ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 2959–2967
Published online 25 May 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13385

ORIGINAL RESEARCH ARTICLE

Long-term variability of blood pressure and incidence of heart failure among individuals with Type 2 diabetes

Arnaud D. Kaze[1], Prasanna Santhanam[2], Sebhat Erqou[3], Alain G. Bertoni[4], Rexford S. Ahima[2] and Justin B. Echouffo-Tcheugui[2]*

[1]*Department of Medicine, University of Maryland Medical Center, Baltimore, MD, USA;* [2]*Department of Medicine, Division of Endocrinology, Diabetes, and Metabolism, Johns Hopkins School of Medicine, Baltimore, MD 21224, USA;* [3]*Department of Medicine, Providence VA Medical Center and Alpert Medical School of Brown University, Providence, RI, USA; and* [4]*Department of Epidemiology and Prevention, Wake Forest University School of Medicine, Winston-Salem, NC, USA*

Abstract

Aims Data on the association of long-term variability of blood pressure (BP) with incident heart failure (HF) in individuals with Type 2 diabetes are scarce. We evaluated this association in a large community-based sample of adults with Type 2 diabetes.

Methods and results A total of 4200 participants with Type 2 diabetes who had available BP measurements at four visits (baseline and 12, 24, and 36 months) in the Look AHEAD (Action for Health in Diabetes) study were included. Variability of systolic BP (SBP) and diastolic BP (DBP) across the four visits was assessed using four metrics. Participants free of HF during the first 36 months were followed for HF events. Cox regression was used to generate hazard ratios (HRs) and 95% confidence intervals (CIs) for HF. Of the 4200 participants, the average age was 59 years [standard deviation (SD): 6.8]; 58.5% were women. Over a median follow-up of 6.7 years, 129 developed HF events. After adjusting for relevant confounders, the HR of incident HF for the highest vs. lowest quartile of SD of SBP was 1.77 (95% CI 1.01–3.09); the HR for the highest (vs. lowest) quartile of variability independent of the mean of SBP was 1.29 (95% CI 0.78–2.14). The adjusted HR for participants in the highest (compared with the lowest) quartile of SD of DBP was 1.61 (95% CI 1.01–2.59), and the adjusted HR for variability independent of the mean of DBP was 1.65 (95% CI 1.03–2.65).

Conclusions A greater variability in SBP and DBP is independently associated with greater risk of incident HF in individuals with Type 2 diabetes.

Keywords Type 2 diabetes; Blood pressure; Epidemiology; Heart failure

Received: 23 November 2020; Revised: 8 April 2021; Accepted: 12 April 2021
**Correspondence to: Justin B. Echouffo-Tcheugui, Department of Medicine, Division of Endocrinology, Diabetes, and Metabolism, Johns Hopkins School of Medicine, Baltimore, MD 21224, USA. Tel: +1-410-550-3054; Fax: +1-410-550-9751. Email: jechouf1@jhmi.edu*

Introduction

Type 2 diabetes and hypertension are common in the USA and often cluster together.[1,2] Among individuals with Type 2 diabetes, high blood pressure (BP) is a major modifiable risk factor for cardiovascular disease (CVD) including heart failure (HF).[3] Accordingly, BP reduction is widely considered a priority in patients with hypertension and diabetes.[3] Extant evidence suggests that visit-to-visit variability in systolic (SBP) and diastolic BP (DBP) is independently associated with higher risks of atherosclerotic CVD events[4–11]; however, most studies have not explored the relation with incident HF, especially among people with Type 2 diabetes.[4–12] Type 2 diabetes is independently associated with an excess risk of HF.[13–15] Moreover, a greater BP variability may be more common in diabetes.[16] Factors contributing to a greater BP variability include autonomic dysfunction and arterial stiffness,[16,17] both of which are a hallmark of Type 2 diabetes,[16,18,19] yet there is a paucity of epidemiological data on the relation of long-term variability of BP measures with incident HF in individuals with Type 2 diabetes.

We evaluated the associations of long-term variability in SBP and DBP with incident HF events, using data from the Look AHEAD (Action for Health in Diabetes)—a large and diverse cohort study of adults with Type 2 diabetes in whom serial annual measurements of BP were obtained at the

outset. We hypothesized that greater BP variability would be associated with a higher risk of incident HF.

Methods

Study design

The data used for the analyses are publicly available through the NIDDK Central Repository. We performed an analysis of the prospective data from prospective cohort analysis of the Look AHEAD, a clinical trial in which participants were enrolled from August 2001 to April 2004 across 16 locations in the USA and randomly assigned to receive either an intensive lifestyle intervention or diabetes support and education. Look AHEAD included 5145 overweight or obese individuals aged 45–76 years at enrolment with a self-reported diagnosis of Type 2 diabetes confirmed via measured plasma glucose, use of anti-diabetic medication, or a physician's documentation. Details about the trial's design including a description of the rationale and protocol have been published elsewhere.[20,21]

The current investigation included participants with full data on BP measurements at baseline and 12, 24, and 36 month visits. We excluded participants who had incident HF events or died before the 36 month visit (n = 701) and those with consent restrictions (n = 244). A total of 4200 participants were included in our main analyses.

The study protocol was approved by the institutional review board at each clinical centre, and each participant provided an informed consent.

Assessment of blood pressure variability

At each study visit and centre, BP was measured twice from the right arm by trained staff with participants in a seated position using an automated device (Dinamap Monitor Pro 100, Chicago, IL). The first BP was obtained after the participant had rested for 5 min, and the second BP was measured after an additional 30 s. The average of the two readings was used as the examination BP.[20,21]

The long-term variability of SBP and DBP variability was evaluated using four metrics: (i) the intra-individual standard deviation (SD) across the four visits; (ii) the variability independent of the mean (VIM) calculated as 100 * SD/mean$^{\beta}$, where β is the regression coefficient based on the natural logarithm of SD as a function of the natural logarithm of the respective average BP measure; (iii) the coefficient of variation; and (iv) the average successive variability defined as the average absolute difference between consecutive values. We included several measures to attempt to capture the full spectrum of variability.

Ascertainment of incident heart failure events

Participants were followed from the 36 month visit until the occurrence of an HF event, death, or end of the study. Annual visits and semi-annual phone calls were conducted, and incident HF events were ascertained by an adjudication committee that reviewed relevant health records. Cases were classified into definite or possible acute decompensated HF, chronic stable HF, HF unlikely, or unclassifiable. Incident HF events referred to the first hospitalization for definite or possible acute HF exacerbation.[22] Further details of the criteria used for the HF adjudication are displayed in the Supporting Information.

Covariates

Potential confounders included age, sex, race/ethnicity, randomization arm, duration of diabetes, history of atherosclerotic CVD (defined as history of prior myocardial infarction or stroke), current smoking, alcohol use, body mass index (BMI), use of BP-lowering medication, and anti-diabetic medications during follow-up and estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[23] Additionally, we used data obtained through the fourth visit to calculate the average ratio of total to high-density lipoprotein cholesterol, average glycosylated haemoglobin, and average SBP and DBP.[20,21]

Statistical analyses

Participants were compared across quartiles of the intra-individual SD of SBP and DBP using the analysis of variance or Kruskal–Wallis test for continuous variables and the χ^2 test for categorical variables. Cox proportional hazards regression was used to compute adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for incident HF. For both SBP and DBP measures, each variability metric was modelled as a continuous variable and quartiles with the bottom quartile used as reference.

Incidence rates per 1000 person-years were calculated as the ratio of the cumulative number of HF events to the at-risk person-years. The person-years were computed from the fourth visit to the earliest of HF event, death, or 14 September 2012 (date of trial's termination).

Regression models to examine the association of BP variability and outcomes were constructed sequentially as follows: (i) first model adjusting for age, sex, race/ethnicity, and randomization arm (Model 1); (ii) second model adjusting for variables in Model 1 with further adjustment for BMI, current smoking, alcohol drinking, use of antihypertensive medication during follow-up, average ratio of total to

high-density lipoprotein cholesterol, estimated glomerular filtration rate, duration of diabetes, average glycosylated haemoglobin, and history of CVD (Model 2); and (iii) third model (except for VIM) including Model 2 variables plus average SBP when assessing SBP variability or average DBP when assessing DBP variability (Model 3).

We also tested the robustness of our analyses by first restricting our sample to individuals without CVD at baseline and then performing additional adjustments for the number of antihypertensive medications, use of angiotensin-converting enzyme inhibitors, use angiotensin receptor blockers, use of beta-blocker, and use of insulin, as these classes of medications can affect cardiac remodelling.[24]

A two-sided *P*-value of less than 0.05 was deemed statistically significant, and all analyses were performed using STATA 14.2 (StataCorp, College Station, TX).

Results

Characteristics of study participants

The characteristics of study participants by quartiles of SD of SBP are displayed in *Table 1*. Compared with those in lower quartiles, participants in the highest quartile were older and more frequently women. They also had longer duration of diabetes, lower eGFR, and higher BMI and SBP. Additionally, participants in the highest quartile of SD of DBP were more frequently Hispanic and had lower eGFR, as well as higher BMI, SBP, and DBP measures (Supporting Information, *Table S1*).

Long-term variability of blood pressure and incident heart failure

Over a median follow-up period of 6.7 years (inter-quartile range 6.0–7.4), 129 participants developed incident HF events [incidence rate per 1000 person-years: 4.8 (95% CI 4.0–5.7)]. In univariate analyses, the cumulative hazards for incident HF were higher among participants in the highest quartile of SD of SBP or DBP (*Figure 1*).

The adjusted HRs of SBP and DBP variability metrics are shown in *Tables 2–4*.

After multivariable adjustment, the HRs for incident HF per each SD in intra-individual SD and VIM of SBP were 1.30 (95% CI 1.11–1.51) and 1.26 (95% CI 1.08–1.49), respectively. Participants in the highest quartile of SD of SBP had a 1.8-fold higher risk of incident HF compared with those in the lowest quartile (HR 1.77, 95% CI 1.01–3.09). The corresponding HR for VIM of SBP was 1.29 (95% CI 0.78–2.14). The equivalent values for other measures of BP variability are displayed in *Table 3*.

The HRs for incident HF per each SD increment in SD and VIM of DBP were 1.29 (95% CI 1.13–1.47) and 1.34 (95% CI 1.16–1.55), respectively (*Table 2*). The HRs for the top compared with the bottom quartiles were 1.61 (95% CI 1.01–2.59) and 1.65 (95% CI 1.03–2.65) for SDV and VIM of DBP, respectively (*Table 4*).

Sensitivity analyses

We tested the robustness of our findings by restricting the analytical sample to participants without prevalent CVD at baseline (Supporting Information, *Tables S2–S4*). Consistent to our main results, each unit-SD increase in intra-individual SD of SBP or DBP was associated with higher risks of incident HF [HR 1.38 (95% CI 1.13–1.69) for SBP; HR 1.24 (95% CI 1.04–1.50) for DBP; Supporting Information, *Table S2*]. Participants in the top quartile of SD of SBP had a higher risk of incident HF compared with those in the bottom quartile (HR 2.71, 95% CI 1.22–6.01; Supporting Information, *Table S3*). The HRs for the top compared with the bottom quartiles were 1.42 (95% CI 0.76–2.66) and 1.35 (95% CI 0.72–2.54) for SD and VIM of DBP, respectively (Supporting Information, *Table S4*).

Even with additional adjustments for the number of antihypertensive medications, use of angiotensin-converting enzyme inhibitors, use angiotensin receptor blockers, use of beta-blocker, and use of insulin, higher variability of BP remained significantly associated with increased risk of HF (Supporting Information, *Tables S5–S7*).

Discussion

This study comprehensively evaluated the associations of long-term variability of SBP and DBP with incident HF in a large sample of adults with Type 2 diabetes. We found that variability in SBP or DBP was each independently associated with a higher risk incident HF, after accounting for other HF risk factors including average BP. Our results were consistent across individuals with or without history of CVD. Our findings underscore the utility of stable and consistent BP control over time in the reduction of HF risk among patients with Type 2 diabetes.

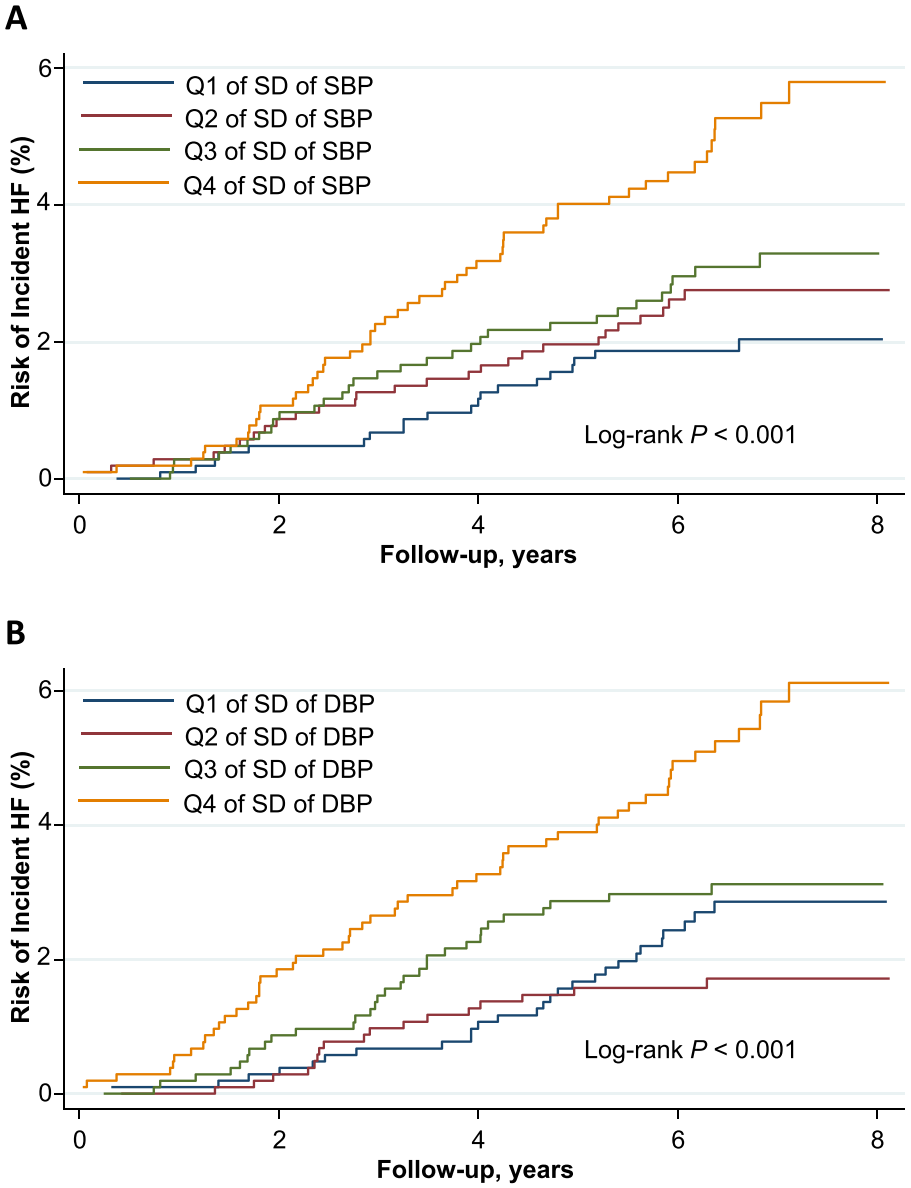
Our study adds to the body of knowledge by investigating the effect of long-term variability in BP on incident HF as the outcome exclusively in people with Type 2 diabetes. Prior studies predominantly focused on atherosclerotic CVD outcomes and did not include HF as an outcome and also found a positive relation with BP variability.[4–12] Our observations of a positive association between BP variability and risk of HF are consistent with the few studies conducted so far, although individuals without Type 2 diabetes were included in some of these reports.[5,12] Contrary to the extant studies,

Table 1 Characteristics of study participants by quartiles of SD of systolic blood pressure

	Entire sample N = 4200	Quartiles of SD of systolic blood pressure (mmHg)				P-value
		Q1 (<6.1) N = 1052	Q2 (6.1–8.9) N = 1048	Q3 (8.9–12.3) N = 1050	Q4 (>12.3) N = 1050	
At baseline						
Age (years)	59.0 (6.8)	58.4 (6.9)	58.7 (6.8)	58.7 (6.6)	60.1 (6.6)	<0.001
Women (%)	58.5	54.7	57.2	60.6	61.4	0.005
Randomization arm (%)						0.058
Diabetes support and education	49.1	51.2	49.4	50.1	45.6	
Intensive lifestyle intervention	50.9	48.8	50.6	49.9	54.4	
Race/ethnicity (%)						0.082
White	67.6	69.9	69.2	64.3	67.2	
Non-Hispanic Black	16.7	15.6	17.2	17.9	16.1	
Hispanic	12.0	11.7	10.8	13.2	12.3	
Body mass index (kg/m^2)	35.9 (5.9)	35.1 (5.6)	35.7 (5.9)	36.2 (5.8)	36.7 (6.0)	<0.001
Current smoking (%)	4.0	3.7	3.7	4.2	4.3	0.857
Alcohol drinking (%)	34.2	34.9	34.0	35.6	32.3	0.408
History of cardiovascular disease (%)	13.7	11.4	13.4	13.5	16.4	0.011
Duration of diabetes (years)	5.0 (2.0–10.0)	5.0 (2.0–9.0)	5.0 (2.0–9.0)	5.0 (2.0–9.0)	6.0 (2.0–10.0)	<0.001
Use of anti-diabetic drug (%)	87.2	85.5	86.9	87.6	88.7	0.186
Use of insulin (%)	18.0	16.5	15.7	18.9	20.9	0.007
Use of lipid-lowering drug (%)	52.6	51.1	54.1	51.8	53.4	0.579
Use of antihypertensive medication (%)	83.1	74.5	82.0	84.1	91.9	<0.001
Use of ACEI (%)	42.9	38.0	42.4	43.1	48.3	<0.001
Use of ARB (%)	15.9	13.5	14.1	15.9	20.0	0.001
Use of CCB (%)	19.7	16.8	17.1	20.2	24.7	<0.001
Use of beta-blocker (%)	22.2	16.4	22.0	21.8	28.7	<0.001
Number of antihypertensive medications	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	1 (1–2)	<0.001
eGFR (mL/min/1.73 m^2)	89.9 (16.0)	90.0 (15.6)	90.1 (16.0)	91.1 (15.9)	88.3 (16.3)	0.001
During follow-up						
Average haemoglobin A_{1C}	7.0 (1.0)	7.0 (0.9)	7.0 (1.0)	7.0 (1.1)	7.1 (1.1)	0.095
Average total-to-HDL cholesterol ratio	4.2 (1.2)	4.2 (1.2)	4.2 (1.1)	4.3 (1.1)	4.2 (1.1)	0.814
SBP (mmHg)						
Baseline SBP	129.0 (17.2)	123.0 (14.5)	126.3 (14.2)	129.9 (15.4)	136.8 (20.9)	<0.001
12 month SBP	124.0 (17.5)	121.4 (14.8)	122.4 (15.8)	123.8 (16.0)	128.5 (21.5)	<0.001
24 month SBP	124.8 (17.7)	122.1 (14.7)	123.0 (16.0)	124.8 (16.5)	129.1 (21.9)	<0.001
36 month SBP	124.8 (18.3)	122.3 (14.5)	123.8 (16.3)	125.3 (17.2)	127.8 (23.6)	<0.001
Average SBP	125.6 (14.1)	122.2 (14.0)	123.9 (13.7)	125.9 (12.6)	130.6 (14.7)	<0.001
DBP (mmHg)						
Baseline DBP	70.2 (9.6)	68.9 (8.8)	69.5 (9.0)	70.9 (9.4)	70.9 (9.4)	<0.001
12 month DBP	67.7 (9.5)	67.9 (9.0)	67.3 (9.3)	67.7 (9.4)	68.0 (10.1)	0.408
24 month DBP	67.7 (9.6)	67.7 (8.7)	67.5 (9.7)	67.9 (9.6)	67.7 (10.5)	0.796
36 month DBP	67.4 (9.7)	67.5 (8.6)	67.4 (9.4)	67.8 (9.9)	67.0 (10.7)	0.315
Average DBP	68.2 (8.0)	68.0 (7.9)	67.9 (8.2)	68.6 (8.0)	68.5 (7.8)	0.131

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation.
Data are mean (SD), median (inter-quartile range), or proportion as appropriate.

Figure 1 Cumulative hazards of incident heart failure (HF) by quartiles (Qs) of (A) standard deviation (SD) of systolic blood pressure (SBP) and (B) SD of diastolic blood pressure (DBP).



our study includes a variety of measures of BP variability, as well as a diverse multi-ethnic/racial sample of participants.[5]

There are causal pathways that could explain the positive relation between long-term variability in BP and risk of HF in Type 2 diabetes. First, BP variability can affect myocardial remodelling. Animal studies suggest that an exaggerated BP variability induces chronic inflammation and fibrosis in the myocardium, leading to adverse cardiac remodelling and impaired systolic function independently of mean BP.[25,26] Second, higher visit-to-visit variability of BP could lead to endothelial damage,[27] which in turn negatively affects coronary blood flow reserve leading to myocardial hypertrophy and diastolic dysfunction.[28,29] Third, the effect of BP variability could be mediated via cardiac dysautonomia whereby sympathetic denervation and depletion of myocardial catecholamine contribute to systolic and diastolic dysfunction.[28,30,31]

Our findings have several implications for individuals with Type 2 diabetes. Current hypertension guidelines focus only on average BP. Further research is needed to assess optimal methods to measure long-term variability of BP in the clinical setting and its exact utility as a therapeutic target. As the exact mechanisms underpinning the pathobiology of diabetes-associated HF remain incompletely understood, our data provide evidence supporting the contribution of visit-to-visit

DOI: 10.1002/ehf2.13385

Table 2 Hazard ratios for incident heart failure by continuous measures of blood pressure variability in the Look AHEAD study

	Model 1		Model 2		Model 3	
Metric (+SD, mmHg)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
SBP variability						
SD (+4.89)	1.50 (1.30–1.73)	<0.001	1.40 (1.20–1.63)	<0.001	1.30 (1.11–1.51)	0.001
CV (+0.04)	1.38 (1.18–1.60)	<0.001	1.28 (1.09–1.50)	0.003	1.30 (1.11–1.52)	0.001
ASV (+6.31)	1.03 (0.87–1.23)	0.712	1.07 (0.90–1.26)	0.436	1.03 (0.87–1.20)	0.754
VIM (+2.14)	1.36 (1.17–1.59)	<0.001	1.26 (1.08–1.49)	0.004	NA	NA
DBP variability						
SD (+2.46)	1.40 (1.24–1.58)	<0.001	1.34 (1.17–1.53)	<0.001	1.29 (1.13–1.47)	<0.001
CV (+0.04)	1.42 (1.23–1.65)	<0.001	1.32 (1.13–1.53)	<0.001	1.34 (1.16–1.56)	<0.001
ASV (+3.12)	0.97 (0.82–1.16)	0.755	1.00 (0.84–1.18)	0.963	1.00 (0.84–1.19)	0.989
VIM (+58.62)	1.42 (1.24–1.63)	<0.001	1.34 (1.16–1.55)	<0.001	NA	NA

AHEAD, Action for Health in Diabetes; ASV, average successive variability; CI, confidence interval; CV, coefficient of variation; DBP, diastolic blood pressure; HR, hazard ratio; NA, not applicable; SBP, systolic blood pressure; SD, standard deviation; VIM, variability independent of the mean.
Hazard ratios are per 1-SD increment in the variability metrics. Model 1 adjusted for age, sex, race/ethnicity, and randomization arm. Model 2 includes variables in Model 1 with further adjustment for body mass index, current smoking, alcohol drinking, use of antihypertensive medications during follow-up, average ratio of total to high-density lipoprotein cholesterol, estimated glomerular filtration rate, duration of diabetes, average glycosylated haemoglobin, and history of cardiovascular disease. Model 3 includes variables in Model 2 with further adjustment for average SBP in models assessing SBP variability or average DBP in models assessing DBP variability.

Table 3 Association of systolic blood pressure variability and incident heart failure in the Look AHEAD study

Variability metric (mmHg)	No. of events/ no. at risk	Rate per 1000 p-y	Estimate of association, hazard ratio (95% CI)		
			Model 1	Model 2	Model 3
Quartiles of SD					
Q1 (<6.07)	20/1052	2.9 (1.9–4.5)	Reference	Reference	Reference
Q2 (6.07–8.90)	27/1048	4.0 (2.7–5.8)	1.35 (0.76–2.41)	1.22 (0.66–2.24)	1.18 (0.64–2.17)
Q3 (8.91–12.34)	31/1050	4.6 (3.2–6.5)	1.62 (0.92–2.85)	1.52 (0.85–2.73)	1.47 (0.82–2.64)
Q4 (>12.34)	51/1050	7.7 (5.8–10.1)	2.56 (1.52–4.31)‡	2.06 (1.19–3.57)*	1.77 (1.01–3.09)*
P for trend	—	—	<0.001	0.004	0.025
Quartiles of CV					
Q1 (<0.05)	28/1050	4.1 (2.8–5.9)	Reference	Reference	Reference
Q2 (0.05–0.07)	20/1050	2.9 (1.9–4.5)	0.70 (0.39–1.24)	0.62 (0.34–1.14)	0.70 (0.38–1.28)
Q3 (0.07–0.10)	38/1050	5.6 (4.1–7.7)	1.44 (0.89–2.36)	1.43 (0.86–2.36)	1.56 (0.94–2.58)
Q4 (>0.10)	43/1050	6.4 (4.8–8.7)	1.56 (0.97–2.52)	1.23 (0.74–2.03)	1.36 (0.82–2.25)
P for trend	—	—	0.009	0.084	0.044
Quartiles of ASV					
Q1 (<−5.33)	40/1090	5.6 (4.1–7.7)	Reference	Reference	Reference
Q2 (−5.17, −1.33)	28/1051	4.1 (2.9–6.0)	0.75 (0.46–1.21)	0.77 (0.46–1.27)	0.80 (0.48–1.32)
Q3 (−1.17, 2.50)	22/1045	3.2 (2.1–4.9)	0.57 (0.34–0.97)	0.61 (0.36–1.04)	0.60 (0.35–1.02)
Q4 (>2.67)	39/1014	6.1 (4.4–8.3)	1.14 (0.73–1.78)	1.24 (0.79–1.94)	1.12 (0.71–1.75)
P for trend	—	—	0.831	0.584	0.936
Quartiles of VIM					
Q1 (<2.81)	27/1050	4.0 (2.7–5.8)	Reference	Reference	Reference
Q2 (2.81–4.12)	21/1050	3.1 (2.0–4.7)	0.76 (0.43–1.35)	0.70 (0.38–1.28)	NA
Q3 (4.12–5.63)	38/1050	5.6 (4.1–7.7)	1.50 (0.92–2.46)	1.47 (0.88–2.44)	NA
Q4 (>5.63)	43/1050	6.5 (4.8–8.7)	1.62 (1.00–2.64)	1.29 (0.78–2.14)	NA
P for trend	—	—	0.007	0.073	NA

AHEAD, Action for Health in Diabetes; ASV, average successive variability; CI, confidence interval; CV, coefficient of variation; NA, not applicable; p-y, person-years; SD, standard deviation; VIM, variability independent of the mean.
Model 1 adjusted for age, sex, race/ethnicity, and randomization arm. Model 2 includes variables in Model 1 with further adjustment for body mass index, current smoking, alcohol drinking, use of antihypertensive medications during follow-up, average ratio of total to high-density lipoprotein cholesterol, estimated glomerular filtration rate, duration of diabetes, average glycosylated haemoglobin, and history of cardiovascular disease. Model 3 includes variables in Model 2 with further adjustment for average systolic blood pressure.
*$P < 0.05$.
†$P < 0.01$.
‡$P < 0.001$.

variability of BP to the genesis of HF. Further data are needed to clarify the mechanisms underlying this association and to address the potential effects of BP variability reduction on the HF risk in people with Type 2 diabetes.

Our findings should be interpreted in the context of a few limitations. First, our study was observational, and there is a possibility of unmeasured, residual confounding. Second, we did not have data on BP medication adherence, as this may

Table 4 Association of diastolic blood pressure variability and incident heart failure in the Look AHEAD study

Variability metric (mmHg)	No. of events/ no. at risk	Rate per 1000 p-y	Estimate of association, hazard ratio (95% CI)		
			Model 1	Model 2	Model 3
Quartiles of SD					
Q1 (<3.09)	27/1050	4.0 (2.7–5.8)	Reference	Reference	Reference
Q2 (3.10–4.49)	17/1051	2.5 (1.5–4.0)	0.66 (0.36–1.21)	0.55 (0.29–1.04)	0.54 (0.29–1.01)
Q3 (4.50–6.19)	31/1049	4.6 (3.2–6.5)	1.19 (0.71–2.00)	0.96 (0.57–1.64)	0.96 (0.56–1.62)
Q4 (>6.19)	54/1050	8.1 (6.2–10.6)	2.08 (1.31–3.31)†	1.70 (1.06–2.73)*	1.61 (1.01–2.59)*
P for trend	—	—	<0.001	0.003	0.006
Quartiles of CV					
Q1 (<0.05)	29/1050	4.2 (2.9–6.1)	Reference	Reference	Reference
Q2 (0.05–0.07)	21/1050	3.1 (2.0–4.7)	0.78 (0.44–1.36)	0.69 (0.38–1.23)	0.71 (0.39–1.27)
Q3 (0.07–0.09)	33/1050	4.9 (3.5–6.9)	1.20 (0.73–1.97)	0.96 (0.57–1.61)	1.01 (0.60–1.69)
Q4 (>0.09)	46/1050	6.9 (5.2–9.2)	1.68 (1.05–2.67)*	1.38 (0.85–2.22)	1.52 (0.94–2.46)
P for trend	—	—	0.009	0.083	0.036
Quartiles of ASV					
Q1 (<−2.83)	45/1135	6.1 (4.6–8.2)	Reference	Reference	Reference
Q2 (−2.67, −1.00)	26/995	4.1 (2.8–6.0)	0.68 (0.42–1.11)	0.78 (0.48–1.29)	0.81 (0.49–1.33)
Q3 (−0.833, 1.00)	27/1029	4.0 (2.8–5.9)	0.68 (0.42–1.10)	0.78 (0.48–1.27)	0.81 (0.49–1.32)
Q4 (>1.16)	31/1041	4.7 (3.3–6.6)	0.82 (0.52–1.29)	0.86 (0.53–1.38)	0.87 (0.54–1.40)
P for trend	—	—	0.330	0.480	0.528
Quartiles of VIM					
Q1 (<74.86)	28/1050	4.1 (2.8–5.9)	Reference	Reference	Reference
Q2 (74.89–107.98)	18/1050	2.6 (1.7–4.2)	0.68 (0.38–1.23)	0.60 (0.32–1.11)	NA
Q3 (107.98–148.84)	30/1050	4.4 (3.1–6.3)	1.11 (0.66–1.86)	0.95 (0.56–1.61)	NA
Q4 (>148.86)	53/1050	8.0 (6.1–10.4)	1.97 (1.25–3.12)†	1.65 (1.03–2.65)*	NA
P for trend	—	—	<0.001	0.007	NA

AHEAD indicates Action for Health in Diabetes; ASV, average successive variability; CI, confidence interval; CV, coefficient of variation; NA, not applicable; SD, standard deviation; p-y, person-years; VIM, variability independent of the mean.
Model 1 adjusted for age, sex, race/ethnicity, and randomization arm. Model 2 includes variables in Model 1 with further adjustment for body mass index, current smoking, alcohol drinking, use of antihypertensive medications during follow-up, average ratio of total to high-density lipoprotein cholesterol, estimated glomerular filtration rate, duration of diabetes, average glycosylated haemoglobin, and history of cardiovascular disease. Model 3 includes variables in Model 2 with further adjustment for average diastolic blood pressure.
*$P < 0.05$.
†$P < 0.01$.

influence BP variability. Third, we did not have access to left ventricular ejection fraction and biomarker data such as natriuretic peptides. We therefore did not examine the relation of BP variability and risk of HF subtypes. This is especially important as HF with reduced ejection fraction and HF with preserved ejection fraction occur at different frequencies in the population,[32] including among people with diabetes.[15] Furthermore, biomarker research has suggested that different set of markers are associated with each of the HF subtypes.[33] Fourth, the study follow-up has not been continuous, as it has not been extended to the current time; thus, we may have missed some cases of HF due to censoring. Finally, given that we relied on only four time points to measure BP variability, we may have underestimated BP variability and consequently the magnitude of our effect estimates. Indeed, it has been previously established that visit-to-visit variability of BP increases with the number of visits used for its calculation.[34]

Our study has several strengths including the use of data from a large and diverse prospective cohort, the assessment of BP measurements at predetermined regular intervals for all participants, the inclusion of several measures of glycaemic variability, the longer duration of follow-up compared with prior studies,[5,7,12] the standardized adjudication of study outcomes, and the accounting for the mean BP in our analyses.

In summary, in a large sample of individuals with Type 2 diabetes, a greater long-term variability of SBP or DBP is associated with higher risk of incident HF, above and beyond average BP levels. Our findings support the notion that BP variability may contribute to the excess risk of HF in people with Type 2 diabetes and underscore the need for stable and consistent BP control in this high-risk population.

Acknowledgements

The authors wish to thank the staff and participants of the Look AHEAD study for their valuable contributions. Look AHEAD was conducted by the Look AHEAD Research Group and supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); the National Heart,

Lung, and Blood Institute (NHLBI); the National Institute of Nursing Research (NINR); the National Institute on Minority Health and Health Disparities (NIMHD); the Office of Research on Women's Health (ORWH); and the Centers for Disease Control and Prevention (CDC). The data from Look AHEAD were supplied by the NIDDK Central Repository. This manuscript was not prepared under the auspices of the Look AHEAD and does not represent analyses or conclusions of the Look AHEAD Research Group, the NIDDK Central Repositories, NIDDK, or the NIH.

Conflict of interest

None declared.

Funding

Dr Echouffo Tcheugui was supported by the National Heart, Lung, and Blood Institute(NHLBI) Grant K23HL153774.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Characteristics of Study Participants by Quartiles of SD of Diastolic Blood Pressure.

Table S2. Hazard Ratios for Incident Heart Failure by Continuous Measures of Blood Pressure Variability Among Participants Without Prevalent Cardiovascular Disease at Baseline (N = 3625).

Table S3. Hazard Ratios for Incident Heart Failure by Quartiles of Systolic Blood Pressure Variability Measures Among Participants Without Prevalent Cardiovascular Disease at Baseline (N = 3625).

Table S4. Hazard Ratios for Incident Heart Failure by Quartiles of Diastolic Blood Pressure Variability Measures Among Participants Without Prevalent Cardiovascular Disease at Baseline (N = 3625).

Table S5. Hazard Ratios for Incident Heart Failure by Continuous Measures of Blood Pressure Variability After Additional Adjustments (N = 4200).

Table S6. Association of Quartiles of Systolic Blood Pressure Variability and Incident Heart Failure After Additional Adjustments (N = 4200).

Table S7. Association of Diastolic Blood Pressure Variability and Incident Heart Failure in the Look AHEAD Study (N = 4200).

References

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Shay CM, Spartano NL, Stokes A, Tirschwell DL, VanWagner LB, Tsao CW, American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. *Circulation* 2020; **141**: e139–e596.
2. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988–2012. *JAMA* 2015; **314**: 1021–1029.
3. American Diabetes Association. 10. Cardiovascular disease and risk management: standards of medical care in diabetes—2020. *Diabetes Care* 2020; **43**: S111–S134.
4. Gosmanova EO, Mikkelsen MK, Molnar MZ, Lu JL, Yessayan LT, Kalantar-Zadeh K, Kovesdy CP. Association of systolic blood pressure variability with mortality, coronary heart disease, stroke, and renal disease. *J Am Coll Cardiol* 2016; **68**: 1375–1386.
5. Mehlum MH, Liestøl K, Kjeldsen SE, Julius S, Hua TA, Rothwell PM, Mancia G, Parati G, Weber MA, Berge E. Blood pressure variability and risk of cardiovascular events and death in patients with hypertension and different baseline risks. *Eur Heart J* 2018; **39**: 2243–2251.
6. Hata J, Arima H, Rothwell PM, Woodward M, Zoungas S, Anderson C, Patel A, Neal B, Glasziou P, Hamet P, Mancia G, Poulter N, Williams B, Macmahon S, Chalmers J. Effects of visit-to-visit variability in systolic blood pressure on macrovascular and microvascular complications in patients with type 2 diabetes mellitus: the ADVANCE trial. *Circulation* 2013; **128**: 1325–1334.
7. Muntner P, Whittle J, Lynch AI, Colantonio LD, Simpson LM, Einhorn PT, Levitan EB, Whelton PK, Cushman WC, Louis GT, Davis BR, Oparil S. Visit-to-visit variability of blood pressure and coronary heart disease, stroke, heart failure, and mortality: a cohort study. *Ann Intern Med* 2015; **163**: 329–338.
8. de Havenon A, Fino NF, Johnson B, Wong K-H, Majersik JJ, Tirschwell D, Rost N. Blood pressure variability and cardiovascular outcomes in patients with prior stroke: a secondary analysis of PRoFESS. *Stroke* 2019; **50**: 3170–3176.
9. Shimbo D, Newman JD, Aragaki AK, LaMonte MJ, Bavry AA, Allison M, Manson JE, Wassertheil-Smoller S. Association between annual visit-to-visit blood pressure variability and stroke in postmenopausal women: data from the Women's Health Initiative. *Hypertens (Dallas, Tex 1979)* 2012; **60**: 625–630.
10. Stevens SL, Wood S, Koshiaris C, Law K, Glasziou P, Stevens RJ, McManus RJ. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *BMJ* 2016; **354**: i4098.

11. Chiriacò M, Pateras K, Virdis A, Charakida M, Kyriakopoulou D, Nannipieri M, Emdin M, Tsioufis K, Taddei S, Masi S, Georgiopoulos G. Association between blood pressure variability, cardiovascular disease and mortality in type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 2019; **21**: 2587–2598.
12. Nuyujukian DS, Koska J, Bahn G, Reaven PD, Zhou JJ. Blood pressure variability and risk of heart failure in ACCORD and the VADT. *Diabetes Care* 2020; **43**: 1471–1478.
13. Ohkuma T, Komorita Y, Peters SAE, Woodward M. Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of 47 cohorts including 12 million individuals. *Diabetologia* 2019; **62**: 1550–1560.
14. Aune D, Schlesinger S, Neuenschwander M, Feng T, Janszky I, Norat T, Riboli E. Diabetes mellitus, blood glucose and the risk of heart failure: a systematic review and meta-analysis of prospective studies. *Nutr Metab Cardiovasc Dis* 2018; **28**: 1081–1091.
15. Greene SJ, Vaduganathan M, Khan MS, Bakris GL, Weir MR, Seltzer JH, Sattar N, McGuire DK, Januzzi JL, Stockbridge N, Butler J. Prevalent and incident heart failure in cardiovascular outcome trials of patients with type 2 diabetes. *J Am Coll Cardiol* 2018; **71**: 1379–1390.
16. Spallone V. Blood pressure variability and autonomic dysfunction. *Curr Diab Rep* 2018; **18**: 137.
17. Zhou TL, Henry RMA, Stehouwer CDA, van Sloten TT, Reesink KD, Kroon AA. Blood pressure variability, arterial stiffness, and arterial remodeling. *Hypertens (Dallas, Tex 1979)* 2018; **72**: 1002–1010.
18. Stehouwer CDA, Henry RMA, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. *Diabetologia* 2008; **51**: 527–539.
19. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. *Diabetes Care* 2003; **26**: 1553–1579.
20. Ryan DH, Espeland MA, Foster GD, Haffner SM, Hubbard VS, Johnson KC, Kahn SE, Knowler WC, Yanovski SZ, Look AHEAD Research Group. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Control Clin Trials* 2003; **24**: 610–628.
21. Look AHEAD Research Group, Bray G, Gregg E, Haffner S, Pi-Sunyer XF, WagenKnecht LE, Walkup M, Wing R. Baseline characteristics of the randomised cohort from the Look AHEAD (Action for Health in Diabetes) study. *Diab Vasc Dis Res* 2006; **3**: 202–215.
22. Pandey A, Patel KV, Bahnson JL, Gaussoin SA, Martin CK, Balasubramanyam A, Johnson KC, McGuire DK, Bertoni AG, Kitzman D, Berry JD. Association of intensive lifestyle intervention, fitness and body mass index with risk of heart failure in overweight or obese adults with type 2 diabetes mellitus: an analysis from the Look AHEAD trial. *Circulation* 2020; **141**: 1295–1306.
23. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604–612.
24. Shiojima I, Yefremashvili M, Luo Z, Kureishi Y, Takahashi A, Tao J, Rosenzweig A, Kahn CR, Abel ED, Walsh K. Akt signaling mediates postnatal heart growth in response to insulin and nutritional status. *J Biol Chem* 2002; **277**: 37670–37677.
25. Kudo H, Kai H, Kajimoto H, Koga M, Takayama N, Mori T, Ikeda A, Yasuoka S, Anegawa T, Mifune H, Kato S, Hirooka Y, Imaizumi T. Exaggerated blood pressure variability superimposed on hypertension aggravates cardiac remodeling in rats via angiotensin II system-mediated chronic inflammation. *Hypertens (Dallas, Tex 1979)* 2009; **54**: 832–838.
26. Egashira K. Molecular mechanisms mediating inflammation in vascular disease: special reference to monocyte chemoattractant protein-1. *Hypertens (Dallas, Tex 1979)* 2003; **41**: 834–841.
27. Diaz KM, Veerabhadrappa P, Kashem MA, Thakkar SR, Feairheller DL, Sturgeon KM, Ling C, Williamson ST, Kretzschmar J, Lee H, Grimm H, Babbitt DM, Vin C, Fan X, Crabbe DL, Brown MD. Visit-to-visit and 24-h blood pressure variability: association with endothelial and smooth muscle function in African Americans. *J Hum Hypertens* 2013; **27**: 671–677.
28. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus—mechanisms, management, and clinical considerations. *Circulation* 2016; **133**: 2459–2502.
29. Seddon M, Looi YH, Shah AM. Oxidative stress and redox signalling in cardiac hypertrophy and heart failure. *Heart* 2007; **93**: 903–907.
30. Falcão-Pires I, Leite-Moreira AF. Diabetic cardiomyopathy: understanding the molecular and cellular basis to progress in diagnosis and treatment. *Heart Fail Rev* 2012; **17**: 325–344.
31. Givertz MM, Sawyer DB, Colucci WS. Antioxidants and myocardial contractility: illuminating the 'Dark Side' of β-adrenergic receptor activation? *Circulation* 2001: 782–783.
32. Brouwers FP, de Boer RA, van der Harst P, Voors AA, Gansevoort RT, Bakker SJ, Hillege HL, van Veldhuisen DJ, van Gilst WH. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. *Eur Heart J* 2013; **34**: 1424–1431.
33. de Boer RA, Nayor M, deFilippi CR, Enserro D, Bhambhani V, Kizer JR, Blaha MJ, Brouwers FP, Cushman M, Lima JAC, Bahrami H, van der Harst P, Wang TJ, Gansevoort RT, Fox CS, Gaggin HK, Kop WJ, Liu K, Vasan RS, Psaty BM, Lee DS, Hillege HL, Bartz TM, Benjamin EJ, Chan C, Allison M, Gardin JM, Januzzi JLJ, Shah SJ, Levy D, Herrington DM, Larson MG, van Gilst WH, Gottdiener JS, Bertoni AG, Ho JE. Association of cardiovascular biomarkers with incident heart failure with preserved and reduced ejection fraction. *JAMA Cardiol* 2018; **3**: 215–224.
34. Levitan EB, Kaciroti N, Oparil S, Julius S, Muntner P. Blood pressure measurement device, number and timing of visits, and intra-individual visit-to-visit variability of blood pressure. *J Clin Hypertens (Greenwich)* 2012; **14**: 744–750.