP and prior CVD – consistent with the key role of coronary artery anatomic and/or functional narrowing in coronary hypoperfusion [31]; low DBP was associated with cardiac events but not with risk of stroke in the ARIC study [14]; and blood pressure variability showed no significant interaction with blood pressure level for stroke events in the current analysis of ACCORD.

Prior investigators have speculated that differences between relationships of variability with coronary outcomes versus stroke might be attributable to chance, inconsistent follow-up duration, different covariates included in the model [32], or uneven histories of myocardial infarction [11]. Alternatively, these differences may in fact reflect physiologic distinctions in these two vascular beds. If the mechanisms linking blood pressure variability with risk of stroke or cardiac outcomes were similar, we would expect low blood pressure levels to also exacerbate the relationship between variability and stroke. The lack of an association with stroke in the current ACCORD data suggests that hypoperfusion may be particularly relevant for cardiac outcomes. This is not surprising as cerebral tissue may be uniquely protected from transient declines in blood pressure [33] via autoregulatory mechanisms that maintain cerebral blood flow [34,35], even in the setting of low blood pressure levels.

The current study has several strengths. In addition to careful adjudication of outcomes and frequent blood pressure measurements, the ACCORD trial involved detailed collection of data on comorbidities and medication use. Neither of these potential confounders influenced the relationship between blood pressure variability and CVD outcomes. The large sample size allowed testing of associations between blood pressure variability and CVD outcomes across standard blood pressure categories compared with cohort-dependent thresholds in prior studies. In addition, patterns we reported for coefficient of variation were confirmed in analysis using the ARV metric. Use of time-dependent estimates in Cox modeling as our major analysis approach is another important advantage of our statistical design; this method permits inclusion of blood pressure measures up to the time of the event in question and has been deemed an effective approach in visit-to-visit variability analysis [36]. Moreover, this time-dependent approach

avoids some pitfalls that have been identified in prior blood pressure variability analysis [37], including conditioning on the future.

One limitation of the current project is that the ACCORD cohort enrolled persons with advanced T2D and high CVD risk, so we do not know if these findings are generalizable to the broad diabetes population. Despite detailed collection of comorbidities, the information on certain serious conditions, such as cancer was not collected, and therefore not included in a modified comorbidity index. As terminal digit rounding was employed in the collection of blood pressure measures in ACCORD, this is another potential limitation, as this practice can in some cases misclassify the prevalence of hypertension in a study sample [38]; however, preferred use of an automatic blood pressure device as in ACCORD mitigates the influence [39] of this practice. Reverse causality has been noted as a potential bias in variability studies: for example, arterial stiffness and target organ damage presage cardiovascular complications but can also lead to increased blood pressure variability [40]. However, we found similar results using the landmark approach in predicting observational ACCORDION events, which signifies that reverse causality is unlikely to explain our findings. Although there were several advantages to including ACCORDION data to confirm key findings in ACCORD, we did not incorporate ACCORDION outcomes in the main analysis because of small number of additional blood pressure measurements with substantially longer between-visit intervals. Furthermore, the trial-defined CVD risk factor intervention was discontinued during the ACCORDION follow-up period. As the ACCORD participants were highly adherent to trial medications, our ability to test nuances in medication adherence in our variability model was somewhat limited by this relatively homogenous level of adherence.

In conclusion, our findings provide further evidence of a link between visit-to-visit variability of both SBP and DBP and cardiovascular risk. Our demonstration that the effect of blood pressure variability was heightened in those with low blood pressure, particularly in those with prior CVD, and was related to dips in blood pressure provides support for the hypothesis that blood pressure variability could contribute to cardiac injury by exacerbating coronary hypoperfusion. These data appear to support cautions raised by both the American Diabetes Association [41] and the European Society of Hypertension [42] concerning increased risk of cardiovascular events in some individuals undergoing more ambitious blood pressure-lowering targets (i.e. SBP < 120 mmHg), suggesting that teasing out the role of blood pressure variability in this excess risk may facilitate a more personalized blood pressure target. Our finding that blood pressure variability may also be associated with CVD risk at higher levels of blood pressure is novel and needs confirmation in additional cohorts. These results contribute to increased understanding of the potential relevance of blood pressure variability in CVD risk and may inform future recommendations for achieving optimal blood pressure control.

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Conflicts of interest

There are no conflicts of interest.

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