

ORIGINAL RESEARCH

Canagliflozin, Blood Pressure Variability, and Risk of Cardiovascular, Kidney, and Mortality Outcomes: Pooled Individual Participant Data From the CANVAS and CREDENCE Trials

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BACKGROUND: Sodium glucose cotransporter-2 inhibitors reduce systolic blood pressure (SBP), but whether they affect SBP variability is unknown. There also remains uncertainty regarding the prognostic value of SBP variability for different clinical outcomes.

METHODS AND RESULTS: Using individual participant data from the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program and CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial, we assessed the effect of canagliflozin on SBP variability in people with type 2 diabetes across 4 study visits over 1.5 years as measured by standard deviation, coefficient of variation, and variability independent of the mean. We used multivariable Cox regression models to estimate associations of SBP variability with cardiovascular, kidney, and mortality outcomes. In 11 551 trial participants, canagliflozin modestly lowered the standard deviation of SBP variability (-0.25 mmHg [95% CI, -0.44 to -0.06]), but there was no effect on coefficient of variation (0.02% [95% CI, -0.12 to 0.16]) or variability independent of the mean (0.08 U [95% CI, -0.11 to 0.26]) when adjusting for correlation with mean SBP. Each 1 standard deviation increase in standard deviation of SBP variability was independently associated with higher risk of hospitalization for heart failure (hazard ratio [HR], 1.19 [95% CI, 1.02–1.38]) and all-cause mortality (HR, 1.12 [95% CI, 1.01–1.25]), with consistent results observed for coefficient of variation and variability independent of the mean. Increases in SBP variability were not associated with kidney outcomes.

CONCLUSIONS: In people with type 2 diabetes at high cardiovascular risk or with chronic kidney disease, higher visit-to-visit SBP variability is independently associated with risks of hospitalization for heart failure and all-cause mortality. Canagliflozin has little to no effect on SBP variability, independent of its established SBP-lowering effect.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifiers: NCT01032629, NCT01989754, NCT02065791.

Key Words: blood pressure variability ■ canagliflozin ■ clinical outcomes ■ clinical trials ■ SGLT2 inhibitors

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This manuscript was sent to Alexandros Briasoulis, MD, PhD, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.028516>

For Sources of Funding and Disclosures, see page xxx.

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CLINICAL PERSPECTIVE

What Is New?

- This study represents the largest and most comprehensive analysis of the relationship between sodium glucose cotransporter-2 inhibition, systolic blood pressure variability, and clinical outcomes in people with type 2 diabetes.
- While canagliflozin lowers systolic blood pressure, it has little to no effect on visit-to-visit systolic blood pressure variability.

What Are the Clinical Implications?

- Cardiorenal protection with sodium glucose cotransporter-2 inhibitors is unlikely to be substantively mediated by benefits on systolic blood pressure variability.

Nonstandard Abbreviations and Acronyms

CANVAS	Canagliflozin Cardiovascular Assessment Study
CREDESCENCE	Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation
CV	coefficient of variation
eGFR	estimated glomerular filtration rate
SBP	systolic blood pressure
SGLT2	sodium glucose cotransporter-2
VIM	variability independent of the mean

Sodium glucose cotransporter-2 (SGLT2) inhibitors reduce the risk of cardiovascular events and kidney failure in people with type 2 diabetes, heart failure, or chronic kidney disease (CKD).^{1–3} The mechanisms by which SGLT2 inhibitors exert these benefits remain incompletely understood, but benefits on cardiometabolic risk factors, including blood glucose, body weight, albuminuria, and blood pressure (BP), all likely contribute.⁴

In individuals with elevated BP, SGLT2 inhibitors lower systolic BP (SBP) by \approx 3 to 5 mmHg, an effect that occurs within weeks of treatment initiation and is sustained over time.⁵ The magnitude of BP lowering is consistent regardless of number of background BP-lowering agents and is also observed in individuals with treatment-resistant hypertension.^{6,7} It has been suggested that BP lowering with SGLT2 inhibitors occurs through enhanced natriuresis and osmotic diuresis, although emerging data indicate that other non-natriuretic mechanisms, including reductions in sympathetic nervous system activation, also potentially contribute.⁸

Higher visit-to-visit SBP variability may be a modifiable risk factor for cardiovascular events and mortality.⁹ However, its associations with kidney outcomes, particularly kidney failure, are not well established.¹⁰ Additionally, the relationship between SBP variability and different types of cardiovascular events has not been well defined. Associations of BP variability with measures of arterial stiffness and endothelial dysfunction have been observed, suggesting possible pathogenetic pathways.¹¹ SGLT2 inhibitors have been demonstrated to improve arterial stiffness, endothelial function, and may reduce sympathetic nervous system activation, which might in turn lead to a reduction in SBP variability.^{12,13}

We aimed to assess whether canagliflozin affects visit-to-visit SBP variability in people with type 2 diabetes at high cardiovascular risk or with CKD, and to evaluate the association of SBP variability with cardiovascular, kidney, and mortality outcomes. We hypothesized that SGLT2 inhibition might reduce SBP variability, which could contribute to cardiorenal protection with this class of agent.

METHODS

Study Design

This post-hoc analysis combined individual participant data from the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program ([ClinicalTrials.gov](https://clinicaltrials.gov) NCT01032629 and NCT01989754) and CREDESCENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial (NCT02065791). Detailed methods and main findings from these studies have been previously published.^{14,15} In brief, the CANVAS Program, comprising 2 companion trials, CANVAS and CANVAS-Renal (CANVAS-R), and the CREDESCENCE trial, were randomized, multicenter, double-blind, placebo-controlled trials that assessed the effects of canagliflozin on cardiovascular, kidney, and safety outcomes in people with type 2 diabetes at high cardiovascular risk (CANVAS) or with CKD (CREDESCENCE).

Results from pooled analyses of the CANVAS Program and the CREDESCENCE trial have been previously published and demonstrated that over a median follow-up of 2.5 years, canagliflozin substantially reduced the risk of major adverse cardiovascular events, hospitalization for heart failure, kidney failure, and cardiovascular and all-cause mortality.¹⁶

Participants

The CANVAS Program enrolled individuals with type 2 diabetes aged either \geq 30 years with a history of cardiovascular disease or \geq 50 years with \geq 2 cardiovascular risk factors. CREDESCENCE enrolled individuals aged

≥30 years with type 2 diabetes and CKD, defined as an estimated glomerular filtration rate (eGFR) 30 to 90 mL/min per 1.73 m² and urine albumin:creatinine ratio >300 to 5000 mg/g. All participants provided written informed consent, and ethics approval was obtained at all participating centers.

Randomized Treatment

Participants in CANVAS were randomized (1:1:1) to receive canagliflozin 300 mg, canagliflozin 100 mg, or matching placebo, while participants in CANVAS-R were randomized (1:1) to receive canagliflozin 100 mg (with optional up-titration to 300 mg) or matching placebo. All participants in CREDENCE were randomized (1:1) to canagliflozin 100 mg or placebo.

BP Variability Assessment

BP was measured at baseline and at each study visit. As mandated in the study protocols, 3 consecutive BP measurements were taken at intervals at least 1 minute apart, with the participant in a sitting position, and the average of the 3 readings was recorded. The same arm was to be used for BP measurements for each individual participant for the duration of the study. If BP was measured manually, it was recommended that it be measured by the same individual using the same equipment at each visit.

We assessed visit-to-visit SBP variability across 3, 6, 12, and 18-month study visits (ie, a 4-visit exposure window). We excluded participants with any missing SBP measures during these visits. We did not use measures of SBP recorded before 3 months post-randomization to avoid including the acute SBP drop resulting from initiation of canagliflozin that would cause misclassification of SBP variability. We also excluded measurements at 24 months to minimize participant exclusions arising from missing measurements (Table S1) and to maximize the number of events following the exposure window. In the main analysis, we estimated variability in 2 ways: (1) SD and (2) coefficient of variation (CV). As a sensitivity analysis, we also estimated SBP variability independent of the mean (VIM).¹⁷ To aid reproducibility, we have hosted R code for computing SD, CV, and VIM, on [GitHub](#).

Follow-Up and Study Outcomes

Participants were followed-up from the end of the exposure window (ie, 18-month visit) to the end of the study. We excluded participants who experienced study outcomes during the exposure window. All outcomes were independently adjudicated by blinded endpoint committees according to rigorous predefined criteria. Cardiovascular outcomes included the following: hospitalization for heart failure; death due to

cardiovascular disease; hospitalization for heart failure or death due to cardiovascular disease; fatal or nonfatal myocardial infarction; fatal or nonfatal stroke; and major adverse cardiovascular event, defined as nonfatal stroke, nonfatal myocardial infarction, or death due to cardiovascular disease. Two kidney outcomes were assessed: kidney failure (defined as chronic dialysis, transplantation, or sustained eGFR <15 mL/min per 1.73 m²); and a composite of doubling of serum creatinine, kidney failure, or death due to kidney disease. All-cause mortality was also assessed.

Statistical Analysis

Continuous variables were reported as mean and SD. Categorical variables were reported as frequency and percentage. Following assessment of the distribution of variables with missing data, we used median and mode imputation to estimate missing values for continuous and categorical variables, respectively.

We used linear mixed models, with trial included as a random effect, to estimate the effect of canagliflozin versus placebo on SBP variability. Owing to the systematic exclusion of participants with events occurring during the first 18 months, which may have selectively excluded more participants from the placebo group, we evaluated variable imbalance between canagliflozin- and placebo-treated participants using χ^2 tests for categorical variables, *t* tests for normally distributed continuous variables, and Wilcoxon rank-sum tests for skewed continuous variables. We then adjusted the models accordingly for any variables with evidence of a significant difference ($P < 0.05$) and a plausible confounding relationship with treatment allocation and SBP variability visualized via causal directed acyclic graph (Figure S1). To ensure that the observed treatment effects in this population were consistent with previously published intention-to-treat analyses, we also assessed the effect of canagliflozin on mean and maximum SBP during the 18-month exposure window using linear mixed models. Sensitivity analyses included extending the exposure window to include the 24-month clinic visit, and assessing the effect of canagliflozin on diastolic blood pressure variability.

We assessed the effect of canagliflozin on SBP variability across clinically important subgroups. Subgroups were selected a priori and included age, sex, baseline SBP, baseline pulse pressure, concomitant use of renin-angiotensin-system inhibitors, calcium channel blockers, and diuretics, history of resistant hypertension,¹⁸ eGFR, and urine albumin:creatinine ratio. We assessed heterogeneity in treatment effects across subgroups using likelihood ratio tests to compare models with and without interaction terms with no correction for multiplicity, but findings were interpreted considering the many comparisons made.

Table. Selected Characteristics of Participants by Quintiles of SD of Systolic Blood Pressure (n=11 551)

Characteristic	Quintile of SD of systolic blood pressure					Test of trend P value*
	Quintile 1 (n=2311)	Quintile 2 (n=2310)	Quintile 3 (n=2310)	Quintile 4 (n=2310)	Quintile 5 (n=2310)	
Range of SD of systolic blood pressure	0–4.7	4.7–6.8	6.8–9.3	9.3–12.8	12.8–51.6	NA
Trial						NA
CANVAS	678 (29.3)	759 (32.9)	703 (30.4)	638 (27.6)	558 (24.2)	
CANVAS-R	995 (43.1)	1002 (43.4)	975 (42.2)	1004 (43.5)	911 (39.4)	
CREDESCENCE	638 (27.6)	549 (23.8)	632 (27.4)	668 (28.9)	841 (36.4)	
Assigned canagliflozin	1308 (56.6)	1324 (57.3)	1320 (57.1)	1313 (56.8)	1197 (51.8)	0.002
Systolic blood pressure parameters measured during the 18-mo exposure window						
CV, mean (SD), %	2.4 (0.8)	4.4 (0.6)	6.1 (0.8)	8.2 (1.1)	12.5 (3.2)	<0.001
VIM, mean (SD), U	3.2 (1.2)	5.9 (0.9)	8.2 (1.2)	11.0 (1.6)	16.7 (4.4)	<0.001
Mean, mean (SD), mm Hg	132.9 (11.8)	132.5 (12.5)	132.8 (12.8)	134.2 (13.2)	138.6 (14.7)	<0.001
Maximum, mean (SD), mm Hg	136.4 (11.9)	138.8 (12.5)	141.8 (12.9)	146.3 (13.5)	158 (17.0)	<0.001
Baseline blood pressure, mean (SD), mm Hg						
Systolic	136.0 (13.6)	135.9 (14.4)	136.1 (15.2)	137.7 (15.9)	141.2 (17.6)	<0.001
Diastolic	78.4 (8.7)	78.1 (9.3)	77.7 (9.5)	77.6 (9.6)	77.7 (10.3)	0.002
Pulse pressure	57.6 (12.1)	57.8 (12.8)	58.4 (13.3)	60.1 (14.2)	63.5 (15.9)	<0.001
Demographics						
Age, mean (SD), y	62.6 (8.1)	62.6 (8.3)	63 (8.3)	63.3 (8.5)	63.9 (8.7)	<0.001
Female	840 (36.3)	834 (36.1)	797 (34.5)	802 (34.7)	853 (36.9)	0.942
White	1803 (78.0)	1793 (77.6)	1757 (76.1)	1726 (74.7)	1653 (71.6)	<0.001
Current smoker	396 (17.1)	405 (17.5)	426 (18.4)	361 (15.6)	340 (14.7)	0.006
Height, mean (SD), cm	167.9 (9.6)	167.2 (10.0)	167.5 (10.2)	167.1 (10.1)	165.8 (10.3)	<0.001
Weight, mean (SD), kg	89.0 (18.8)	89.1 (19.8)	89.8 (20.0)	89.3 (20.9)	87.3 (20.3)	0.012
Body-mass index, mean (SD), kg/m ²	31.5 (5.5)	31.7 (5.8)	31.9 (5.8)	31.8 (6.1)	31.6 (6.0)	0.388
Clinical measurements						
Heart rate, mean (SD), bpm	72.9 (9.5)	73.3 (10.2)	73.1 (10.5)	72.4 (10.9)	72.3 (11.2)	0.003
eGFR, mean (SD), mL/min per 1.73 m ²	74.3 (19.8)	75.1 (20.1)	73.2 (20.4)	71.7 (20.9)	68.3 (20.9)	<0.001
UACR, mean (SD), mg/g	414.8 (923.8)	345.4 (781.8)	386.5 (852.5)	455.7 (903.5)	623.8 (1112.1)	<0.001
Total cholesterol, mean (SD), mmol/L	4.5 (1.2)	4.5 (1.2)	4.4 (1.2)	4.4 (1.2)	4.4 (1.1)	0.023
HbA1c, mean (SD), %	8.2 (1.1)	8.2 (1.0)	8.3 (1.0)	8.3 (1.0)	8.3 (1.1)	0.065
Medical history						
Duration of diabetes, mean (SD), y	13.2 (7.6)	13.5 (7.6)	13.9 (7.7)	14.5 (8.3)	15.2 (8.5)	<0.001
Cardiovascular disease	1371 (59.3)	1343 (58.1)	1399 (60.6)	1434 (62.1)	1417 (61.3)	0.013
Myocardial infarction	528 (22.8)	498 (21.6)	572 (24.8)	551 (23.9)	501 (21.7)	0.019

(Continued)

Table. Continued

Characteristic	Quintile of SD of systolic blood pressure					Test of trend <i>P</i> value*
	Quintile 1 (n=2311)	Quintile 2 (n=2310)	Quintile 3 (n=2310)	Quintile 4 (n=2310)	Quintile 5 (n=2310)	
Heart failure	441 (19.1)	351 (15.2)	324 (14.0)	302 (13.1)	282 (12.2)	<0.001
Peripheral vascular disease	462 (20.0)	475 (20.6)	453 (19.6)	487 (21.1)	579 (25.1)	<0.001
Retinopathy	620 (26.8)	593 (25.7)	590 (25.5)	647 (28.0)	743 (32.2)	<0.001
Neuropathy	820 (35.5)	795 (34.4)	785 (34)	824 (35.7)	886 (38.4)	0.026
Medication use						
Statins	1632 (70.6)	1643 (71.1)	1704 (73.8)	1722 (74.5)	1765 (76.4)	<0.001
RAS inhibitors	1958 (84.7)	1928 (83.5)	1988 (86.1)	2015 (87.2)	2069 (89.6)	<0.001
β-blockers	1099 (47.6)	1101 (47.7)	1107 (47.9)	1158 (50.1)	1203 (52.1)	<0.001
Calcium-channel blockers	838 (36.3)	849 (36.8)	824 (35.7)	912 (39.5)	982 (42.5)	<0.001
Diuretics	955 (41.3)	959 (41.5)	1021 (44.2)	1066 (46.1)	1156 (50.0)	<0.001

Data are n (%) and mean (SD). CANVAS indicates Canagliflozin Cardiovascular Assessment Study; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; NA, no test for trend was applied; RAS, renin-angiotensin-system; UACR, urine albumin:creatinine ratio; and VIM, variability independent of the mean.

* Test of trend *P* value was estimated by regressing quintiles of SD of systolic blood pressure variability against each characteristic using linear regression for continuous variables and logistic regression for binary variables.

We used multivariable Cox proportional hazards models stratified by trial to assess the association of SBP variability with cardiovascular, kidney, and mortality outcomes. Study participants who did not experience a study outcome during the follow-up period were censored at their date of death or the end of the trial observation period, whichever occurred first. Measures of SBP variability were standardized (by subtracting the mean of the SBP variability variable from each participant’s SBP variability value and dividing by the SD of the SBP variability variable) to have a mean of 0 and an SD of 1, with hazard ratios (HRs) and 95% CIs estimated per 1 SD increase in each parameter. Variables adjusted for in each model are listed in Data S1. We selected adjustment variables based on prior knowledge as potentially relevant clinically meaningful factors with an association between the exposure and each outcome (Figure S1). We assessed the shape of the association and potential for a dose–response relationship between measures of SBP variability and each outcome across quintiles of SBP variability and visualized this through plotting. The association of diastolic blood pressure variability with clinical outcomes was also assessed. To aid comparison between the HRs for each group of SBP variability, we calculated the variance of the log risk in each group, including the reference group, from the variances and covariances of the log HRs in all groups except the reference group, to obtain group-specific 95% CIs.¹⁹

All analyses were performed with R version 4.1.2. The authors declare that all supporting data are available within the article (and its online supplementary files).

RESULTS

Of 14543 participants in the CANVAS Program (n=10142) and CREDENCE trial (n=4401), 2992 were excluded as they experienced a clinical outcome during the 18-month exposure window or had missing data for at least 1 SBP measurement at any of the 4 study visits (Figure S2). The study timeline is depicted in Figure S3. The Table describes baseline characteristics of the 11551 participants included in the main analysis, stratified by quintile of SD of SBP variability. Overall, mean age was 63.1 years, 4126 (35.7%) were female, and 6964 (60.3%) had prior cardiovascular disease (documented coronary artery disease, cerebrovascular disease, or peripheral vascular disease). 3307 (28.6%) participants had eGFR <60 mL/min per 1.73 m², and 5669 (49.1%) had a urine albumin:creatinine ratio ≥30 mg/g. Across increasing quintiles of SBP variability, participants were more likely to be older and less likely to be White; have a longer duration of diabetes; have heart failure; have peripheral vascular disease; higher SBP; lower eGFR;

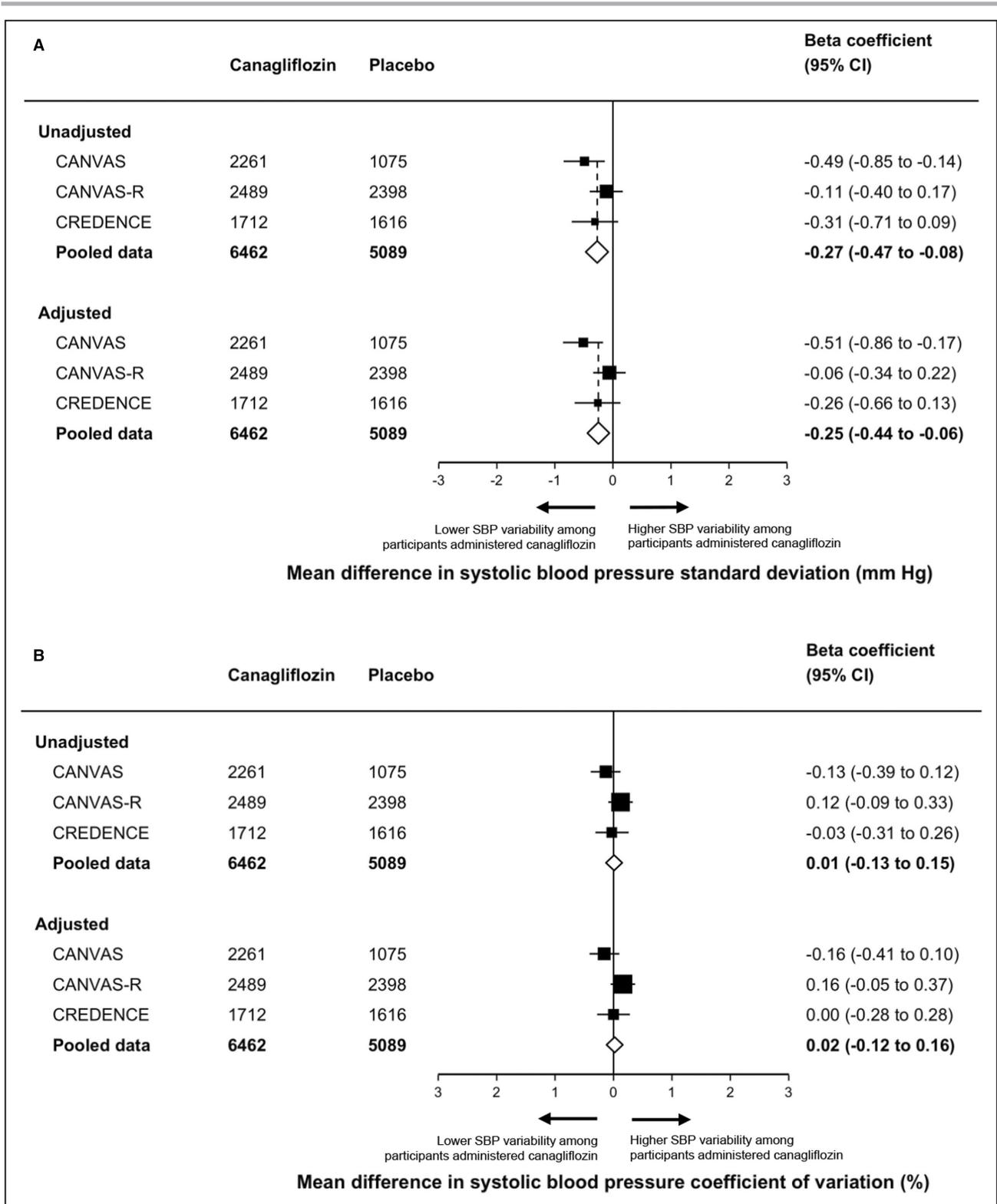


Figure 1. Mean difference in visit-to-visit systolic blood pressure variability as measured by (A) SD and (B) coefficient of variation in participants administered canagliflozin compared with participants administered placebo.

Square markers show beta coefficients, and horizontal bars show 95% CIs. The area of each square marker is inversely proportional to the variance of the beta coefficient estimate. Variables adjusted for included age (years; continuous), sex, race, height (cm; continuous), weight (kg; continuous), estimated glomerular filtration rate (mL/min per 1.73m²; continuous), urine albumin:creatinine ratio (mg/g; continuous), history of hypertension, history of heart failure, history of peripheral vascular disease, duration of diabetes (years; continuous), and baseline use of calcium-channel blockers. CANVAS indicates Canagliflozin Cardiovascular Assessment Study; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy; and SBP, systolic blood pressure.

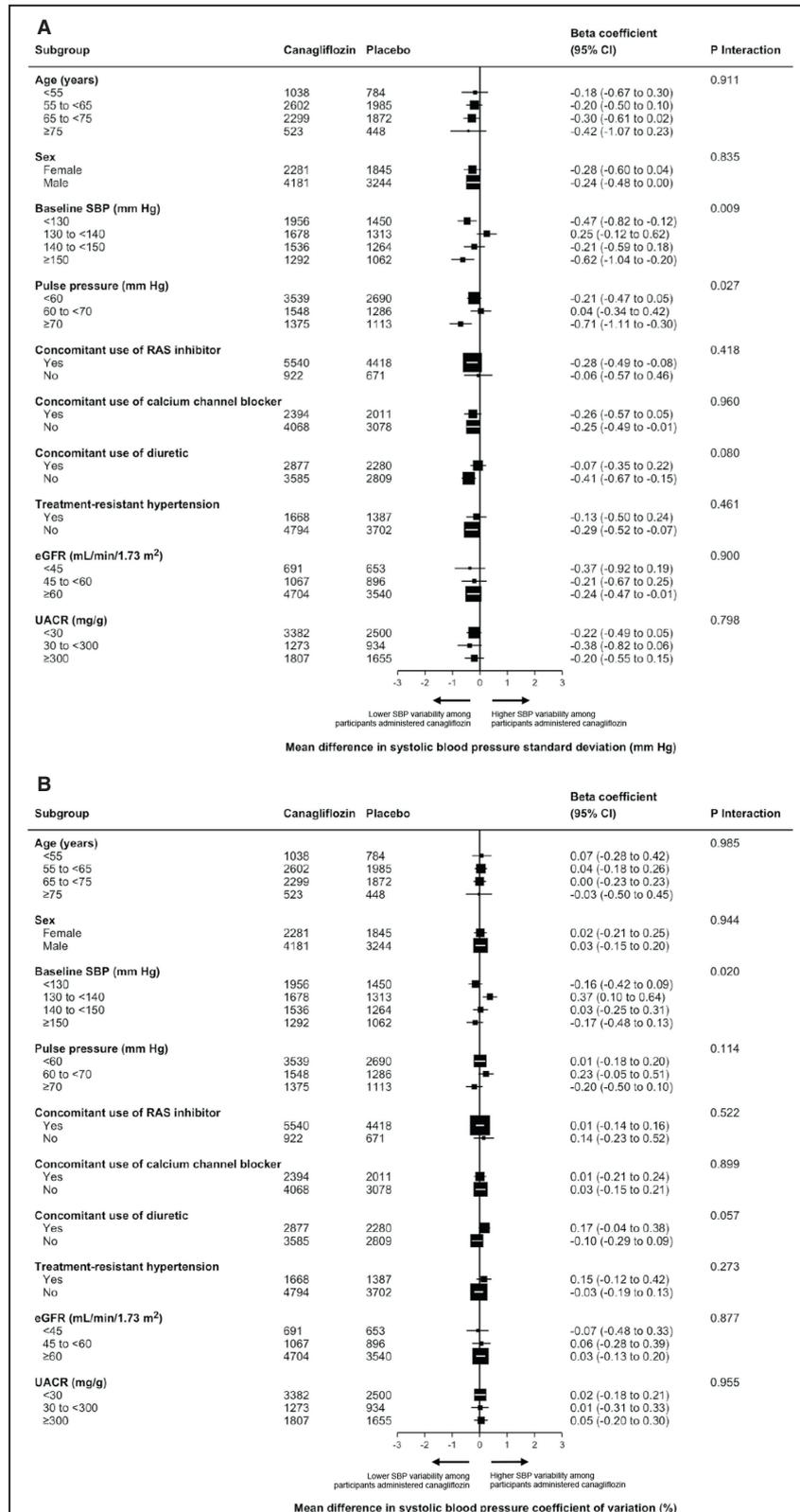


Figure 2. Mean difference in visit-to-visit systolic blood pressure variability as measured by (A) SD and (B) coefficient of variation in canagliflozin- and placebo-treated participants, by participant characteristic, baseline blood pressure, blood-pressure-lowering therapy, and biomarker subgroups from fully adjusted linear mixed models.

Square markers show beta coefficients, and horizontal bars show 95% CIs. The area of each square marker is inversely proportional to the variance of the beta coefficient estimate. Interaction *P* values refer to the interaction between each group and randomized treatment allocation. eGFR indicates estimated glomerular filtration rate; RAS, renin-angiotensin-system; SBP, systolic blood pressure; and UACR, urine albumin:creatinine ratio.

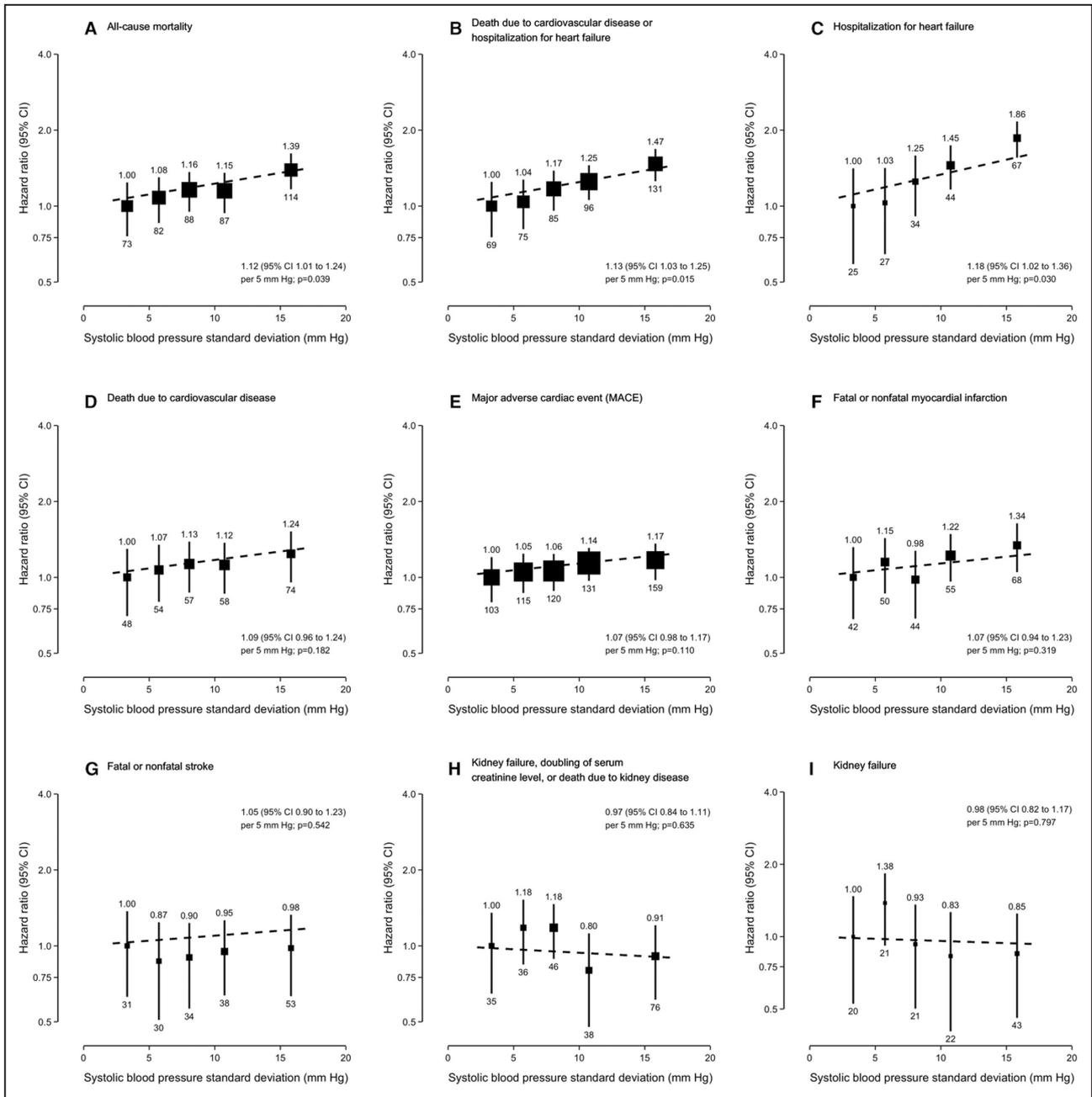


Figure 3. Shape of associations of SD of SBP variability with cardiovascular, kidney, and mortality outcomes in fully adjusted Cox proportional hazards models.

Shape of associations are displayed for (A) all-cause mortality, (B) death due to cardiovascular disease or hospitalization for heart failure, (C) hospitalization for heart failure, (D) death due to cardiovascular disease, (E) MACE, (F) fatal or nonfatal myocardial infarction, (G) fatal or nonfatal stroke, (H) kidney failure, doubling of serum creatinine level, or death due to kidney disease, and (I) kidney failure. Square markers show HRs for quintiles of SD of SBP variability relative to the reference group (quintile 1) and are positioned on the x-axis according to the median SD value of each quintile. Numbers above each upper CI limit denote HR estimates for each quintile, and numbers below each lower CI limit denote number of events in each quintile. The slope of the fitted line gives the inverse-variance weighted mean change in HR (95% CI) for the 3 trials per 5 mmHg increase in SD of SBP variability. The HR is plotted on a log scale, and the area of each square marker is inversely proportional to the variance of the log risk. Group-specific 95% CIs, calculated from this variance, are shown by vertical bars. HR indicates hazard ratio; MACE, major adverse cardiac event; and SBP, systolic blood pressure.

higher urine albumin:creatinine ratio; and be receiving all classes of blood pressure-lowering medications (all $P < 0.001$; Table). Missing data, on average, were very

low, with at most 0.92% missingness for any 1 variable. The extent of missingness and the imputation method used for each variable are displayed in Table S2.

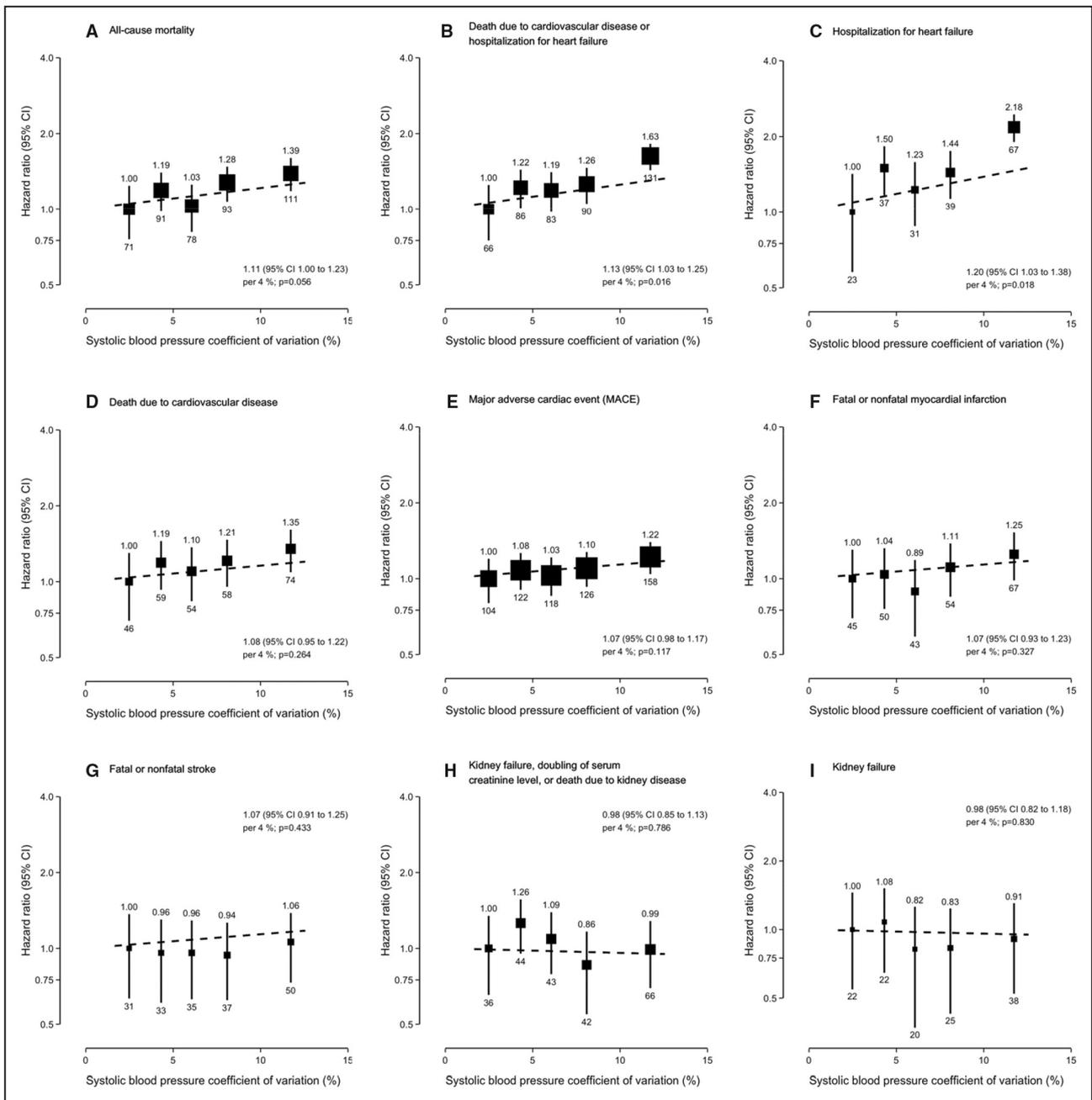


Figure 4. Shape of associations of CV of SBP variability with cardiovascular, kidney, and mortality outcomes in fully adjusted Cox proportional hazards models.

Shape of associations are displayed for (A) all-cause mortality, (B) death due to cardiovascular disease or hospitalization for heart failure, (C) hospitalization for heart failure, (D) death due to cardiovascular disease, (E) MACE, (F) fatal or nonfatal myocardial infarction, (G) fatal or nonfatal stroke, (H) kidney failure, doubling of serum creatinine level, or death due to kidney disease, and (I) kidney failure. Square markers show HRs for quintiles of CV of SBP variability relative to the reference group (quintile 1) and are positioned on the x-axis according to the median CV value of each quintile. Numbers above each upper CI limit denote HR estimates for each quintile, and numbers below each lower CI limit denote number of events in each quintile. The slope of the fitted line gives the inverse-variance weighted mean change in HR (95% CI) for the 3 trials per 4% increase in CV of SBP variability. The HR is plotted on a log scale, and the area of each square marker is inversely proportional to the variance of the log risk. Group-specific 95% CIs, calculated from this variance, are shown by vertical bars. CV indicates coefficient of variation; HR, hazard ratio; MACE, major adverse cardiac event; and SBP, systolic blood pressure.

During a median follow-up of 1.0 year (25th and 75th centile, 0.6 and 4.3 years), 456 (3.9%) participants were hospitalized for heart failure or died due to cardiovascular

disease, 628 (5.4%) experienced a major adverse cardiovascular event, 231 (2.0%) experienced the composite kidney outcome, and 444 (3.8%) died of any cause.

Canagliflozin and SBP Variability

The effect of canagliflozin versus placebo on SBP variability is displayed in [Figure 1](#). In an unadjusted model, canagliflozin modestly lowered SD of SBP variability (-0.27 mmHg [95% CI, -0.47 to -0.08]). This effect was similar after adjusting for differences between treatment arms ([Table S3](#); -0.25 mmHg [95% CI, -0.44 to -0.06]). The distribution of SD of SBP variability at an individual level for canagliflozin versus placebo is displayed in [Figure S4](#). Canagliflozin had no effect on SBP variability, as measured by CV ([Figure 1](#)) and VIM ([Figure S5](#)) in either adjusted and or unadjusted analyses. Similar results were observed in sensitivity analyses using a 24-month exposure window to measure SBP variability. Effects were consistent across most subgroups, although reductions in SD of SBP variability were more evident at high and low baseline BP and for participants with higher pulse pressure (P -interaction 0.009 and 0.027, respectively; [Figure 2](#)). Consistent with published data from intention-to-treat analyses, canagliflozin reduced mean and maximum SBP compared with placebo in adjusted models (-4.04 mmHg [95% CI, -4.49 to -3.59] and -4.36 mmHg [95% CI, -4.90 to -3.82], respectively, [Figure S6](#)). No effect of canagliflozin on diastolic blood pressure variability was observed ([Figure S7](#)).

SBP Variability and Clinical Outcomes

Associations of SBP variability, as measured by SD and CV, with risk of cardiovascular, kidney, and mortality outcomes are displayed in [Figures 3](#) and [4](#), and [Figure S8](#). In multivariable Cox regression analyses, each 1 SD increase in SD of SBP variability was independently associated with a 19% increased risk of hospitalization for heart failure (HR, 1.19 [95% CI, 1.02–1.38]), 14% increased risk of hospitalization for heart failure or cardiovascular death (HR, 1.14 [95% CI, 1.03–1.27]), and 12% increased risk of all-cause mortality (HR, 1.12 [95% CI, 1.01–1.25]). Similar associations were observed when SBP variability was assessed by CV ([Figure S8](#)). In unadjusted analyses, higher SBP variability was associated with risks of myocardial infarction and stroke ([Figures S9](#) and [S10](#)). However, these associations were completely attenuated in multivariable models, particularly following adjustment for maximum SBP over the 18-month exposure window ([Figure S11](#)).

No association between SBP variability and kidney outcomes was observed overall ([Figures 3](#) and [4](#)). While significant associations were observed in unadjusted analyses ([Figures S9](#) and [S10](#)), these were attenuated, again following adjustment for maximum SBP during the exposure window ([Figure S11](#)).

Associations of diastolic blood pressure variability with clinical outcomes were similar to those of SBP variability and are displayed in [Figures S12](#) and [S13](#).

DISCUSSION

In this pooled post-hoc analysis of the CANVAS Program and CREDENCE trial, canagliflozin reduced SBP, but there was little to no effect on visit-to-visit SBP variability after adjusting for correlation with mean SBP. While higher SBP variability was prognostically important for hospitalization for heart failure and all-cause mortality, associations of SBP variability with myocardial infarction, stroke, and kidney outcomes were completely attenuated after adjustment for baseline and maximum SBP and other recognized risk factors. Taken together, these results suggest that cardiorenal protection with SGLT2 inhibition is unlikely to be substantially mediated by benefits on SBP variability.

The BP-lowering effect of SGLT2 inhibitors has been ascribed to their natriuretic and osmotic diuretic effects, which is predicated on normal kidney function.⁵ However, while the glucose-lowering effect of SGLT2 inhibitors diminishes substantially as kidney function declines, BP lowering appears at least as large down to eGFR <30 mL/min per 1.73 m².^{6,20} The reason for the striking contrast between glucose and BP lowering in people with CKD is uncertain but suggests that the mechanisms for BP lowering may be different in people with and without CKD and that other non-natriuretic mechanisms might also contribute. Indeed, during standardized sodium intake, SGLT2 inhibitors reduce BP without any clear changes in urinary sodium excretion.²¹ In experimental animal models, SGLT2 inhibition reduces norepinephrine levels, and conversely, chemical denervation reduces SGLT2 expression, suggesting that SGLT2 inhibitors lower BP at least partly by reducing sympathetic nervous system activity, although the exact mechanism remains unclear.²²

While canagliflozin reduced the SD of SBP variability, the small magnitude of this difference renders it unlikely to contribute meaningfully to the substantial reductions in cardiovascular and kidney outcomes achieved with these agents. Indeed, several direct effects on cellular and metabolic functions are likely to be more important for end-organ protection.²³ The apparent difference in the effect of canagliflozin on BP variability, as measured by SD versus CV and VIM, is likely due to the normalization for mean SBP involved in the calculation of CV and transformation of SD such that it is uncorrelated with mean SBP for VIM, as individuals with higher SBP are likely to have higher SD of BP variability. As such, the effect of canagliflozin on SD of SBP variability likely reflects the reduction in overall SBP. The lack of effect of canagliflozin compared with placebo on any of these measures in subgroups defined by background

BP-lowering agents and history of resistant hypertension further underscores this point.

The CANVAS Program and CREDENCE trial allowed for assessment of the association of SBP variability across a spectrum of specific, adjudicated, cardiovascular, kidney, and mortality outcomes with large numbers of events. While our results showed a consistent association with all-cause mortality, we were unable to replicate results of other studies showing increased risk of myocardial infarction or stroke,^{24,25} owing to attenuation of HR estimates in multivariable models, particularly by maximum SBP over the exposure period. Previous data have indicated a relationship between SBP variability and coronary atheroma progression.²⁶ It is possible that with longer follow-up, this may translate to an increased risk of atherosclerotic cardiovascular events; however, our findings are consistent with similar analyses from SPRINT (the Systolic Blood Pressure Intervention Trial), in which participants were followed for a median 2.3 years.²⁷ In our data, associations were clearest for hospitalization for heart failure, which may reflect changes in volume status that are characteristic of individuals at increased risk of this outcome. For kidney outcomes, the role of BP variability is even less well defined, with often conflicting evidence limited to studies with low numbers of events and incomplete adjustment for potential confounders.¹⁰ However, our results are consistent with data from ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) and the TRANSCEND (Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease) trial, which showed no association of SBP variability with clinical kidney outcomes, lending weight to findings in the present study.²⁸

Despite the recognized risk conferred by higher SBP variability, strategies to modify this risk have remained elusive. In part, research into the therapeutic potential of reducing SBP variability has been hampered by variations in how this complex phenomenon is defined and assessed across studies.²⁹ Observational analyses of the SPRINT trial suggest that calcium-channel blocker use, and potentially thiazide diuretic use, are associated with lower visit-to-visit SBP variability in people at high cardiovascular risk without diabetes.^{27,30} Use of renin-angiotensin-system inhibitors in combination with either a calcium-channel blocker or thiazide diuretics also appears to produce more sustained and smoother SBP reductions than monotherapy with renin-angiotensin-system inhibitors alone.³¹ Whether affecting SBP variability through choice and timing of BP-lowering agents provides additional benefit beyond BP lowering remains to be demonstrated in randomized trials. As baseline and maximum SBP capture most of the risk conferred by SBP variability, at least for myocardial infarction, stroke, and kidney outcomes, these results give confidence to current

recommendations to focus on absolute BP targets, not BP variability.

The CANVAS and CREDENCE trials were international multicenter randomized trials conducted to a high standard. The adjudication of clinical outcomes by blinded expert committees according to strict pre-specified definitions allowed for a more granular assessment of the association of SBP variability with different types of cardiovascular events than has been previously possible. The relatively large number of events, particularly for kidney outcomes, contributed to the precision of observed associations. The use of directed acyclic graphs to inform careful multivariable adjustment allowed us to better understand the relationship between SBP variability and clinical outcomes.

However, some limitations also need to be considered when interpreting these findings. Owing to the exclusion of participants after randomization who experienced a cardiovascular or kidney outcome or had missing data for SBP during the exposure window, the analyses of the effects of canagliflozin on SBP variability were not intention-to-treat assessments of all randomized participants. However, the magnitude of absolute SBP lowering with canagliflozin was consistent with previously reported intention-to-treat comparisons. Furthermore, data on SBP were only available at study visits, and 24-hour ambulatory BP and home BP monitoring may yield additional insights about the effect of SGLT2 inhibition on other measures of SBP variability, including hour-to-hour and day-to-day variability.³² Longer follow-up might allow better assessment of the association of SBP variability with kidney failure and atherosclerosis-mediated events. Finally, whether SGLT2 inhibitors affect SBP variability in other populations, including those without diabetes, remains to be determined.

In summary, in people with type 2 diabetes, higher visit-to-visit SBP variability is independently associated with increased risk of hospitalization for heart failure and all-cause mortality; however, canagliflozin has little to no effect on SBP variability.

ARTICLE INFORMATION

Received October 16, 2022; accepted May 1, 2023.

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Acknowledgements

The authors received no financial support for the research, authorship, and/or publication of this article and agreed on the decision to submit for publication. R.A. Fletcher and B.L. Neuen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Fletcher, Arnott, Rockenschaub, Neuen. Acquisition, analysis, or interpretation of data: Fletcher, Arnott, Rockenschaub, Schutte, Carpenter, Vaduganathan, Agarwal, Bakris, Chang, Heerspink, Jardine, Mahaffey, Neal, Pollock, Jun, Rodgers, Perkovic, Neuen. Drafting of the manuscript: Fletcher, Neuen. Critical revision of the manuscript for important intellectual content: Fletcher, Arnott, Rockenschaub, Schutte, Carpenter, Vaduganathan, Agarwal, Bakris, Chang, Heerspink, Jardine, Mahaffey, Neal, Pollock, Jun, Rodgers, Perkovic, Neuen. Statistical analysis: Fletcher, Rockenschaub, Carpenter. Obtained funding: NA. Administrative, technical, or material support: Arnott. Supervision: Arnott, Rockenschaub, Neuen.

Sources of Funding

None.

Disclosures

R.A. Fletcher is supported by a PhD studentship from the Health Data Research UK-The Alan Turing Institute Wellcome Trust Programme in Health Data Science. This funding had no role in the production of this article. C. Arnott is supported by an NHMRC/MRFF Priority Fellowship and a NSW Health EMC Grant. P. Rockenschaub is supported by the Alexander von Humboldt Foundation. A.E. Schutte has received speaker honoraria from Omron and IEM and has conducted accuracy studies for Aktia. L. Carpenter is a full-time employee of Sensyne Health PLC and has received personal fees from Pfizer. Dr Vaduganathan is supported by the KL2/Catalyst Medical Research Investigator Training award from Harvard Catalyst (National Institutes of Health/ National Center for Advancing Translational Sciences Award UL1TR002541); has received research grant support from Amgen and Boehringer Ingelheim; served on advisory boards for Amgen, American Regent, AstraZeneca, Baxter Healthcare, Bayer AG, Boehringer Ingelheim, Cytokinetics, and Relypsa; and served on clinical end point committees for studies sponsored by Galmed, Novartis, and the National Institutes of Health. Dr Agarwal reports personal fees and nonfinancial support from Bayer Healthcare Pharmaceuticals, Akebia Therapeutics, Boehringer Ingelheim, Eli Lilly, Relypsa, Vifor Pharma, Lexicon and Reata; is a member of data safety monitoring committees for Vertex and Chinook and a member of steering committees of randomized trials for Akebia Therapeutics, Bayer and Reata; has served as an associate editor of the *American Journal of Nephrology and Nephrology Dialysis and Transplantation* and has been an author for *UpToDate*; and has received research grants from the National Institutes of Health and the US Veterans Administration. Dr Bakris reports research funding, paid to the University of Chicago Medicine, from Bayer, Novo Nordisk, and Vascular Dynamics; has acted as a consultant and received personal fees from Alnylam, Merck, and Relypsa; is an editor of the *American Journal of Nephrology, Nephrology and Hypertension*, and section editor of *UpToDate*; and is an associate editor of *Diabetes Care and Hypertension Research*. Dr Chang reports personal fees from Novo Nordisk, Janssen, and Fresenius Medical Care Renal Therapies Group LLC, Tricida, Gilead, and AstraZeneca, as well as grants from Satellite Healthcare. H.J.L. Heerspink is a consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Pharma, Gilead, Janssen, Merck, Mundi Pharma, Mitsubishi Tanabe, Novo Nordisk, and Traver. M.J. Jardine is supported by a Medical Research Future Fund Next Generation Clinical Researchers Program Career Development Fellowship; is responsible for research projects that have received unrestricted funding from Baxter, Amgen, Eli Lilly, and Merck Sharpe Dohme; serves on a steering committee sponsored by CSL; has served on advisory boards sponsored by

Akebia, Baxter, Boehringer Ingelheim, and Vifor; and has spoken at scientific meetings sponsored by Janssen; with any consultancy, honoraria, or travel support paid to her institution. Dr Mahaffey has received research support from Afferent, Amgen, Apple Inc, AstraZeneca, Cardiva Medical Inc, Daiichi, Ferring, Google (Verily), Johnson & Johnson, Luitpold, Medtronic, Merck, National Institutes of Health, Novartis, Sanofi, St. Jude, and Tenax, and has served as a consultant (speaker fees for continuing medical education events only) for Abbott, Ablynx, AstraZeneca, Baim Institute, Boehringer Ingelheim, Bristol-Myers Squibb, Elsevier, GlaxoSmithKline, Johnson & Johnson, MedErgy, Medscape, Mitsubishi Tanabe, Myokardia, NIH, Novartis, Novo Nordisk, Portola, Radiometer, Regeneron, Springer Publishing, and University of California, San Francisco. B. Neal has held research grants for large-scale cardiovascular outcome trials of SGLT2 from Janssen, and his institution has received consultancy, honoraria, and travel support for contributions he has made to advisory boards and/or the continuing medical education programs of Janssen. V. Perkovic has received fees for advisory boards, steering committee roles, or scientific presentations from AbbVie, Astellas, AstraZeneca, Bayer, Baxter, BMS, Boehringer Ingelheim, Dimerix, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Retrophin, Sanofi, Servier, Tricida, and Vitae. C. Pollock has received honoraria for serving on advisory boards and as a speaker for Merck Sharpe. M. Jun has received unrestricted grant support from VentureWise (a wholly own commercial subsidiary of NPS MedicineWise) to conduct a commissioned project funded by AstraZeneca. B.L. Neuen has received fees for travel support, advisory board membership, and steering committee roles from AstraZeneca, Bayer, Boehringer Ingelheim, and Janssen, with all honoraria paid to his institution. The remaining authors have no disclosures to report.

Supplemental Material

Data S1

Tables S1–S3

Figures S1–S13

REFERENCES

1. Neuen BL, Young T, Heerspink HJL, Neal B, Perkovic V, Billot L, Mahaffey KW, Charytan DM, Wheeler DC, Arnott C. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2019;7:845–854. doi: [10.1016/S2213-8587\(19\)30256-6](https://doi.org/10.1016/S2213-8587(19)30256-6)
2. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, Brueckmann M, Ofstad AP, Pfarr E, Jamal W. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-reduced and DAPA-HF trials. *Lancet*. 2020;396:819–829. doi: [10.1016/S0140-6736\(20\)31824-9](https://doi.org/10.1016/S0140-6736(20)31824-9)
3. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, Mann JF, McMurray JJ, Lindberg M, Rossing P. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383:1436–1446. doi: [10.1056/NEJMoa2024816](https://doi.org/10.1056/NEJMoa2024816)
4. Pollock C, Neuen BL. Sodium-glucose cotransporter 2 inhibition: rationale and mechanisms for kidney and cardiovascular protection in people with and without diabetes. *Adv Chronic Kidney Dis*. 2021;28:298–308. doi: [10.1053/j.ackd.2021.02.006](https://doi.org/10.1053/j.ackd.2021.02.006)
5. Heerspink HJL, Perkins BA, Fitchett DH, Husain M, Cherney DZI. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation*. 2016;134:752–772. doi: [10.1161/CIRCULATIONAHA.116.021887](https://doi.org/10.1161/CIRCULATIONAHA.116.021887)
6. Ye N, Jardine MJ, Oshima M, Hockham C, Heerspink HJ, Agarwal R, Bakris G, Schutte AE, Arnott C, Chang TI. Blood pressure effects of canagliflozin and clinical outcomes in type 2 diabetes and chronic kidney disease: insights from the CREDENCE trial. *Circulation*. 2021;143:1735–1749. doi: [10.1161/CIRCULATIONAHA.120.048740](https://doi.org/10.1161/CIRCULATIONAHA.120.048740)
7. Ferreira JP, Fitchett D, Ofstad AP, Kraus BJ, Wanner C, Zwiener I, Zinman B, Lauer S, George JT, Rossignol P. Empagliflozin for patients with presumed resistant hypertension: a post hoc analysis of the EMPA-REG OUTCOME trial. *Am J Hypertens*. 2020;33:1092–1101. doi: [10.1093/ajh/hpaa073](https://doi.org/10.1093/ajh/hpaa073)
8. Sternlicht H, Bakris GL. Blood pressure lowering and sodium-glucose co-transporter 2 inhibitors (SGLT2is): more than osmotic diuresis. *Curr Hypertens Rep*. 2019;21:1–5. doi: [10.1007/s11906-019-0920-4](https://doi.org/10.1007/s11906-019-0920-4)

9. 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. doi: [10.1136/bmj.i4098](https://doi.org/10.1136/bmj.i4098)
10. Li H, Xue J, Dai W, Chen Y, Zhou Q, Chen W. Visit-to-visit blood pressure variability and risk of chronic kidney disease: a systematic review and meta-analysis. *PLoS ONE*. 2020;15:e0233233. doi: [10.1371/journal.pone.0233233](https://doi.org/10.1371/journal.pone.0233233)
11. Tataschiere A, Di Nicola M, Tommasi R, Santarelli F, Palombo C, Parati G, De Caterina R. From short-term blood pressure variability to atherosclerosis: relative roles of vascular stiffness and endothelial dysfunction. *J Clin Hypertens*. 2020;22:1218–1227. doi: [10.1111/jch.13871](https://doi.org/10.1111/jch.13871)
12. Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE, Woerle H-J, von Eynatten M, Broedl UC. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. *Cardiovasc Diabetol*. 2014;13:1–8. doi: [10.1186/1475-2840-13-28](https://doi.org/10.1186/1475-2840-13-28)
13. Solini A, Giannini L, Seghieri M, Vitolo E, Taddei S, Ghiadoni L, Bruno RM. Dapagliflozin acutely improves endothelial dysfunction, reduces aortic stiffness and renal resistive index in type 2 diabetic patients: a pilot study. *Cardiovasc Diabetol*. 2017;16:1–9. doi: [10.1186/s12933-017-0621-8](https://doi.org/10.1186/s12933-017-0621-8)
14. Neal B, Perkovic V, Mahaffey KW, De Zeeuw D, Fulcher G, Erondou N, Shaw W, Law G, Desai M, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–657. doi: [10.1056/NEJMoa1611925](https://doi.org/10.1056/NEJMoa1611925)
15. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295–2306. doi: [10.1056/NEJMoa1811744](https://doi.org/10.1056/NEJMoa1811744)
16. Barraclough JY, Yu J, Figtree GA, Perkovic V, Heerspink HJL, Neuen BL, Cannon CP, Mahaffey KW, Schutte AE, Neal B, et al. Cardiovascular and renal outcomes with canagliflozin in patients with peripheral arterial disease: data from the CANVAS program and CREDENCE trial. *Diabetes Obes Metab*. 2022;24:1072–1083. doi: [10.1111/dom.14671](https://doi.org/10.1111/dom.14671)
17. Dasa O, Smith SM, Howard G, Cooper-DeHoff RM, Gong Y, Handberg E, Pepine CJ. Association of 1-year blood pressure variability with long-term mortality among adults with coronary artery disease: a post hoc analysis of a randomized clinical trial. *JAMA Network Open*. 2021;4:e218418. doi: [10.1001/jamanetworkopen.2021.8418](https://doi.org/10.1001/jamanetworkopen.2021.8418)
18. Carey RM, Whelton PK; Committee* AAHWG. Prevention, detection, evaluation, and management of high blood pressure in adults: synopsis of the 2017 American College of Cardiology/American Heart Association hypertension guideline. *Ann Intern Med*. 2018;168:351–358. doi: [10.7326/M17-3203](https://doi.org/10.7326/M17-3203)
19. Plummer M. Improved estimates of floating absolute risk. *Stat Med*. 2004;23:93–104. doi: [10.1002/sim.1485](https://doi.org/10.1002/sim.1485)
20. Cherney DZI, Cooper ME, Tikkanen I, Pfarr E, Johansen OE, Woerle HJ, Broedl UC, Lund SS. Pooled analysis of phase III trials indicate contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin. *Kidney Int*. 2018;93:231–244. doi: [10.1016/j.kint.2017.06.017](https://doi.org/10.1016/j.kint.2017.06.017)
21. Scholtes RA, Muskiet MH, van Baar MJ, Hesp AC, Greasley PJ, Karlsson C, Hammarstedt A, Arya N, van Raalte DH, Heerspink HJ. Natriuretic effect of two weeks of dapagliflozin treatment in patients with type 2 diabetes and preserved kidney function during standardized sodium intake: results of the DAPASALT trial. *Diabetes Care*. 2021;44:440–447. doi: [10.2337/dc20-2604](https://doi.org/10.2337/dc20-2604)
22. Herat LY, Magno AL, Rudnicka C, Hricova J, Carnagarin R, Ward NC, Arcambal A, Kiuchi MG, Head GA, Schlaich MP. SGLT2 inhibitor-induced sympathoinhibition: a novel mechanism for cardiorenal protection. *JACC*. 2020;5:169–179.
23. Packer M. Critical reanalysis of the mechanisms underlying the cardiorenal benefits of SGLT2 inhibitors and reaffirmation of the nutrient deprivation signaling/autophagy hypothesis. *Circulation*. 2022;146:1383–1405. doi: [10.1161/CIRCULATIONAHA.122.061732](https://doi.org/10.1161/CIRCULATIONAHA.122.061732)
24. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. 2010;375:895–905. doi: [10.1016/S0140-6736\(10\)60308-X](https://doi.org/10.1016/S0140-6736(10)60308-X)
25. Muntner P, Whittle J, Lynch AI, Colantonio LD, Simpson LM, Einhorn PT, Levitan EB, Whelton PK, Cushman WC, Louis GT. 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. doi: [10.7326/M14-2803](https://doi.org/10.7326/M14-2803)
26. Clark D, Nicholls SJ, St John J, Elshazly MB, Ahmed HM, Khraishah H, Nissen SE, Puri R. Visit-to-visit blood pressure variability, coronary atherosclerosis progression, and clinical outcomes. *JAMA Cardiol*. 2019;4:437–443. doi: [10.1001/jamacardio.2019.0751](https://doi.org/10.1001/jamacardio.2019.0751)
27. Chang TI, Reboussin DM, Chertow GM, Cheung AK, Cushman WC, Kostis WJ, Parati G, Raj D, Riessen E, Shapiro B. Visit-to-visit office blood pressure variability and cardiovascular outcomes in SPRINT (systolic blood pressure intervention trial). *Hypertension*. 2017;70:751–758. doi: [10.1161/HYPERTENSIONAHA.117.09788](https://doi.org/10.1161/HYPERTENSIONAHA.117.09788)
28. Mancia G, Schumacher H, Böhm M, Mann JF, Redon J, Facchetti R, Schmieder RE, Lonn EM, Teo KK, Yusuf S. Visit-to-visit blood pressure variability and renal outcomes: results from ONTARGET and TRANSCEND trials. *J Hypertens*. 2020;38:2050–2058. doi: [10.1097/HJH.0000000000002567](https://doi.org/10.1097/HJH.0000000000002567)
29. Wang KM, Chang TI. Blood pressure variability: not to be discounted. *Am J Hypertens*. 2022;35:118–120. doi: [10.1093/ajh/hpab160](https://doi.org/10.1093/ajh/hpab160)
30. de Havenon A, Petersen N, Wolcott Z, Goldstein E, Delic A, Sheibani N, Anadani M, Sheth KN, Lansberg M, Turan T. Effect of dihydropyridine calcium channel blockers on blood pressure variability in the SPRINT trial: a treatment effects approach. *J Hypertens*. 2022;40:462–469. doi: [10.1097/HJH.0000000000003033](https://doi.org/10.1097/HJH.0000000000003033)
31. Omboni S, Kario K, Bakris G, Parati G. Effect of antihypertensive treatment on 24-h blood pressure variability: pooled individual data analysis of ambulatory blood pressure monitoring studies based on olmesartan mono or combination treatment. *J Hypertens*. 2018;36:720–733. doi: [10.1097/HJH.0000000000001608](https://doi.org/10.1097/HJH.0000000000001608)
32. Schutte AE, Kollias A, Stergiou GS. Blood pressure and its variability: classic and novel measurement techniques. *Nat Rev Cardiol*. 2022;1-12:643–654. doi: [10.1038/s41569-022-00690-0](https://doi.org/10.1038/s41569-022-00690-0)

Supplementary Online Content

Table S1. Extent of missing data for systolic blood pressure by post-randomisation clinic visit.

Figure S1. Causal directed acyclic graph showing relationship between variables selected for analyses in the present study.

Appendix S1. Variables adjusted-for in multivariable Cox regression analyses.

Figure S2. Flow diagram depicting inclusion and exclusion of study participants.

Table S2. Coverage of missing data and imputation method used to remove missing values for variables used in analyses.

Table S3. Selected characteristics of participants by randomised treatment allocation (n=11 551).

Figure S3. Flow diagram for study participants.

Figure S4. Distribution of A) standard deviation, B) coefficient of variation, C) mean D) maximum of systolic blood pressure during the exposure window in canagliflozin- and placebo-treated participants in the pooled individual participant data (n=11 551).

Figure S5. Mean difference in visit-to-visit systolic blood pressure variability as measured by variability independent of the mean in participants administered canagliflozin compared with participants administered placebo.

Figure S6. Mean difference in A) mean and B) maximum systolic blood pressure measured over the exposure window in participants administered canagliflozin compared with participants administered placebo.

Figure S7. Mean difference in A) standard deviation, B) coefficient of variation, and C) variability independent of the mean of diastolic blood pressure variability measured over the exposure window in participants administered canagliflozin compared with participants administered placebo.

Figure S8. Associations of measures of systolic blood pressure variability with cardiovascular, kidney, and mortality outcomes in fully-adjusted Cox proportional hazards models.

Figure S9. Shape of associations of standard deviation of systolic blood pressure variability with cardiovascular, kidney, and mortality outcomes in minimally-adjusted (adjusted for age, sex, race, and randomised treatment allocation only) Cox proportional hazards models.

Figure S10. Shape of associations of coefficient of variation of systolic blood pressure variability with cardiovascular, kidney, and mortality outcomes in minimally-adjusted (adjusted for age, sex, race, and randomised treatment allocation only) Cox proportional hazards models.

Figure S11. Effect of serial adjustment for systolic blood pressure variables on associations of A) standard deviation of systolic blood pressure, and B) coefficient of variation of systolic blood pressure with cardiovascular, kidney, and mortality outcomes.

Figure S12. Shape of associations of standard deviation of diastolic blood pressure variability with cardiovascular, kidney, and mortality outcomes in fully-adjusted Cox proportional hazards models.

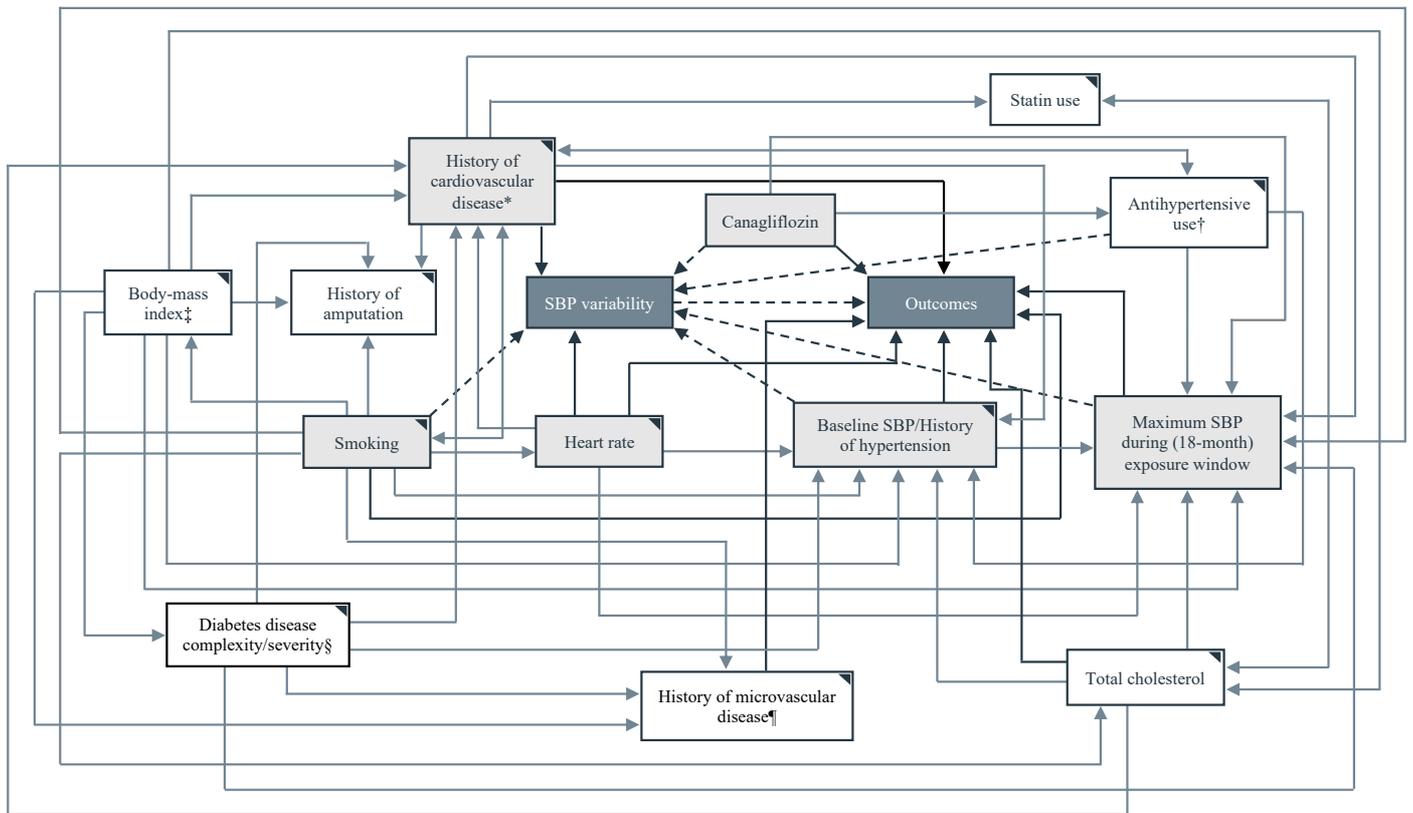
Figure S13. Shape of associations of coefficient of variation of diastolic blood pressure variability with cardiovascular, kidney, and mortality outcomes in fully-adjusted Cox proportional hazards models.

Table S1. Extent of missing data for systolic blood pressure by post-randomisation clinic visit.

Trial	Post-Randomisation Clinic Visit				
	3 months	6 months	12 months	18 months	24 months
CANVAS	268/4330 (6.2)	477/4330 (11.0)	537/4330 (12.4)	735/4330 (17.0)	792/4330 (18.3)
CANVAS-R	126/5812 (2.2)	278/5812 (4.8)	367/5812 (6.3)	651/5812 (11.2)	2033/5812 (35.0)
CREDENCE	174/4401 (4.0)	319/4401 (7.2)	567/4401 (12.9)	830/4401 (18.9)	1166/4401 (26.5)
Pooled data	568/14 543 (3.9)	1074/14 543 (7.4)	1471/14 543 (10.1)	2216/14 543 (15.2)	3391/14 543 (23.3)

Data are n/N (%).

Figure S1. Causal directed acyclic graph showing relationship between variables selected for analyses in the present study. Age, sex, and race were not included to preserve clarity, owing to their known relationship with nearly all variables depicted. Abbreviations: SBP, systolic blood pressure.



Legend	
	Causality
	Potential causality
	Main exposure/outcome
	Direct confounder
	Indirect confounder
	Variable recorded at baseline

Black arrows indicate causal relationship with exposure or outcome. Grey arrows indicate causal relationship with direct or indirect confounder.

*Inclusive of myocardial infarction, heart failure, and peripheral vascular disease.

†Renin-angiotensin-system (RAS) inhibitors, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, calcium channel blockers, and diuretics.

‡Body mass index was calculated as weight in kilograms divided by height in meters squared.

§Glycated haemoglobin (HbA1c) and duration of diabetes.

¶History of retinopathy, history of neuropathy, and estimated glomerular filtration rate and urinary albumin-creatinine ratio (indicating severity of nephropathy).

Appendix S1. Variables adjusted-for in multivariable Cox regression analyses.

Variables adjusted-for in multivariable Cox regression analyses to assess the association of visit-to-visit systolic blood pressure (SBP) variability with cardiovascular, kidney, and mortality outcomes were age, sex, race (White/Black/Asian/Other), randomised treatment, current smoking, body-mass index, baseline SBP, maximum SBP over the 18-month exposure window, heart rate, duration of diabetes, glycated haemoglobin (HbA1c), total cholesterol, estimated glomerular filtration rate (eGFR), urine albumin:creatinine ratio (UACR), concomitant use of blood pressure lowering medications, diuretics, statins, history of cardiovascular disease, history of amputation, history of neuropathy, and history of retinopathy.

Figure S2. Flow diagram depicting inclusion and exclusion of study participants. Abbreviations: BP, blood pressure; SBP, systolic blood pressure.

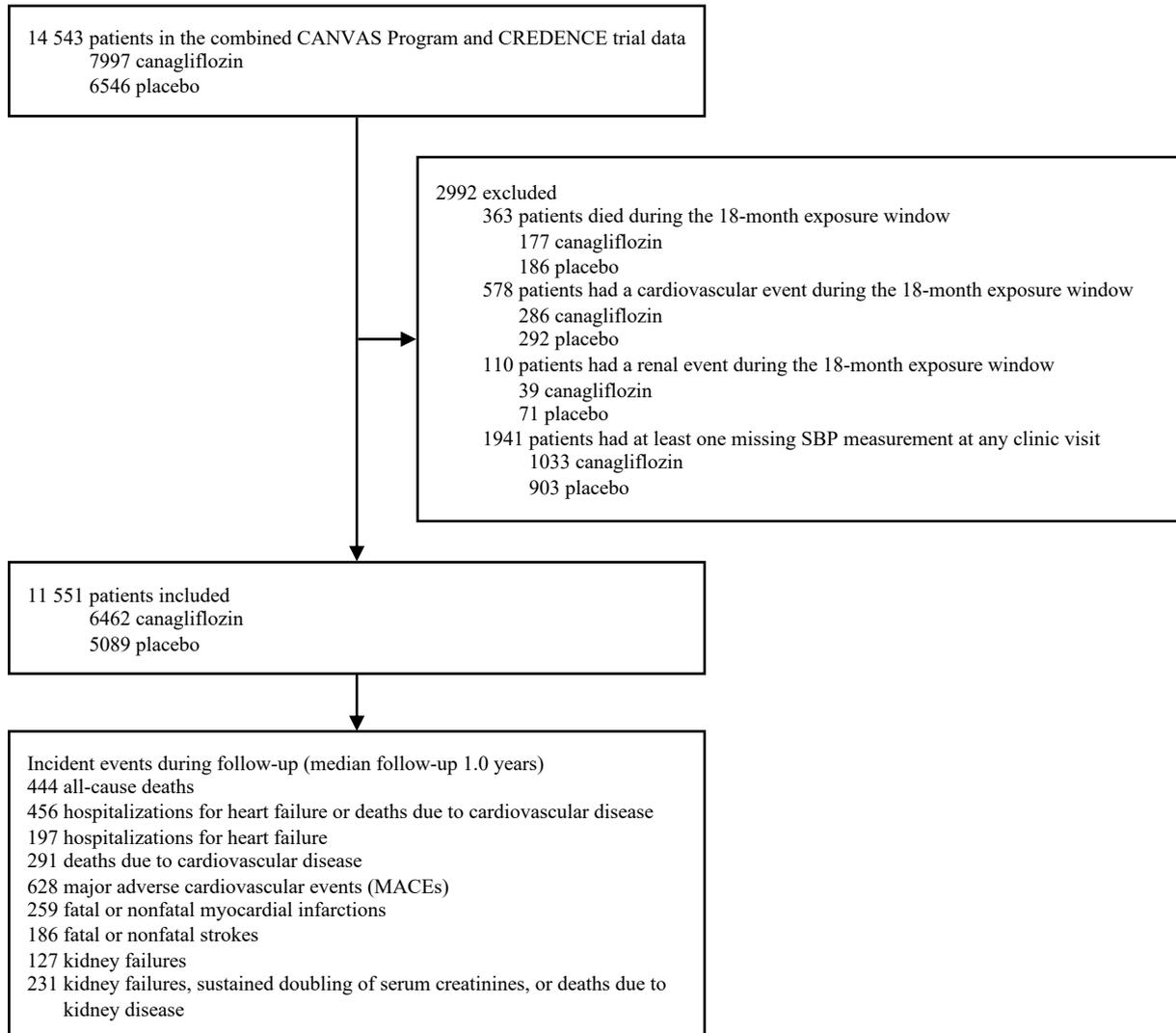


Figure S3. Flow diagram for study participants. Blood pressure measured at four occasions (3, 6, 12, and 18 months post-randomisation) was used to determine visit-to-visit blood pressure variability, and mean and maximum of systolic and diastolic blood pressure. After excluding participants who had experienced cardiovascular, kidney, or mortality outcomes within the first 18 months, and excluding participants with missing blood pressure measurements at any of the four visits, 11 551 participants were eligible for the present study.

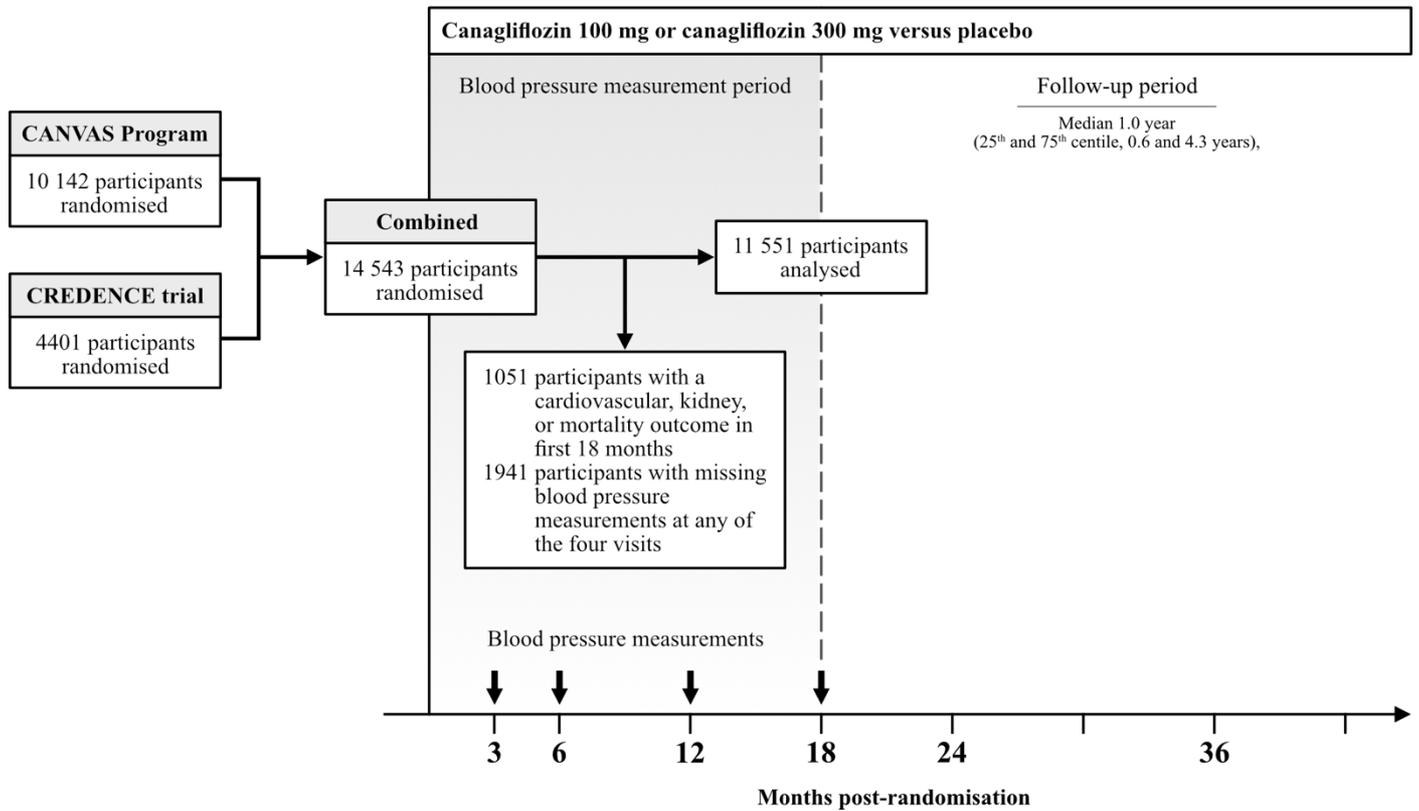


Table S2. Coverage of missing data and imputation method used to remove missing values for variables used in analyses.

Characteristic	Missing	Imputation Method Used
Total cholesterol, mmol/L	106/11 551 (0.92)	Median
UACR, mg/g	92/11 551 (0.80)	Median
Height, cm	17/11 551 (0.15)	Median
Body-mass index, kg/m ²	17/11 551 (0.15)	Median
Duration of diabetes, years	7/11 551 (0.06)	Median
eGFR, mL/min/1.73m ²	2/11 551 (0.02)	Median
Current smoking (mode value: "no")	1/11 551 (0.01)	Mode

Data are n/N (%). Abbreviations: UACR, urinary albumin/creatinine ratio; eGFR, estimated glomerular filtration rate.

Table S3. Selected characteristics of participants by randomised treatment allocation (n=11 551).

Characteristic	Canagliflozin (n=6462)	Placebo (n=5089)	P Value
Trial			<0.001
CANVAS	2261 (35.0)	1075 (21.1)	
CANVAS-R	2489 (38.5)	2398 (47.1)	
CREDENCE	1712 (26.5)	1616 (31.8)	
Systolic blood pressure parameters measured during the 18-month exposure window			
SD, mean (SD), mm Hg	8.8 (5.1)	9.2 (5.5)	<0.001
CV, mean (SD), %	6.7 (3.8)	6.7 (3.9)	0.668
VIM, mean (SD), U	9.0 (5.1)	9.0 (5.2)	0.899
Mean, mean (SD), mm Hg	132.2 (12.9)	136.8 (13.2)	<0.001
Maximum, mean (SD), mm Hg	142.0 (15.2)	147.1 (15.8)	<0.001
Baseline blood pressure, mean (SD), mm Hg			
Systolic	137.2 (15.6)	137.6 (15.5)	0.123
Diastolic	77.9 (9.5)	77.9 (9.5)	0.753
Pulse pressure	59.3 (13.9)	59.7 (13.9)	0.131
Demographics			
Age, mean (SD), years	62.9 (8.4)	63.3 (8.4)	0.023
Female	2281 (35.3)	1845 (36.3)	0.296
White	4922 (76.2)	3810 (74.9)	0.111
Current smoker	1099 (17.0)	829 (16.3)	0.319
Height, mean (SD), cm	167.3 (10.1)	166.8 (10.0)	0.006
Weight, mean (SD), kg	89.3 (20.1)	88.4 (19.9)	0.022
Body-mass index, mean (SD), kg/m ²	31.7 (5.9)	31.6 (5.8)	0.387
Clinical measurements			
Heart rate, mean (SD), bpm	72.8 (10.4)	72.8 (10.6)	0.797
eGFR, mean (SD), mL/min/1.73m ²	73.5 (20.4)	71.9 (20.8)	<0.001
UACR, median (IQR), mg/g	25.4 (8.0, 399.9)	33.8 (8.3, 535.3)	<0.001
Total cholesterol, median (IQR), mmol/L	4.2 (3.6, 5.1)	4.2 (3.6, 5.1)	0.616
HbA1c, mean (SD), %	8.2 (1.0)	8.2 (1.1)	0.389
Medical history			
Duration of diabetes, median (IQR), years	13.0 (8.0, 18.0)	13.0 (8.6, 19.0)	0.032
Hypertension	5913 (92.3)	4730 (93.9)	0.001
Cardiovascular disease	3877 (60.0)	3087 (60.7)	0.481
Myocardial infarction	1495 (30.5)	1155 (31.9)	0.165
Heart failure	921 (18.4)	779 (20.9)	0.003
Peripheral vascular disease	1365 (26.5)	1091 (28.6)	0.029
Nephropathy	2534 (39.2)	2227 (43.8)	<0.001
Retinopathy	1739 (26.9)	1454 (28.6)	0.050
Neuropathy	2282 (35.3)	1828 (35.9)	0.512
Medication use			
Statins	4750 (73.5)	3716 (73.0)	0.572
RAS inhibitors	5540 (85.7)	4418 (86.8)	0.099
Beta blockers	3171 (49.1)	2497 (49.1)	1.000
Calcium channel blockers	2394 (37.0)	2011 (39.5)	0.007
Diuretics	2877 (44.5)	2280 (44.8)	0.778

Data are n (%), mean (SD), and median (IQR). Abbreviations: SD, standard deviation; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; UACR, urinary albumin/creatinine ratio; HbA1c, glycated haemoglobin; RAS, renin-angiotensin-system; ACE, angiotensin-converting enzyme.

Figure S4. Distribution of A) standard deviation, B) coefficient of variation, C) variability independent of the mean, D) mean, and E) maximum of systolic blood pressure during the exposure window in canagliflozin- and placebo-treated participants in the pooled individual participant data (n=11 551).

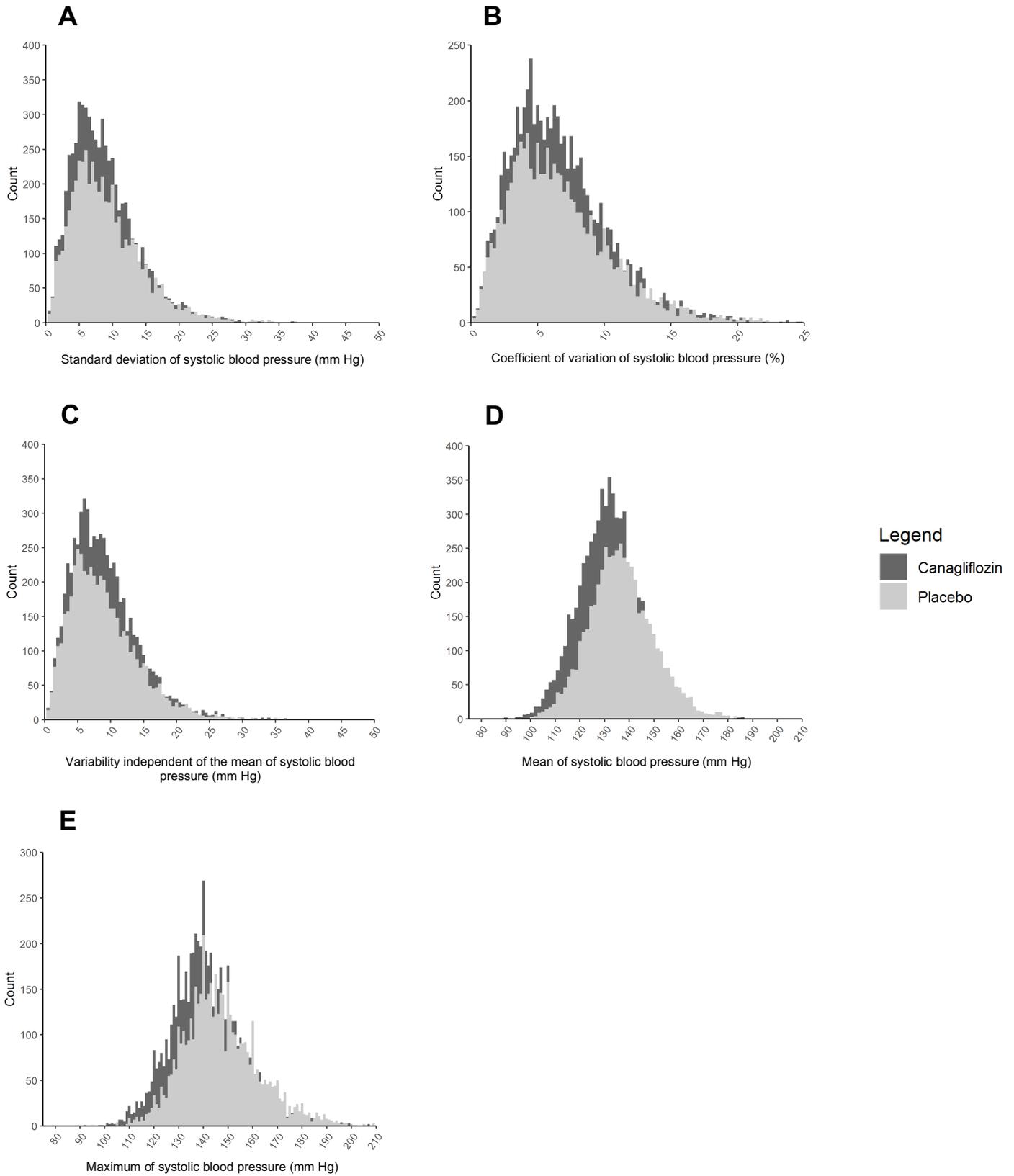
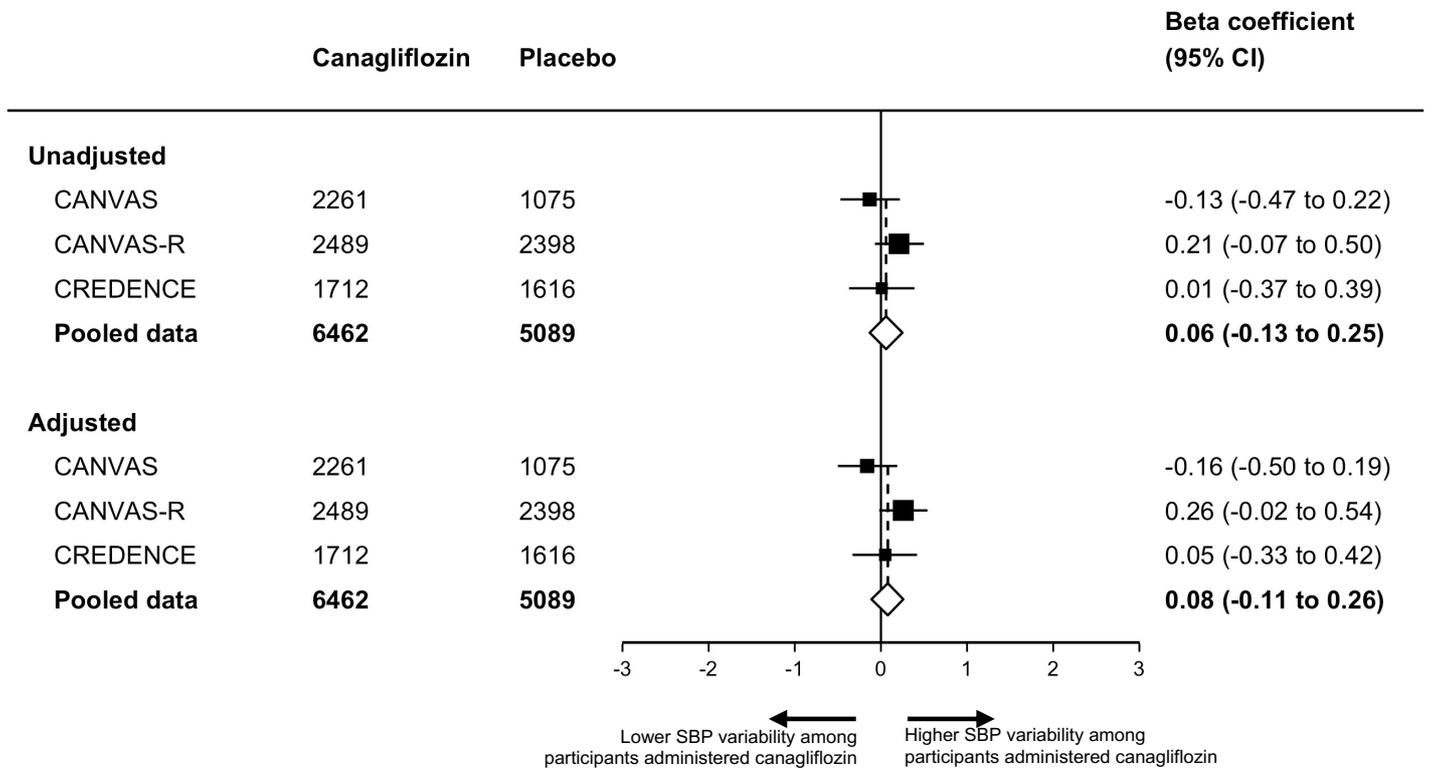


Figure S5. Mean difference in visit-to-visit systolic blood pressure variability as measured by variability independent of the mean in participants administered canagliflozin compared with participants administered placebo. Square markers show beta coefficients and horizontal bars show 95% confidence intervals (CIs). The area of each square marker is inversely proportional to the variance of the beta coefficient estimate.



Mean difference in systolic blood pressure variability independent of the mean (U)

Figure S6. Mean difference in A) mean and B) maximum systolic blood pressure measured over the exposure window in participants administered canagliflozin compared with participants administered placebo. Square markers show beta coefficients and horizontal bars show 95% confidence intervals (CIs). The area of each square marker is inversely proportional to the variance of the beta coefficient estimate.

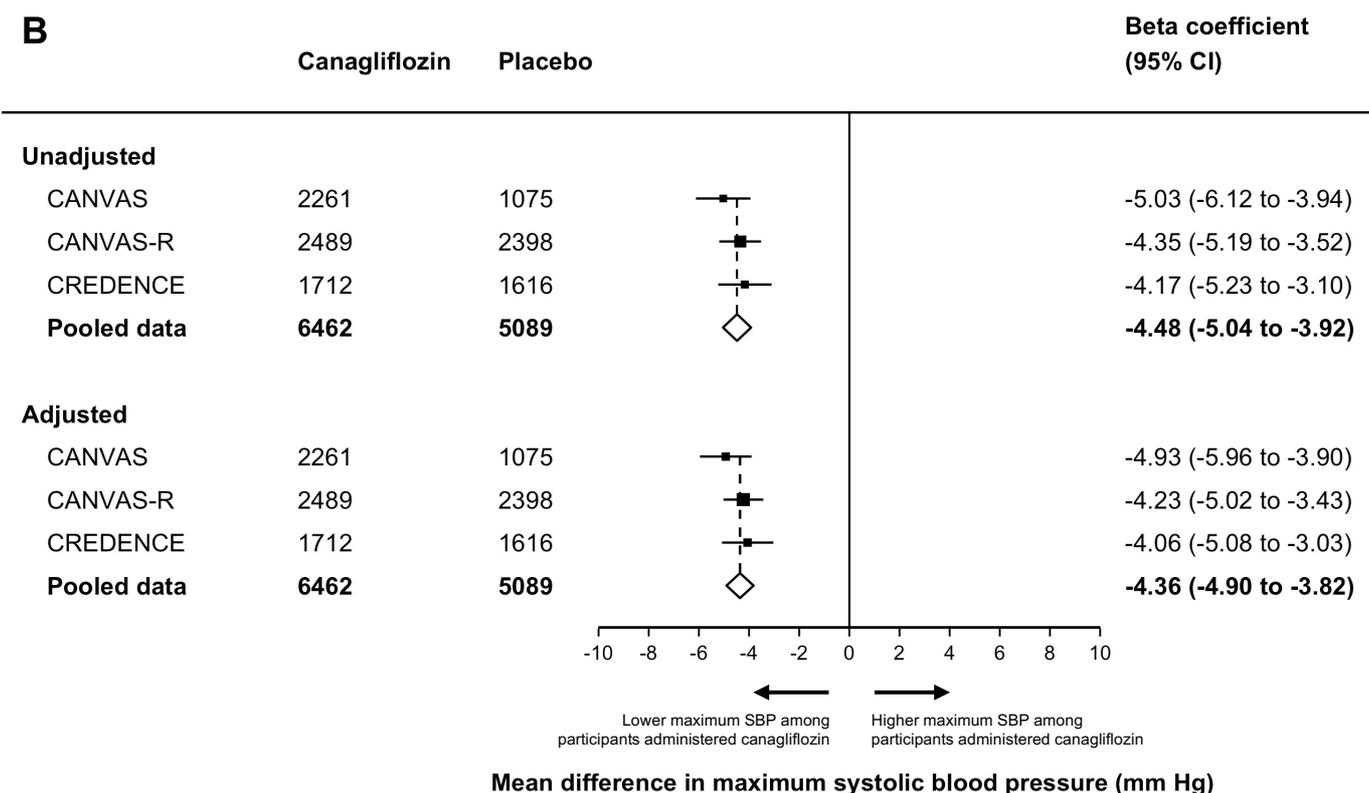
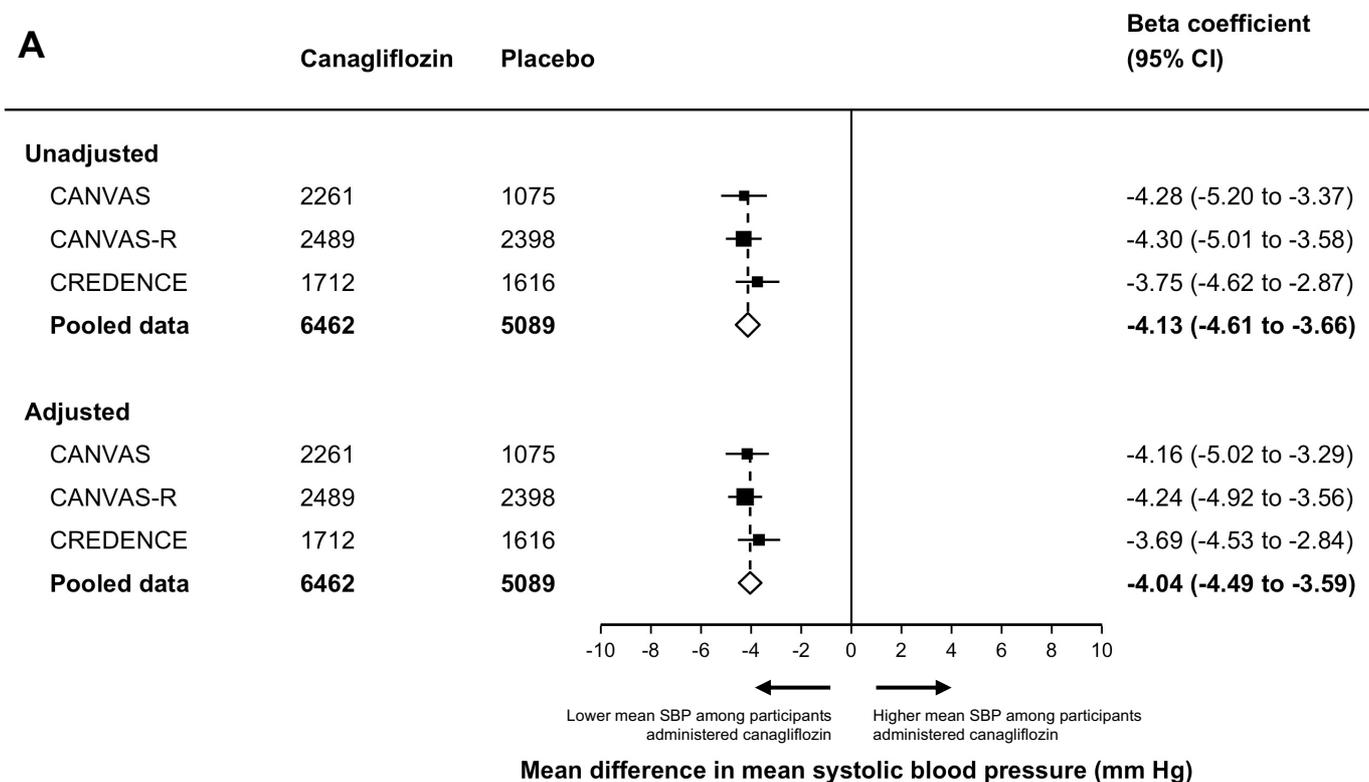


Figure S7. Mean difference in A) standard deviation, B) coefficient of variation, and C) variability independent of the mean of diastolic blood pressure variability measured over the exposure window in participants administered canagliflozin compared with participants administered placebo. Square markers show beta coefficients and horizontal bars show 95% confidence intervals (CIs). The area of each square marker is inversely proportional to the variance of the beta coefficient estimate.

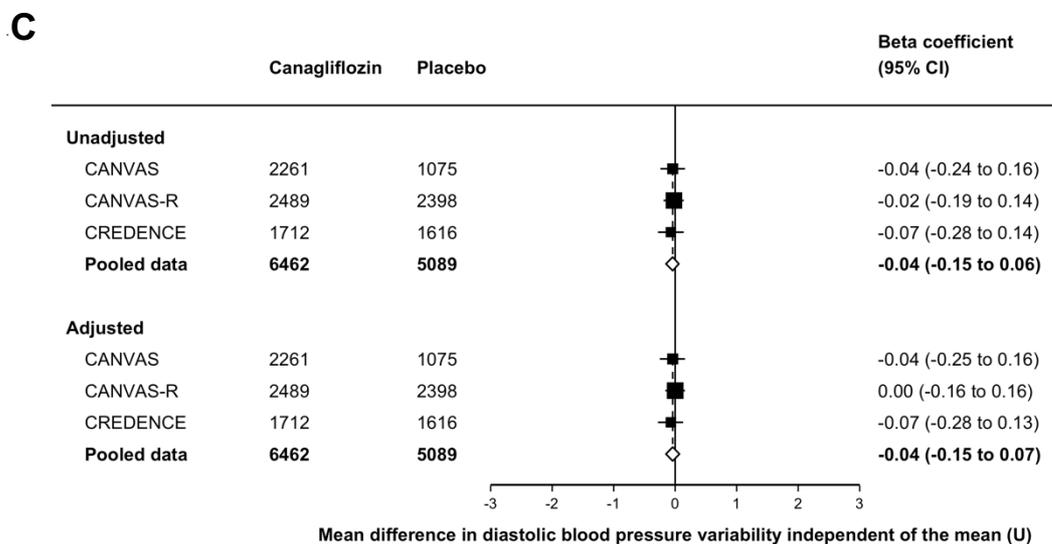
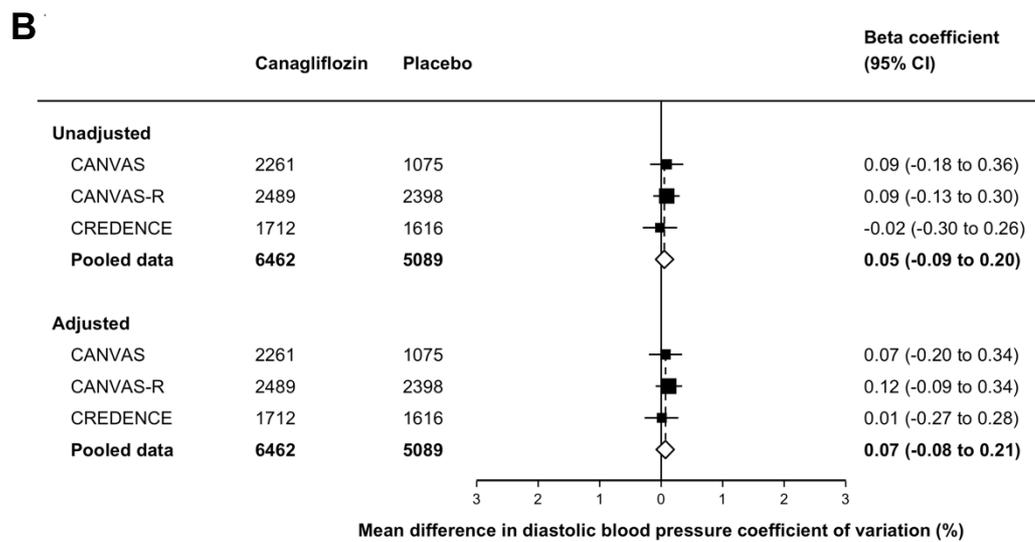
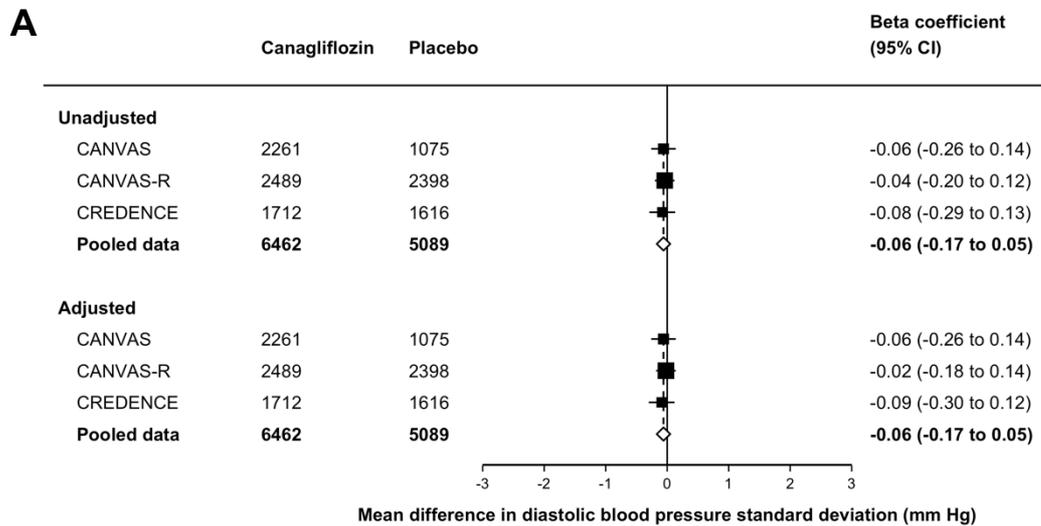


Figure S8. Associations of measures of systolic blood pressure variability with cardiovascular, kidney, and mortality outcomes in fully-adjusted Cox proportional hazards models. Square markers show hazard ratios (HRs) and horizontal bars show 95% confidence intervals (CIs) for a 1 standard deviation (SD) increase in each parameter, corresponding to an increase in 5.3 mm Hg in SD and 3.8 % in coefficient of variation (CV) of systolic blood pressure variability. The area of each square marker is inversely proportional to the variance of the HR estimate.

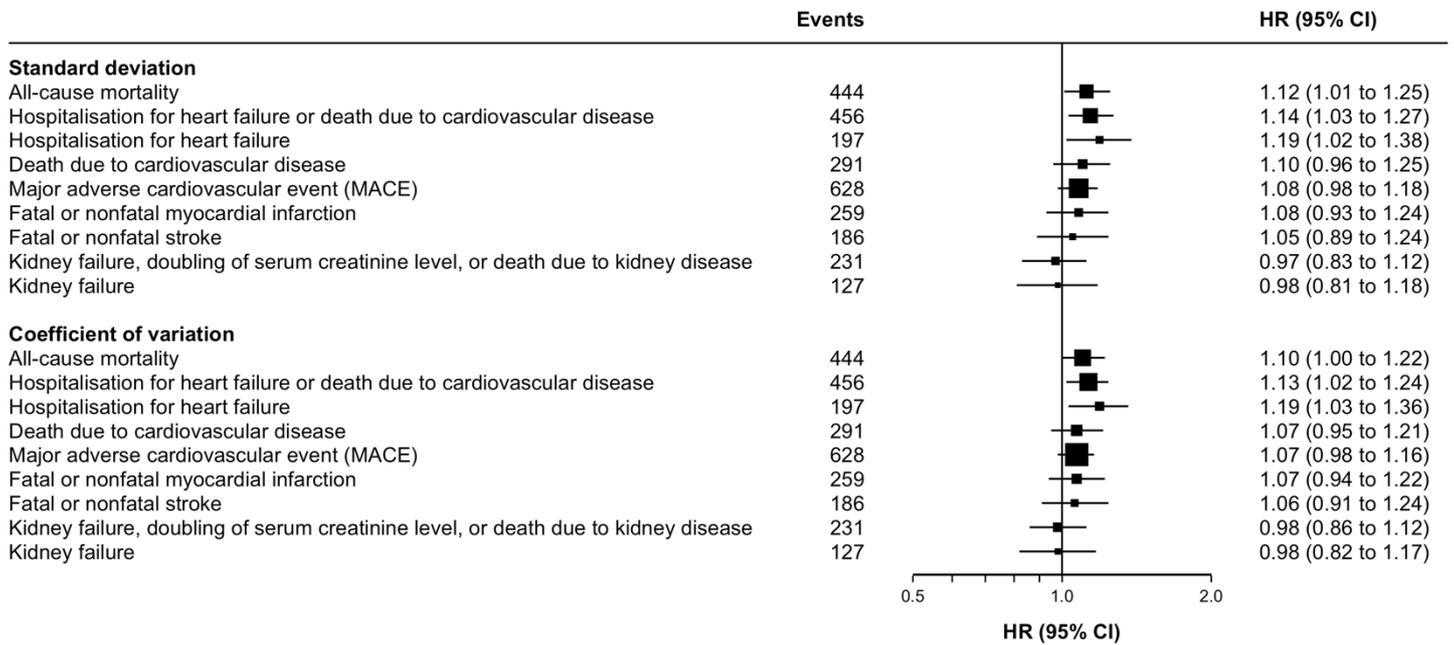
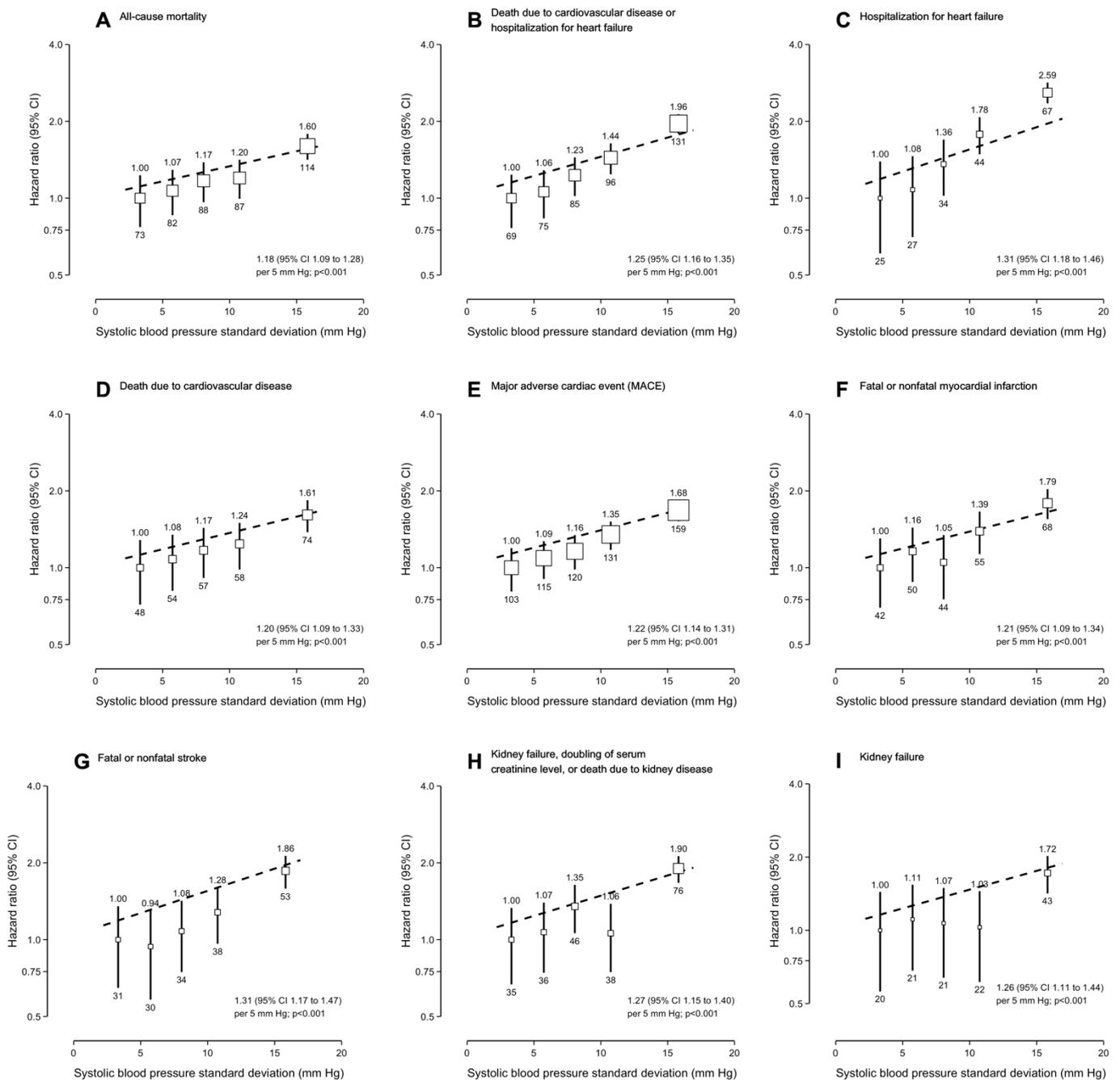


Figure S9. Shape of associations of standard deviation of systolic blood pressure variability with cardiovascular, kidney, and mortality outcomes in minimally-adjusted (adjusted for age, sex, race, and randomised treatment allocation only) Cox proportional hazards models. Square markers show hazard ratios (HRs) for quintiles of standard deviation (SD) of systolic blood pressure (SBP) variability relative to the reference group (quintile 1) and are positioned on the x-axis according to the median SD value of each quintile. Numbers above each upper confidence interval (CI) limit denote HR estimates for each quintile, and numbers below each lower CI limit denote number of events in each quintile. The slope of the fitted line gives the inverse-variance weighted mean change in HR (95% CI) for the three trials per 5 mm Hg increase in SD of SBP variability. The HR is plotted on a log



scale and the area of each square marker is inversely proportional to the variance of the log risk. Group-specific 95% CIs, calculated from this variance, are shown by vertical bars.

Figure S10. Shape of associations of coefficient of variation of systolic blood pressure variability with cardiovascular, kidney, and mortality outcomes in minimally-adjusted (adjusted for age, sex, race, and randomised treatment allocation only) Cox proportional hazards models. Square markers show hazard ratios (HRs) for quintiles of coefficient of variation (CV) of systolic blood pressure (SBP) variability relative to the reference group (quintile 1) and are positioned on the x-axis according to the median SD value of each quintile. Numbers above each upper confidence interval (CI) limit denote HR estimates for each quintile, and numbers below each lower CI limit denote number of events in each quintile. The slope of the fitted line gives the inverse-variance weighted mean change in HR (95% CI) for the three trials per 4 % increase in CV of SBP variability. The HR is plotted on a log scale and the area of each square marker is inversely proportional to the variance of the log risk. Group-specific 95% CIs, calculated from this variance, are shown by vertical bars.

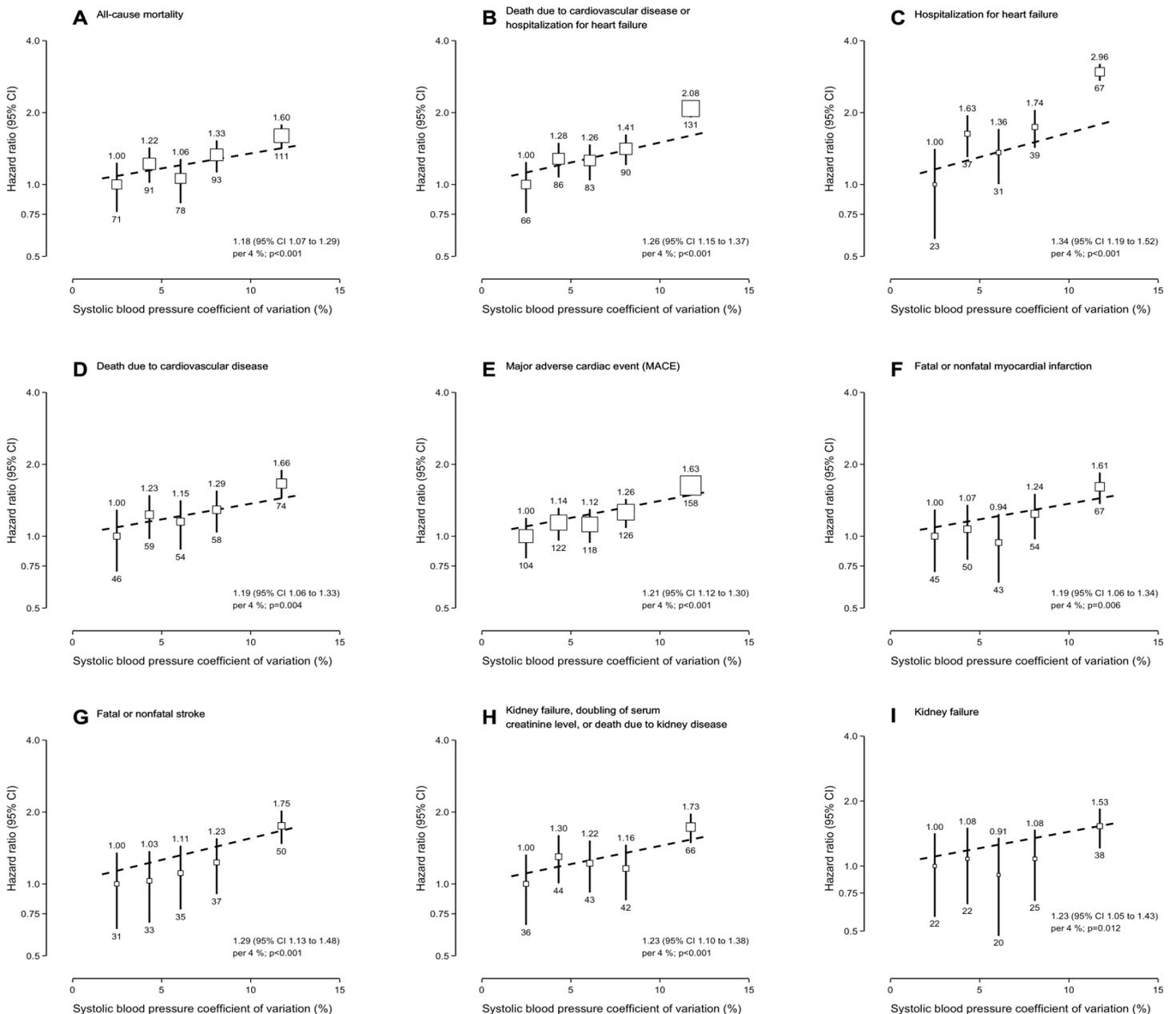
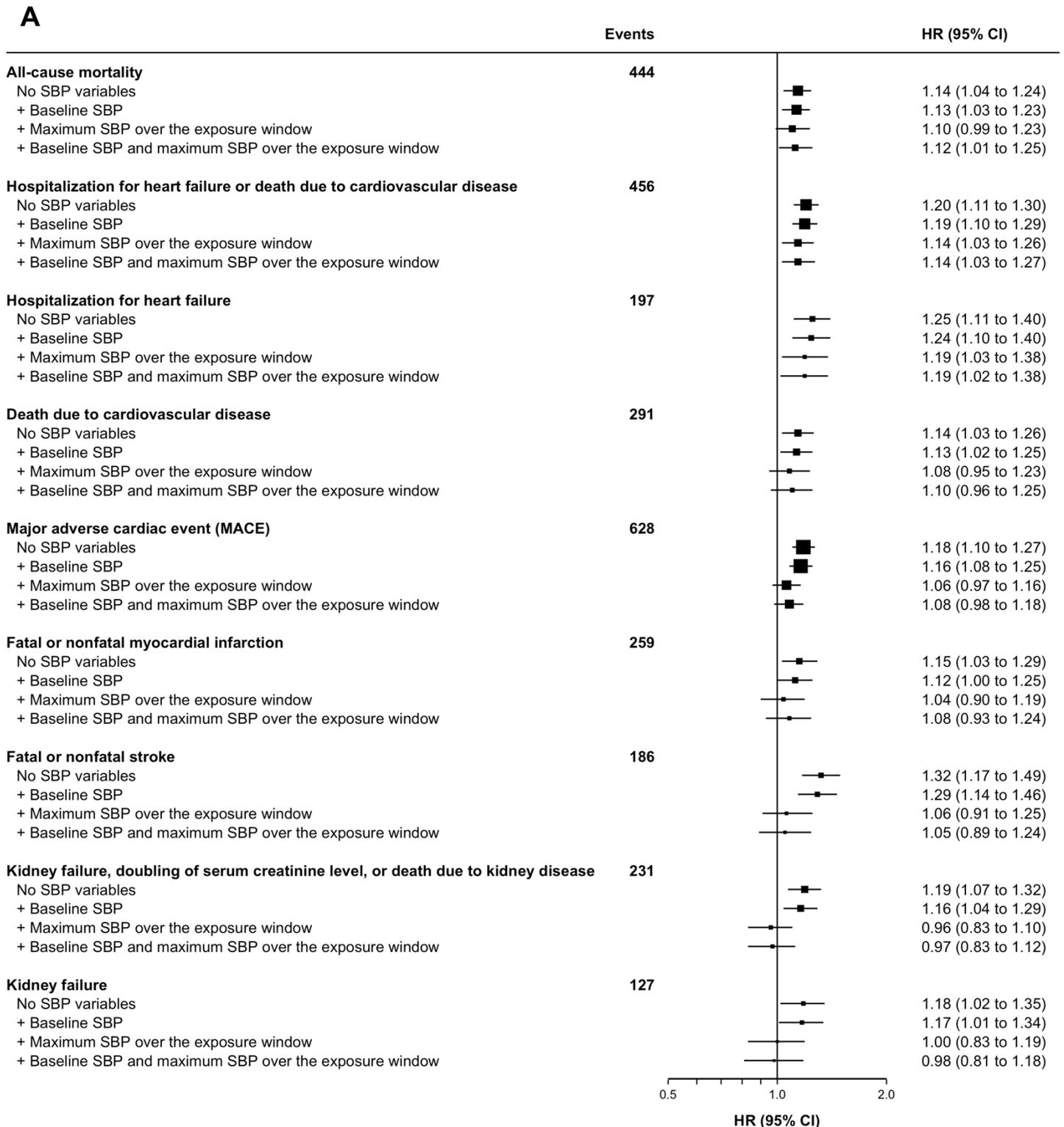


Figure S11. Effect of serial adjustment for systolic blood pressure variables on associations of A) standard deviation and B) coefficient of variation of systolic blood pressure with cardiovascular, kidney, and mortality outcomes. Square markers show hazard ratios (HRs) and horizontal bars show 95% confidence intervals (CIs) for a 1 standard deviation (SD) increase in each parameter, corresponding to an increase in 5.3 mm Hg in SD and 3.8 % in coefficient of variation (CV) of systolic blood pressure variability. The area of each square marker is inversely proportional to the variance of the HR estimate.



B

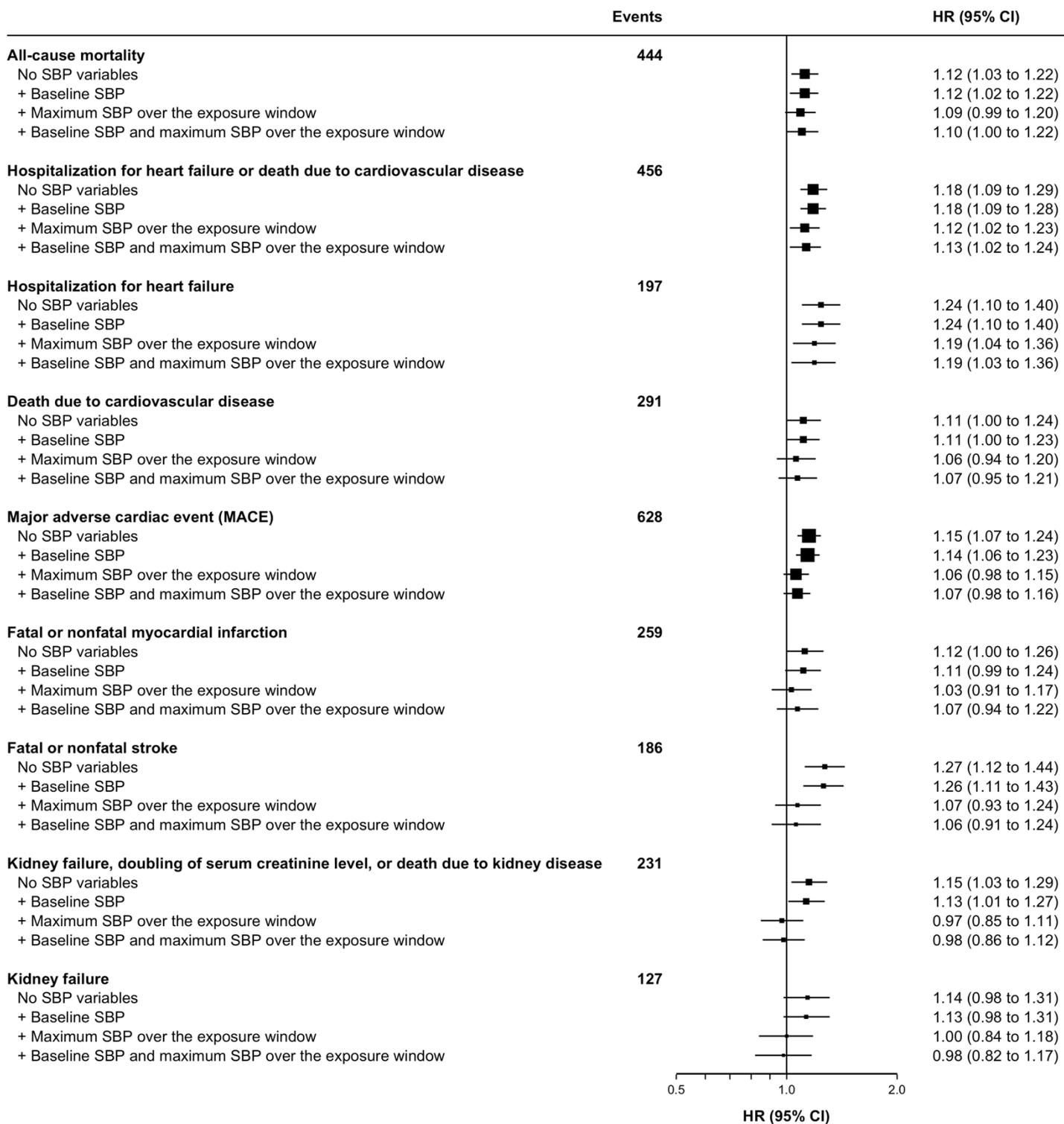


Figure S12. Shape of associations of standard deviation of diastolic blood pressure variability with cardiovascular, kidney, and mortality outcomes in fully-adjusted Cox proportional hazards models. Square markers show hazard ratios (HRs) for quintiles of standard deviation (SD) of diastolic blood pressure (DBP) variability relative to the reference group (quintile 1) and are positioned on the x-axis according to the median SD value of each quintile. Numbers above each upper confidence interval (CI) limit denote HR estimates for each quintile, and numbers below each lower CI limit denote number of events in each quintile. The slope of the fitted line gives the inverse-variance weighted mean change in HR (95% CI) for the three trials per 5 mm Hg increase in SD of DBP variability. The HR is plotted on a log scale and the area of each square marker is inversely proportional to the variance of the log risk. Group-specific 95% CIs, calculated from this variance, are shown by vertical bars.

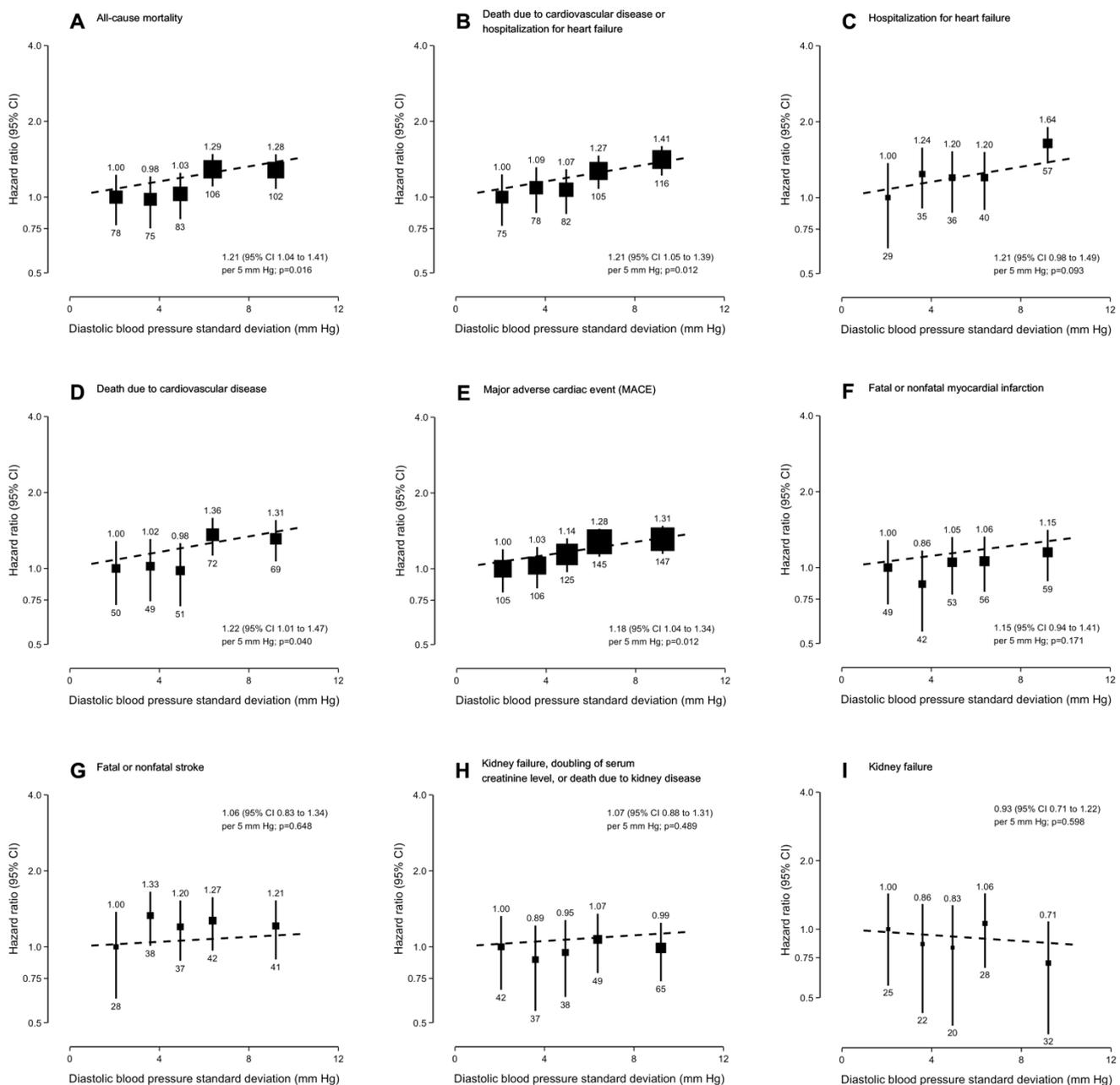


Figure S13. Shape of associations of coefficient of variation of diastolic blood pressure variability with cardiovascular, kidney, and mortality outcomes in fully-adjusted Cox proportional hazards models. Square markers show hazard ratios (HRs) for quintiles of coefficient of variation (CV) of diastolic blood pressure (DBP) variability relative to the reference group (quintile 1) and are positioned on the x-axis according to the median CV value of each quintile. Numbers above each upper confidence interval (CI) limit denote HR estimates for each quintile, and numbers below each lower CI limit denote number of events in each quintile. The slope of the fitted line gives the inverse-variance weighted mean change in HR (95% CI) for the three trials per 4 % increase in CV of DBP variability. The HR is plotted on a log scale and the area of each square marker is inversely proportional to the variance of the log risk. Group-specific 95% CIs, calculated from this variance, are shown by vertical bars.

