



ORIGINAL RESEARCH

# Age-Specific Associations of Usual Blood Pressure Variability With Cardiovascular Disease and Mortality: 10-Year Diabetes Mellitus Cohort Study

Eric Yuk Fai Wan , PhD; Esther Yee Tak Yu , MBBS; Weng Yee Chin, MD; Jessica K. Barrett, PhD; Ian Chi Kei Wong , PhD; Esther Wai Yin Chan , PhD; Celine Sze Ling Chui, PhD; Shiqi Chen, BSocSc; Cindy Lo Kuen Lam, MD

**BACKGROUND:** The detrimental effects of increased variability in systolic blood pressure (SBP) on cardiovascular disease (CVD) and mortality risk in patients with diabetes mellitus remains unclear. This study evaluated age-specific association of usual SBP visit-to-visit variability with CVD and mortality in patients with type 2 diabetes mellitus.

**METHODS AND RESULTS:** A retrospective cohort study investigated 155 982 patients with diabetes mellitus aged 45 to 84 years without CVD at baseline (2008–2010). Usual SBP variability was estimated using SBP SD obtained from a mixed-effects model. Age-specific associations (45–54, 55–64, 65–74, 75–84 years) between usual SBP variability, CVD, and mortality risk were assessed by Cox regression adjusted for patient characteristics. After a median follow-up of 9.7 years, 49 816 events (including 34 039 CVD events and 29 211 mortalities) were identified. Elevated SBP variability was independently, positively, and log-linearly associated with higher CVD and mortality risk among all age groups, with no evidence of any threshold effects. The excess CVD and mortality risk per 5 mm Hg increase in SBP variability within the 45 to 54 age group is >3 times higher than the 70 to 79 age group (hazard ratio, 1.66; 95% CI, 1.49–1.85 versus hazard ratio, 1.19; 95% CI, 1.15–1.23). The significant associations remained consistent among all subgroups. Patients with younger age had a higher association of SBP variability with event outcomes.

**CONCLUSIONS:** The findings suggest that SBP visit-to-visit variability was strongly associated with CVD and mortality with no evidence of a threshold effect in a population with diabetes mellitus. As well as controlling overall blood pressure levels, SBP visit-to-visit variability should be monitored and evaluated in routine practice, in particular for younger patients.

**Key Words:** blood pressure ■ cardiovascular disease ■ diabetes mellitus ■ mortality ■ visit-to-visit variability

**D** diabetes mellitus (DM) is one of the most common chronic diseases, affecting 425 million people worldwide, and the number is estimated to rise to 629 million by the year 2045.<sup>1</sup> With a high prevalence of 8.8%, DM is a source of great burden for global health care because of its high incident complications.<sup>2</sup> Compared with patients without DM, patients

with DM have at a 2- to 3-fold higher risk of cardiovascular disease (CVD), which is a key factor contributing to mortality and disability, leading to 5 million deaths in 2015.<sup>3</sup> The benefits of blood pressure control, in particular systolic blood pressure (SBP), in preventing CVD is well studied in populations with DM,<sup>4–7</sup> and thus several international guidelines on DM management

Correspondence to: Eric Yuk Fai Wan, PhD, and Esther Yee Tak Yu, MBBS, Department of Family Medicine and Primary Care, the University of Hong Kong, 3/F Ap Lei Chau Clinic, 161 Main Street, Ap Lei Chau, Hong Kong. E-mail: yfwan@hku.hk; ytyu@hku.hk

Preprint posted on Research Square March 10, 2020. DOI: 10.21203/rs.3.rs-16513/v1.

Supplementary Material for this article is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.019026>

For Sources of Funding and Disclosures, see page 11.

© 2021 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

JAHA is available at: [www.ahajournals.org/journal/jaha](http://www.ahajournals.org/journal/jaha)

## CLINICAL PERSPECTIVE

### What Is New?

- Since visit-to-visit variability in systolic blood pressure is a relatively new concept in the clinical field, its effects on cardiovascular disease and mortality risk in patients with diabetes mellitus remain unclear.
- This large cohort study updates our understanding by using a longer follow-up period and using statistical methods to correct for regression dilution bias to evaluate the age-specific association between usual systolic blood pressure variability and risk of cardiovascular disease and mortality among Chinese patients with diabetes mellitus.

### What Are the Clinical Implications?

- As well as controlling overall blood pressure levels, systolic blood pressure visit-to-visit variability should be monitored and evaluated in routine practice, in particular for younger patients.

## Nonstandard Abbreviations and Acronyms

<b>DM</b>	diabetes mellitus
<b>HA</b>	Hospital Authority
<b>SBP</b>	systolic blood pressure
<b>T2DM</b>	type 2 diabetes mellitus

have established the SBP target.<sup>8,9</sup> Since visit-to-visit variability in SBP is a relatively new concept in the clinical field and more solid evidence is needed to prove its value in risk prediction. The effect of SBP variability has received particular attention in the context of patients with DM.

A recent systematic review found a relationship between long-term SBP variability and higher risk of CVD and mortality in the population with DM.<sup>10</sup> However, only 7 of 18 studies included in the review contributed results for the effect of the long-term variability of SBP on CVD and mortality outcomes (6 for CVD; 5 for mortality). One of the more recent studies included in this review was conducted in a Swedish population with DM managed in primary care settings. It showed that SBP variability was associated with all-cause mortality only for patients without CVD and not taking blood pressure (BP)-lowering medications but not for other patients with DM.<sup>11</sup> Furthermore, among these 7 studies, 4 studies had a small ( $n < 3000$ ) number of patients, and 5 studies had  $< 10$  years of follow-up. More importantly, the measures of SBP variability are

estimated on a person-by-person basis and thus subject to measurement error, which causes regression dilution bias in the estimated association between SBP variability and event outcomes.<sup>12</sup> In addition, the association between SBP and cardiovascular diseases may vary in different age groups,<sup>13–15</sup> but there is no available study evaluating the age-specific effects of usual SBP variability on CVD and mortality among patients with DM.

This cohort study updates our previous study using a longer follow-up period (10 years versus 5 years) and using statistical methods to correct for regression dilution bias to evaluate the age-specific association between usual SBP variability and CVD and mortality in patients with type 2 DM (T2DM) managed in Hong Kong primary care settings.<sup>16</sup> The pattern of variability among patients with different baseline characteristics was also explored. More comprehensive knowledge of the effect of usual SBP variability could help enable clinicians to better identify patients at higher risk earlier on.

## METHODS

Because of the confidentiality of the data used for this study and strict privacy policy from the data holder that the data can be kept among the designated research personnel only, the data cannot be provided to anyone else, irrespective of whether or not the data are anonymized.

### Study Design

This is a retrospective cohort study, which obtained the data from the prospectively collected population clinical database from the Hong Kong Hospital Authority (HA). Patients were included if they were aged 45 to 84 years, with a clinical diagnosis of T2DM, with no prior diagnosis of CVD at baseline, and managed in public primary care clinics of the Hong Kong HA from January 1, 2008, to December 31, 2010. The HA is the chief regulatory institution for all 42 public-sector hospitals, 47 specialist outpatient clinics, and 73 primary care clinics in Hong Kong. Over 90% of the local population with chronic disease receive medical treatments through the HA.<sup>17</sup> No consent was needed from the subjects because the data were analyzed anonymously. Diagnosis of T2DM was made by HA clinic doctors and recorded using the International Classification of Primary Care-2 code of T90. All confidential data, including patients' characteristics and event outcomes, are kept in the electronic health database of the HA's clinical management system. The validity and coding accuracy of the clinical management system database has been well established and

adopted in several previous high-quality population-based epidemiologic studies.<sup>16,18,19</sup> Clinicians and other healthcare professionals receive training in using the clinical management system to record a variety of the clinical information and patient demographics simultaneously during the doctor's consultation, including patients' diagnoses, prescriptions, laboratory tests and results, emergency department visits, hospitalizations, and specialist and primary care outpatient clinic visits. The timeline of the measurements of SBP and outcome determination is presented in Figure S1. Most patients with DM managed in public primary care clinics are typically followed-up once per quarter. Hence, a first SBP reading with a repeated reading every 3 months until the end of the 2-year follow-up (total 9 readings) was used to estimate the SBP variability. Each patient was continuously tracked until the incident date of the outcome event, death, or the last follow-up visit before December 31, 2017, whichever occurred first.

### Outcome Measures

The primary outcome was the incidence of the composite of CVD and all-cause mortality. The secondary outcomes consisted of individual CVD, the subtype of coronary heart disease (CHD), stroke, heart failure, all-cause mortality, CVD mortality, and non-CVD mortality. The outcome events were defined using the International Classification of Primary Care-2 or the *International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM)*, which are officially recognized diagnostic codes. The Hong Kong Government Death Registry provided the mortality reports retrieved from their internal population data, where CVD-related mortality was classified as death with a history of CVD or the main cause of death was recorded according to the *International Classification of Diseases, Tenth Edition* codes of I20 to I25, I50, and I60 to I69. In a previous local study, these codes have revealed a high coding accuracy in diagnosing myocardial infarction and stroke with positive predictive values of 85.4% (95% CI, 78.8%–90.6%) and 91.1% (83.2%–96.1%), respectively.<sup>19</sup> Table S1 also summarizes all event definitions.

### Ethical Approval

Institutional review boards of the Hong Kong Hospital Authority have reviewed and approved the ethical examination in this study.

### Clinical BP Measurements

In the process of obtaining and documenting SBP readings in patients during the consultations, all clinics strictly followed a standardized guideline.<sup>20</sup> Patients

are instructed to maintain a seated position for 5 minutes without any distraction before the start of measurements of SBP, and to have at least 1 minute of rest between 2 measurements of SBP. Nurses or trained patient care assistants used a standardized automated sphygmomanometer (UA-853, Tokyo, Japan; EDAN M3A, Shenzhen, P.R. China; or other equivalent measurements). Previous studies showed that the technology used by the UA-853 has been clinically validated by the general population.<sup>21</sup> However, a validation study for EDAN M3A or other equivalent measurements is unavailable. If the difference between the 2 readings exceeded 5 mm Hg, an extra measurement would be taken. The average of all SBP readings taken at a single visit was calculated and recorded as the SBP measurement result for the corresponding visit in the database. Note that, given the limitation of the setting, the BP measurements were not necessarily implemented at the same time of day for each patient.

### Usual SBP and SBP Variability Measurements

To minimize measurement error, and therefore regression dilution bias in the corresponding hazard ratio, usual SBP, and SBP variability measures were obtained using a mixed effects model, which allows the within-individual variability to differ between individuals. (Regression dilution bias occurs when random measurement error in the values of an explanatory variable causes an attenuation or "flattening" of the slope of the regression line.) Longitudinal trajectories were modeled by including a slope term as both a fixed and random effect. Bayesian Markov chain Monte Carlo was used to fit the mixed-effects model. The usual SBP and SBP variability were estimated by the posterior mean of the random intercept and the residual standard deviation, respectively. The mixed-effects model was not adjusted for other covariates. In general, the usual SBP and SBP variability were the individual (subject-specific) mean and SD of SBP from the mixed-effects model. Details of the calculation of the usual SBP and SBP variability measures have been described in Data S1 and elsewhere in the literature.<sup>12</sup> Patients with <4 SBP records were excluded from this study to increase the precision of the usual SBP and SBP variability estimates. The average total number of SBP measurements was 4.5 (SD, 1.3; range, 4–9). The analysis was implemented using JAGS Version 3.4.0 and the R2jags package in R.<sup>22,23</sup>

### Baseline Characteristics

Baseline covariates encompassed sex, age, smoking status, body mass index (BMI), SBP, diastolic blood

pressure, hemoglobin A1c, low-density lipoprotein cholesterol, estimated glomerular filtration rate (eGFR), the Charlson comorbidity index (a composite index representing a patient's comorbid conditions),<sup>24,25</sup> the use of anti-hypertensive drugs (eg, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker,  $\beta$ -blocker, calcium channel blocker, diuretics, and others [hydralazine, methyldopa, and prazosin]), oral antidiabetic drugs, insulin, and lipid-lowering agents. The latest record on or before baseline (defined in Figure S1) was used. The eGFR was computed in accordance with the creatinine level from blood testing along with the abbreviated Modification of Diet in Renal Disease Study formula recalibrated for Chinese (eGFR in mL/min per 1.73 m<sup>2</sup>=186×[(serum creatinine in  $\mu$ mol/L)×0.011]<sup>-1.154</sup>×(age)<sup>-0.203</sup>×(0.742 if female)×1.233), where 1.233 is the adjusted coefficient for local population.<sup>26</sup> All laboratory assays were performed in accredited laboratories by the College of American Pathologists, the Hong Kong Accreditation Service, or the National Association of Testing Authorities, Australia.

## Statistical Analysis

Multiple imputation was used to impute missing data for all baseline characteristics apart from blood pressure. The chained equation method was used to impute each missing value 5 times, adjusted for all baseline covariates and outcomes including CVD and all-cause mortality. The same analysis method was adopted for each of the 5 imputed data sets, and the results were pooled using Rubin's rule.<sup>27</sup>

All patients were allocated into 1 of 5 groups defined by their usual SBP variability (<10, 10–11.9, 12–13.9, 14–15.9, and  $\geq$ 16 mm Hg). After multiple imputation, descriptive statistics were displayed for integration of the baseline characteristics for each group. The cumulative incidence and incidence rate of CVD, mortality, and their composite events were reported, and the CI of the incidence rate was estimated using the Poisson distribution. Age-specific associations (45–54, 55–64, 65–74, and 75–84 years) between usual SBP variability and the risk of an event were estimated by multivariable Cox proportional hazards regressions adjusted for usual SBP and all baseline covariates including the use of antihypertensive drugs. The hazard ratio (HR), which is a measure of the effect of SBP variability on the hazard of the event of interest, and its CI were reported. An additional term was fitted to allow the HR within each age group to be assessed as the geometric mean of the HRs in the first and second half of that decade.<sup>28</sup> Thus, the HRs comparing event risk between different SBP variability groups were not assumed to be similar for different age decades. The 95% CIs of the HRs were estimated using the floating absolute risk, without the requirement of selecting

a reference group for displaying the standard error.<sup>29</sup> Details of the above methods have previously been described in the literature,<sup>28,29</sup> and they have been widely adopted in several large epidemiologic studies.<sup>30–32</sup> To confirm the shape of the association, Cox models were fitted with SBP variability treated as a continuous variable and using restricted cubic splines with 3 knots to model the association.<sup>33</sup> To enhance the robustness of the results and minimize the potential bias attributable to multiple imputation, reverse causality, and the number of SBP measurements, 5 sensitivity analyses were conducted. First, Rosner's regression method, rather than the mixed-effects model, was used to adjust for regression dilution bias.<sup>34</sup> The details of this approach are described in Data S1. Second, a complete case analysis was performed. Third, patients were excluded if they attended <1-year of follow-up. Fourth, the analyses were implemented for patients with  $\geq$ 2 and  $\geq$ 7 rather than  $\geq$ 4 SBP measurements to evaluate the potential selection bias attributable to the cutoff in the number of SBP measurements. Fifth, the use of aspirin was included as one of the covariates in the regression analysis.

To further explore the effect of usual SBP variability on the outcomes for patients with different characteristics, subgroup analyses were performed, which were stratified by sex (male, female), age at risk (45–54, 55–64, 65–74, 75–84 years), smoking status (nonsmoker, smoker), BMI (<25,  $\geq$ 25 kg/m<sup>2</sup>), baseline SBP (<130, 130–139, 140–149,  $\geq$ 150 mm Hg), usual SBP (<130, 130–139, 140–150,  $\geq$ 150 mm Hg), low-density lipoprotein cholesterol (<2.6,  $\geq$ 2.6 mmol/L), hemoglobin A<sub>1c</sub> (<7,  $\geq$ 7%), eGFR (<90,  $\geq$ 90 mL/min per 1.73 m<sup>2</sup>), Charlson index (<4,  $\geq$ 4), the number of types of antihypertensive drugs prescribed (0, 1, 2, 3), and the use of different antihypertensive drugs.

All significance tests were 2-tailed and those with a  $P$ <0.05 were considered statistically significant. The statistical analysis was executed in Stata Version 13.0.

## RESULTS

### Patient Population

A cohort of 155 982 patients with T2DM satisfied the inclusion criteria and was included in the analyses. Table S2 illustrates that the data completion rate for all baseline characteristics was higher than 84.3%, except for eGFR (77.1%), BMI (64.6%), and low-density lipoprotein cholesterol (63.6%). In Table 1, patient characteristics are summarized by usual SBP variability group at baseline after multiple imputation. Overall, the mean age was 63.9 years (SD, 10.0) and men account for 45.2%. Usual SBP mean and SBP variability were 137.1 mm Hg (SD, 10.7) and 12.7 mm Hg (SD, 2.3), respectively.

**Table 1. Descriptive Statistics for Baseline Characteristics Among Patients Stratified by SBP Variability**

	SBP variability					Overall (N=155 982)
	<10 mm Hg (N=7315)	10–11 mm Hg (N=42 878)	12–13 mm Hg (N=59 851)	14–15 mm Hg (N=29 422)	≥16 mm Hg (N=16 516)	
Baseline characteristics						
Male, %	47.6	47.6	44.9	44.1	41.4	45.2
Age, y	58.3±9.2	61.6±9.8	64.2±9.8	65.9±9.7	67.2±9.7	63.9±10.0
Current smoker	13.6	11.4	9.8	9.5	9.3	10.3
SBP, mm Hg	114.3±9.3	128.4±11.1	138.4±13.8	143.7±17.9	149.6±25.2	136.7±17.6
DBP, mm Hg	69.2±8.1	74.0±9.2	75.9±9.8	76.4±10.8	77.2±12.4	75.3±10.2
HbA <sub>1c</sub> , %	7.3±1.5	7.4±1.4	7.4±1.5	7.4±1.5	7.4±1.5	7.4±1.4
BMI, kg/m <sup>2</sup>	24.6±4.4	25.4±4.4	25.7±4.5	25.7±5.5	25.8±4.8	25.6±4.9
LDL-C, mmol/L	3.1±0.9	3.1±1.0	3.2±1.0	3.2±1.0	3.2±1.0	3.2±1.1
eGFR, mL/min per 1.73 m <sup>2</sup>	109.3±33.4	104.0±41.6	99.8±73.9	96.3±47.4	92.5±46.8	100.0±62.1
Charlson index	2.4±1.1	2.7±1.2	3.0±1.2	3.2±1.3	3.4±1.3	3.0±1.3
Use of oral antidiabetic drugs	79.7	80.5	81.5	81.0	80.9	81.0
Use of insulin	1.1	0.7	0.9	1.2	1.7	1.0
Use of ACEI/ARB	11.1	20.4	31.9	39.2	44.6	30.5
Use of β-blocker	16.8	23.5	29.2	34.9	44.6	29.8
Use of CCB	17.3	29.0	37.7	47.4	59.2	38.4
Use of diuretic	7.9	12.3	14.4	15.1	15.9	13.8
Use of other antihypertensive drugs	5.1	7.6	10.8	13.5	17.1	10.8
Use of lipid-lowering agents	7.9	9.8	9.8	10.0	10.6	9.8
Variables assessed during the assessment period						
Number of SBP measurements	4.7±1.5	4.6±0.6	4.5±0.4	4.5±0.6	4.6±0.9	4.5±1.3
Usual SBP, mm Hg	116.8±6.9	129.6±3.0	138.5±2.5	143.3±3.8	149.2±5.8	137.1±10.7
SBP variability, mm Hg	9.0±0.4	10.7±0.2	12.5±0.2	14.3±0.3	17.4±1.2	12.7±2.3

All parameters are expressed in either percentage or mean (SD). Other antihypertensive drugs included acarbose, glucagon-like peptide-1 agonist, meglitinides. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; LDL-C, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

## Outcomes

Table 2 demonstrates the cumulative incidence and incidence rate of CVD, all-cause mortality, and their composite event by usual SBP variability group. After a median follow-up of 9.7 years (16.4 million person-years), the overall number of any event is 49 816 incidents, incorporating 34 039 CVDs and 29 211 mortalities. There was a trend for both cumulative incidence and incidence rates of all outcomes to increase with SBP variability, from the lowest group (usual SBP variability <10 mm Hg) to the highest group (usual SBP variability ≥18 mm Hg), including CVD from 12.8 to 42.7, mortality from 10.3 to 34.2, and all events from 20.6 to 60.9 per 1000 person-years. Age-specific associations are shown in Figure 1 and Figure S2. Figure S3 presents the positive and log-linear association (curvilinear) between usual SBP variability and all outcomes after adjustment for the patient's baseline characteristics. The results of the Cox models with a

restricted cubic spline SBP variability association also suggested direct log-linear associations, as indicated in Figure S4. In general, positive and log-linear associations are found between SBP and the risk of CVD, including CHD, stroke, heart failure, all-cause mortality, CVD mortality, non-CVD mortality, and their composite event for all age groups.

Figure 2 demonstrates the relationship between usual SBP variability as a continuous variable and the risk of all outcome events. Each 5 mm Hg increase in usual SBP variability was associated with 27% (HR, 1.27; 95% CI, 1.23–1.32), 30% (HR, 1.30; 95% CI, 1.25–1.35), and 26% (HR, 1.26; 95% CI, 1.23–1.30) higher risk of CVD, all-cause mortality, and their composite, respectively. Moreover, the HR for stroke (HR, 1.33; 95% CI, 1.27–1.40) is higher than that for CHD (HR, 1.21; 95% CI, 1.15–1.27) and heart failure (HR, 1.21; 95% CI, 1.14–1.28), indicating that the association with CVD may be driven predominantly by stroke. Similarly,

**Table 2. Number, Incidence Rate, and Hazard Ratio of CVD and Mortality, Stratified by SBP Variability**

	SBP variability				
	<10 mm Hg (N=7315)	10–12 mm Hg (N=42878)	13–15 mm Hg (N=59 851)	16–18 mm Hg (N=29 422)	≥18 mm Hg (N=16 516)
<b>CVD</b>					
Cumulative cases with event	819	7306	13 031	7731	5152
Incidence rate (95% CI)*	12.8 (12.0–13.8)	20.1 (19.6–20.6)	26.6 (26.1–27.0)	33.7 (32.9–34.4)	42.7 (41.5–43.9)
Hazard ratio† (95% CI)	1.00 (0.92–1.08)	1.18 (1.15–1.21)	1.27 (1.25–1.29)	1.41 (1.37–1.44)	1.58 (1.52–1.64)
<b>Coronary heart disease</b>					
Cumulative cases with event	417	3543	6093	3513	2331
Incidence rate (95% CI)*	6.4 (5.8–7.0)	9.4 (9.1–9.7)	11.8 (11.5–12.1)	14.3 (13.8–14.7)	17.7 (17.0–18.5)
Hazard ratio† (95% CI)	1.00 (0.90–1.12)	1.15 (1.11–1.20)	1.19 (1.17–1.22)	1.27 (1.23–1.33)	1.42 (1.35–1.50)
<b>Stroke</b>					
Cumulative cases with event	381	3614	6500	3990	2667
Incidence rate (95% CI)*	5.8 (5.3–6.4)	9.6 (9.2–9.9)	12.6 (12.3–12.9)	16.3 (15.8–16.8)	20.5 (19.8–21.3)
Hazard ratio† (95% CI)	1.00 (0.89–1.12)	1.26 (1.21–1.31)	1.39 (1.36–1.42)	1.59 (1.53–1.65)	1.81 (1.72–1.90)
<b>Heart failure</b>					
Cumulative cases with event	126	1693	3726	2406	1821
Incidence rate (95% CI)*	1.9 (1.6–2.3)	4.4 (4.2–4.6)	7.0 (6.8–7.3)	9.5 (9.2–9.9)	13.6 (12.9–14.2)
Hazard ratio† (95% CI)	1.00 (0.82–1.23)	1.38 (1.30–1.46)	1.48 (1.44–1.53)	1.56 (1.49–1.64)	1.76 (1.65–1.87)
<b>All-cause mortality</b>					
Cumulative cases with event	689	5976	11 070	6707	4769
Incidence rate (95% CI)*	10.3 (9.6–11.1)	15.3 (14.9–15.6)	20.5 (20.1–20.9)	25.9 (25.3–26.5)	34.2 (33.3–35.2)
Hazard ratio† (95% CI)	1.00 (0.91–1.09)	1.06 (1.03–1.10)	1.14 (1.12–1.16)	1.25 (1.21–1.29)	1.46 (1.40–1.52)
<b>Cardiovascular mortality</b>					
Cumulative cases with event	209	2501	5186	3441	2670
Incidence rate (95% CI)*	3.1 (2.7–3.6)	6.4 (6.1–6.6)	9.6 (9.3–9.9)	13.3 (12.9–13.8)	19.2 (18.5–19.9)
Hazard ratio† (95% CI)	1.00 (0.85–1.18)	1.26 (1.20–1.33)	1.38 (1.34–1.42)	1.59 (1.52–1.66)	1.90 (1.79–2.01)
<b>Non-cardiovascular mortality</b>					
Cumulative cases with event	480	3475	5884	3266	2099
Incidence rate (95% CI)*	7.2 (6.6–7.8)	8.9 (8.6–9.2)	10.9 (10.6–11.2)	12.6 (12.2–13.1)	15.1 (14.5–15.7)
Hazard ratio† (95% CI)	1.00 (0.90–1.11)	1.02 (0.97–1.06)	1.08 (1.06–1.11)	1.13 (1.09–1.18)	1.26 (1.19–1.34)
<b>All composite events</b>					
Cumulative cases with event	1311	10 893	19 129	11 138	7345
Incidence rate (95% CI)*	20.6 (19.5–21.7)	30.0 (29.4–30.5)	39.0 (38.4–39.5)	48.5 (47.6–49.4)	60.9 (59.5–62.3)
Hazard ratio† (95% CI)	1.00 (0.94–1.07)	1.13 (1.10–1.15)	1.22 (1.20–1.23)	1.33 (1.30–1.36)	1.50 (1.46–1.55)

CKD indicates chronic kidney disease; CVD, cardiovascular disease; and SBP, systolic blood pressure.

\*Incidence rate (cases/1000 person-years) with 95% CI based on Poisson Distribution.

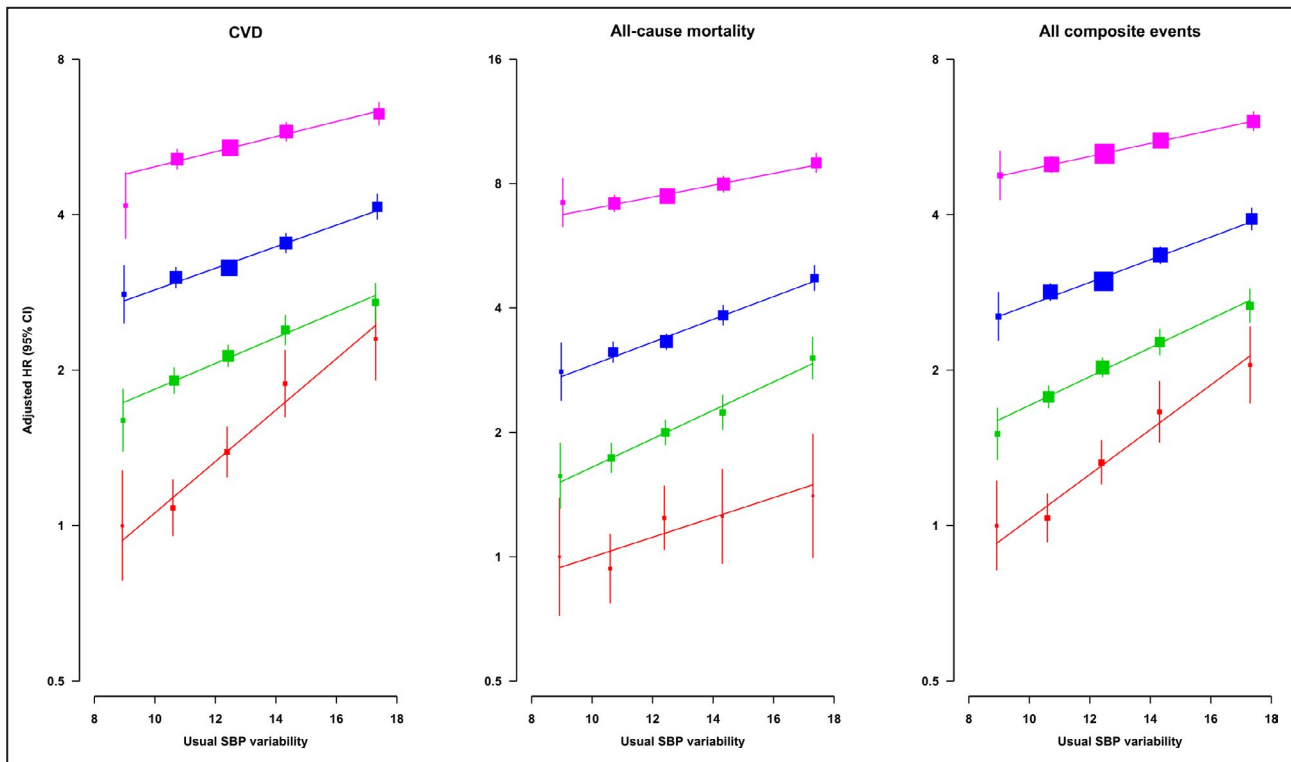
†Hazard ratio was adjusted by age at risk, sex, smoking status, body mass index, SBP, diastolic blood pressure, hemoglobin A<sub>1c</sub>, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of oral antidiabetic drugs, insulin, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, β-blocker, calcium channel blocker, diuretic, other antihypertensive drugs, lipid-lowering agent, Charlson's index and usual SBP.

the HR for non-CVD related mortality (HR, 1.18; 95% CI, 1.12–1.25) was lower than that for CVD-related mortality (HR, 1.40; 95% CI, 1.33–1.48), implying that mortality may be mainly attributable to CVD-related mortality. Five sensitivity analyses including (1) the use of Rosner's regression method (the regression dilution ratio was 4.13) in Figure S5, (2) complete case analysis in Figure S6, (3) excluding patients with <1-year follow-up period in Figure S7, (4) including patients with ≥2 and ≥7 rather than ≥4 SBP measurements in

Figures S8 and S9, (5) including the use of aspirin on or before baseline in Figure S10, demonstrated similar results.

### Subgroup Analyses

The forest plots in Figure 3 and Figures S11 and S12 show that usual SBP variability is associated with a significant increase in the risk of each outcome event across all selected subgroups. In general, the HRs for



**Figure 1.** Age-specific adjusted HRs for the risk of CVD, all-cause mortality, and their composite with increasing usual SBP variability by multivariable Cox regressions.

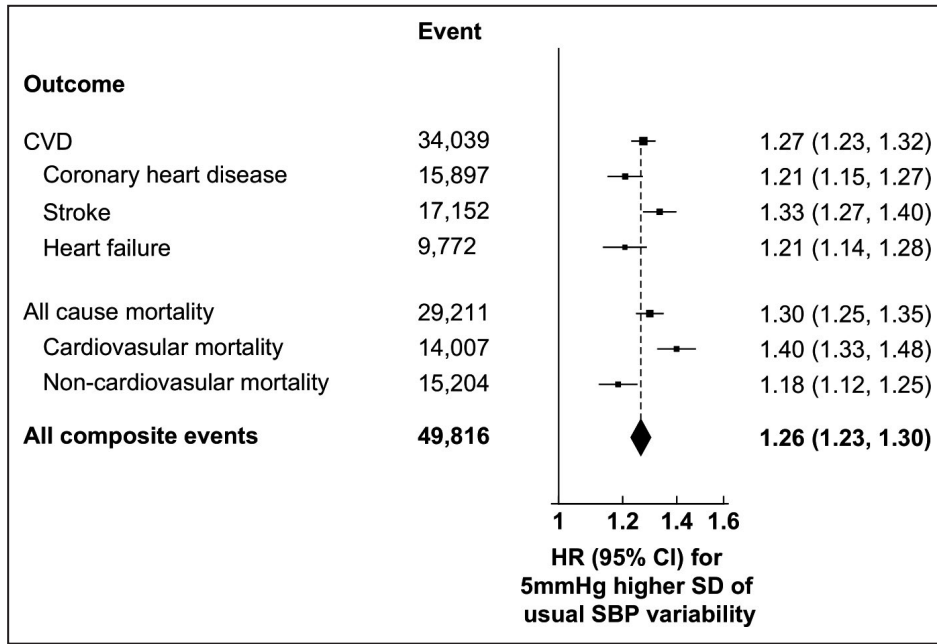
HR was adjusted by age at risk, sex, smoking status, body mass index, SBP, diastolic blood pressure, hemoglobin A<sub>1c</sub>, low-density lipoprotein cholesterol, estimated glomerular filtration rate, the usages of oral antidiabetic drugs, insulin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker,  $\beta$ -blocker, calcium channel blocker, diuretic, other antihypertensive drugs, lipid-lowering agent, Charlson's index, and usual SBP. Red, green, blue, and pink line were 45 to 54, 55 to 64, 65 to 74, and 75 to 84 age at-risk group. The area of each square was inversely proportional to the variance of the category-specific log risk. CIs are displayed as floating absolute risks. CVD indicates cardiovascular disease; HR, hazard ratio; and SBP, systolic blood pressure.

the composite of CVD and all-cause mortality demonstrate that age and usual SBP is inversely related to the SBP variability HR. The HRs are higher among patients with low comorbidity (Charlson index <4), and patients without prescription of antihypertensive drugs. Comparable effects are observed when stratified by male patients, smoking status, BMI, baseline SBP, hemoglobin A<sub>1c</sub>, eGFR, and low-density lipoprotein cholesterol, and use of diverse antihypertensive drugs. The age at which at-risk subgroups have the most pronounced difference in SBP variability HRs for the risk of CVD and all-cause mortality, with a 66% higher risk per 5 mm Hg increase is in the 45 to 54 age group (all composite outcomes HR, 1.66; 95% CI, 1.49–1.85), compared with a 19% higher risk in the 70 to 79 age group (all composite outcomes HR, 1.19; 95% CI, 1.15–1.23), which indicates that the excess risk in the 45 to 54 age group per 5 mm Hg increase in SBP variability is >3 times higher than for the 70 to 79 age group. A similar trend for the usual SBP was obtained in that patients with usual SBP <130 mm Hg had doubled the risk compared with those with usual SBP  $\geq$ 150 mm Hg (HR, 1.39; 95% CI, 1.29–1.49 versus 1.17; 95% CI,

1.11–1.23). Different effects of usual SBP variability were observed in terms of the comorbidity (HR, 1.36; 95% CI, 1.32–1.41] in Charlson index <4 versus 1.23; 95% CI, 1.19–1.27 in Charlson index  $\geq$ 4) and the number of types of antihypertensive drug prescribed (HR, 1.49; 95% CI, 1.39–1.60 in none versus 1.27; 1.21–1.33 in  $\geq$ 3 types).

## DISCUSSION

This large cohort study is the first to estimate usual SBP variability using mixed-effects models to reduce regression dilution in the estimated association with outcome events, and to determine the positive and log-linear age-specific association between usual SBP variability and risk of CVD, CHD, stroke, heart failure, all-cause mortality, CVD mortality, and non-CVD mortality among Chinese patients with DM. The effect of SBP variability on the risk of various outcome events remained significant regardless of patient characteristics after adjusting for usual and baseline SBP, suggesting that SBP variability may provide additional valuable information as a potential predictor for the incidence of



**Figure 2.** Adjusted HRs for the risk of CVD, coronary heart disease, stroke, heart failure, all-cause mortality, CVD mortality, non-CVD mortality, and their composite with each 5 mm Hg increasing usual SBP variability using multivariable Cox regression.

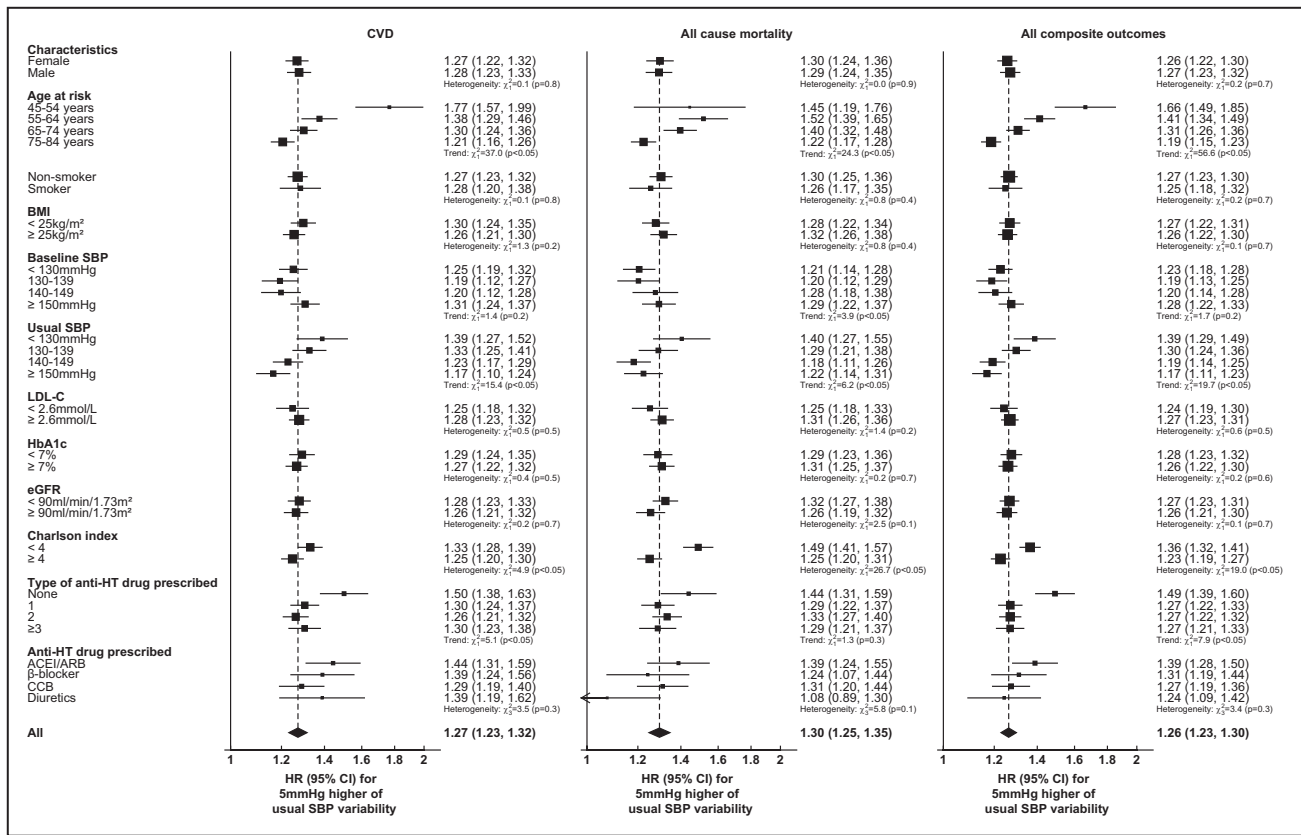
HR was adjusted by age at risk, sex, smoking status, body mass index, SBP, diastolic blood pressure, hemoglobin A<sub>1c</sub>, low-density lipoprotein cholesterol, estimated glomerular filtration rate, the usages of oral antidiabetic drugs, insulin, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, β-blocker, calcium channel blocker, diuretic, other antihypertensive drugs, lipid-lowering agent, Charlson’s index, and usual SBP. Squares show the HR while the diamond shows the pooled HR, and the dotted line indicates the center of the diamond. CVD indicates cardiovascular disease; HR, hazard ratio; and SBP, systolic blood pressure.

CVD events and mortality in the population with DM, irrespective of the absolute SBP readings. There was no threshold for SBP variability, indicating that the lower the SBP variability, the better the outcome. These findings suggest that clinicians should be mindful of the effect of BP fluctuation on the incidence of CVD and all-cause mortality, as well as the focus on an optimal BP target. Moreover, the impact of usual SBP variability is strengthened in patients at a younger age, lower usual SBP, Charlson index, and the number of types of antihypertensive drugs prescribed. This is suggestive that additional attention may be needed for these specific patient groups when they also experience higher SBP variability.

There is currently no literature investigating the age-specific effects of usual SBP variability on CVD and mortality among patients with DM. In general, our results demonstrated a direct log-linear or linear association between SBP variability and outcome events, which confirmed the results of previous studies. For instance, a posttrial follow-up study of the landmark ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation) trial, on 9113 patients with DM with a medium follow-up of 7.6 years also

illustrated the positive log-linear associations that each 5 mm Hg increment in SD of SBP was associated with a 13%, 8%, and 11% increase in the risk of all-cause mortality, CVD, and myocardial infarction, respectively.<sup>35</sup> No significant association for stroke and CVD mortality was obtained.<sup>35</sup> Nevertheless, they acknowledged that the small sample size and number of events (668 stroke events and 614 CVD mortality events) may have affected the generalizability of these results. A few studies have shown no evidence of any significant associations between SBP variability and outcome events.<sup>11,36</sup> In a cohort study on 2161 patients with DM in Taiwan, over a 5.5-year follow-up, SBP variability was significantly associated with all-cause mortality but not with CVD mortality. This was likely attributable to the small sample size and the small number of events as only 25 CVD mortality events among 2161 patients were observed.<sup>36</sup> Furthermore, the measurement of SBP variability was determined by SBP readings taken after baseline, which may have resulted in informative censoring or immortal time bias.<sup>15,37</sup> Compared with these studies, we have incorporated a significantly larger number of patients without CVD, longer follow-up periods, and a much larger number of





**Figure 3. Adjusted HRs for the risk of CVD, all-cause mortality, and their composite events with each 5 mm Hg increasing usual SBP variability by stratifying patient’s characteristics at baseline using multivariable Cox regression.**

HR was adjusted by age at risk, sex, smoking status, BMI, SBP, diastolic blood pressure, HbA<sub>1c</sub>, LDL-C, estimated glomerular filtration rate, the usages of oral antidiabetic drugs, insulin, ACEI/ARB, β-blocker, CCB, diuretic, other antihypertensive drugs, lipid-lowering agent, Charlson’s index, and usual SBP. Squares show the HR while the diamond shows the pooled HR, and the dotted line indicates the centre of the diamond. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; HR, hazard ratio; HT, hypertensive; LDL-C, low-density lipoprotein-cholesterol; and SBP, systolic blood pressure.

incident outcome events. In this current study, SBP variability was based on measurements taken before baseline; hence, the results should be less subject to bias and better powered to demonstrate the etiological associations between SBP variability and adverse outcomes. Note that none of the previous studies corrected their results for regression dilution bias, and thus their findings may underestimate the effect of SBP variability. Hence, it is expected that the strength of the association of SBP variability on the risk of event outcomes in this study will be greater.

In this current study, the analyses of individual CVD events identified a stronger impact of SBP variability on stroke compared with CHD and heart failure. Indeed, a recent meta-analysis, which mostly included either studies involving patients with severe diseases such as CVD or studies of the general population, also showed a similar pattern that SBP variability, as with usual BP,<sup>30</sup> contributes more to stroke than cardiac events.<sup>15</sup> Our results extend these findings that the effect of SBP

variability on CVD events may be driven primarily by stroke in the population with DM.

A recent post hoc analysis of the VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) trial on 13 803 patients with hypertension over a mean follow-up period of 4.2 years reported that SBP variability was associated with a significantly higher risk of multiple diseases in patients aged <68 years than in those aged ≥68 years.<sup>38</sup> Additionally, our findings from subgroup analyses showed a trend for those within the study age range of 45 to 85 years that not only younger people, but also those with lower-than-usual SBP, lower Charlson index, and with fewer types of antihypertensive drugs prescribed, were more susceptible to the adverse influence of SBP variability. The reasons may be that these patients were more likely to have lower SBP variability, as shown in Table 1 and the literature.<sup>39</sup> As a consequence, these patients may be more vulnerable to differences in SBP variability. Also, patients with these characteristics (eg younger and low comorbidity)

were more likely to have fewer vascular risk factors, and thus may be more sensitive to blood pressure variability. In contrast, other risk factors in patients with higher age and morbidity may overshadow the detrimental effect of SBP variability. A few studies have concluded that poor antihypertensive medication adherence and use of different types of antihypertensive drugs may cause patients to be more prone to higher SBP variability and CVD risk.<sup>40–42</sup> However, although drug adherence information was unavailable in this current study, many previous studies have found no significant difference in SBP variability among different levels of drug adherence or types of antihypertensive medications used.<sup>43–45</sup> Therefore, these factors may not explain the links between SBP variability and the incidence of CVD and all-cause mortality.<sup>39,44</sup> Further studies are required to clarify the mechanism of this relationship.

### Strengths and Limitations

Our study has several strengths. First, we included a T2DM cohort with nearly 10 years of follow-up, which to our knowledge was the largest and longest study conducted to date and well powered to demonstrate the associations between usual SBP variability and outcome events in different subgroups. Second, we used appropriate statistical analysis methods to correct for regression dilution bias and conducted sensitivity analyses, which allowed us to make a comprehensive evaluation of the relationship between SBP and diverse clinical outcomes. Multiple imputation was used to impute missing data to reduce selection bias. Third, relevant baseline covariates, such as patients' laboratory results, disease attributes, and treatment modalities, were considered to generate reliable results with the aid of HA's computerized administrative database.

There were also limitations to our study. First, the study design of a retrospective cohort study can yield a conclusion only about association but not causation. However, a low probability of reverse causation was observed as patients with CVD at baseline were excluded in this study, and the results were very similar in the sensitivity analysis when we included only patients with a follow-up period of over 1 year. Second, potential confounding factors related to lifestyles, such as physical activity level and dietary intake, were not assessed in this study. Instead, we have examined the individuals' disease history and anthropometric and clinical parameters, including BMI, hemoglobin A<sub>1c</sub>, and lipid profile, which could reflect both the severity of their comorbidities and their lifestyle habits. Third, the validation study for the standardized automated sphygmomanometer (EDAN M3A, Shenzhen, China, or other equivalent measurements) used, and the record of adherence to the protocol for measuring BP are not available, and thus the recorded BP

measurements may be subject to measurement error. Moreover, covariates such as medication and smoking habits were not included in the calculation of SBP variability. Finally, the association between SBP variability and increased CVD risk was well demonstrated in this study. However, this could be affected by differences between our study population and the general population and the T2DM populations from other Chinese regions. Temporal variations and variations in risk factors or interventions not included in this study might also induce heterogeneity in the association. Therefore, our findings might not be generalizable to other settings.

### CONCLUSIONS

In this population-based cohort study of Chinese primary care patients with T2DM, usual SBP variability was associated with increased CVD risk and all-cause mortality independently of usual and baseline SBP. We demonstrated positive log-linear age-specific associations between usual SBP variability and the risk of CVD, CHD, stroke, heart failure, all-cause mortality, CVD mortality, and non-CVD mortality. The clinical implication of these findings is that SBP variability should be monitored and evaluated in routine practice, as this appears to be a risk factor for developing CVD and all-cause mortality. The impact of usual SBP variability was more significant in patients with younger age, lower-than-usual SBP, fewer comorbidities, and fewer types of antihypertensive drugs being prescribed. We suggest that additional monitoring may be needed for these patients if they have higher SBP variability. Future studies are needed to confirm these findings, standardize the definition of the variability of BP, evaluate the prediction power and relative importance between different features of BP (eg, variability and absolute value) and other risk factors, the mechanism of BP variability and CVD, potential interventions for high BP variability, and to determine a therapeutic target for SBP variability to provide better outcomes for patients with T2DM.

### ARTICLE INFORMATION

Received August 26, 2020; accepted June 1, 2021.

#### Affiliations

Department of Family Medicine and Primary Care (E.Y.F.W., E.Y.T.Y., W.Y.C., S.C., C.L.K.L.); and Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy (E.Y.F.W., I.C.K.W., E.W.Y.C., C.S.L.C.), The University of Hong Kong, Hong Kong SAR, China; Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, Sha Tin, Hong Kong, China (E.Y.F.W., I.C.K.W., E.W.Y.C., C.S.L.C.); Department of Family Medicine and Primary Care, The University of Hong Kong Shenzhen Hospital, Shenzhen, China (E.Y.T.Y.); Medical Research Council Biostatistics Unit, University of Cambridge, Cambridge, United Kingdom (J.K.B.); and Research Department of Practice and Policy, School of Pharmacy, University College London, London, United Kingdom (I.C.K.W.).

## Acknowledgments

The authors wish to acknowledge the contributions of the Risk Assessment Management Program for program team at the Hospital Authority head office, and the chiefs of service and Risk Assessment Management Program coordinators in each cluster, and the Statistics and Workforce Planning Department at the Hong Kong Hospital Authority.

Author Contributions: Dr Wan and Professor Lam contributed to the study design and acquisition of data, researched the data, contributed to the statistical analysis and interpretation of the results, and wrote the manuscript. All authors contributed to the interpretation of the results and reviewed and edited the manuscript. Dr Wan is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## Sources of Funding

This work was supported by the Health Services Research Fund, Food and Health Bureau, HKSAR (Ref. no 14151181). Barrett was funded by the MRC Unit Programme number MC\_UU\_00002/5. No funding organization had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation of the manuscript.

## Disclosures

Professor Wong received funding from Pfizer, Bayer, and Novartis to evaluate real-world evidence on pharmacologic treatments of cardiovascular diseases but not related to the current study. Dr Chan received research grants from Bayer, Bristol-Myers Squibb, Janssen, a Division of Johnson and Johnson, Pfizer, and Takeda to evaluate real-world evidence on pharmacologic treatments of cardiovascular diseases but not related to the current study. The remaining authors have no disclosures to report.

## Supplementary Material

Data S1

Tables S1–S2

Figures S1–S12

## REFERENCES

- International Diabetes Federation. *IDF Diabetes Atlas Eighth Edition 2017*. Brussels: International Diabetes Federation; 2017.
- Papatheodorou K, Banach M, Bekiari E, Rizzo M, Edmonds M. Complications of Diabetes 2017. *J Diabetes Res*. 2018;2018:1–4. DOI: 10.1155/2018/3086167.
- International Diabetes Federation Diabetes and cardiovascular disease. 2016.
- Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, He H, Chen J, Whelton PK, He J. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. *JAMA Cardiol*. 2017;2:775–781. DOI: 10.1001/jamacardio.2017.1421.
- Brunstrom M, Carlberg B. Association of blood pressure lowering with mortality and cardiovascular disease across blood pressure levels: a systematic review and meta-analysis. *JAMA Intern Med*. 2018;178:28–36. DOI: 10.1001/jamainternmed.2017.6015.
- American Diabetes Association. 8. Cardiovascular disease and risk management. *Diabetes Care*. 2016;39(suppl 1):S60–S71.
- Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2015;313:603–615. DOI: 10.1001/jama.2014.18574.
- American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2019. *Diabetes Care*. 2019;42:S13–S28.
- Aschner P, Group IDFW. New IDF clinical practice recommendations for managing type 2 diabetes in primary care. *Diabetes Res Clin Pract*. 2017;132:169–170. DOI: 10.1016/j.diabres.2017.09.002.
- Chiriaco M, Pateras K, Virdis A, Charakida M, Kyriakopoulou D, Nannipieri M, Emdin M, Tsioufis K, Taddei S, Masi S, et al. 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. DOI: 10.1111/dom.13828.
- Bell KJL, Azizi L, Nilsson PM, Hayen A, Irwig L, Ostgren CJ, Sundrom J. Prognostic impact of systolic blood pressure variability in people with diabetes. *PLoS One*. 2018;13:e0194084. DOI: 10.1371/journal.pone.0194084.
- Barrett JK, Huille R, Parker R, Yano Y, Griswold M. Estimating the association between blood pressure variability and cardiovascular disease: an application using the ARIC study. *Stat Med*. 2019;38:1855–1868. DOI: 10.1002/sim.8074.
- Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, White IR, Caulfield MJ, Deanfield JE, Smeeth L, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet*. 2014;383:1899–1911. DOI: 10.1016/S0140-6736(14)60685-1.
- Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet*. 2010;375:938–948. DOI: 10.1016/S0140-6736(10)60309-1.
- 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.
- Wan EYF, Fung CSC, Yu EYT, Fong DYT, Chen JY, Lam CLK. Association of visit-to-visit variability of systolic blood pressure with cardiovascular disease and mortality in primary care Chinese patients with type 2 diabetes—a retrospective population-based cohort study. *Diabetes Care*. 2017;40:270–279. DOI: 10.2337/dc16-1617.
- Lau IT. A clinical practice guideline to guide a system approach to diabetes care in Hong Kong. *Diabetes Metab J*. 2017;41:81–88. DOI: 10.4093/dmj.2017.41.2.81.
- Chan EW, Lau WC, Leung WK, Mok MT, He Y, Tong TS, Wong IC. Prevention of dabigatran-related gastrointestinal bleeding with gastroprotective agents: a population-based study. *Gastroenterology*. 2015;149:586–595.e583. DOI: 10.1053/j.gastro.2015.05.002.
- Wong AY, Root A, Douglas IJ, Chui CS, Chan EW, Ghebremichael-Weldeselassie Y, Siu C-W, Smeeth L, Wong IC. Cardiovascular outcomes associated with use of clarithromycin: population based study. *BMJ*. 2016;352:h6926. DOI: 10.1136/bmj.h6926.
- Centre for Health Protection. How to measure blood pressure using digital monitors script—video. 2013.
- Bonso E, Ragazzo F, Palatini P. Validation of A&D UA-85X device for blood pressure measurement. *Blood Press Monit*. 2008;13:339–341.
- Plummer M. Jags version 4.3.0 user manual. 2017.
- Su Y-S, Yajima M. R2jags: using R to run 'JAGS'. *R package version 0.5-7*. 2015;34.
- Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol*. 1994;47:1245–1251. DOI: 10.1016/0895-4356(94)90129-5.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383. DOI: 10.1016/0021-9681(87)90171-8.
- Ma Y-C, Zuo LI, Chen J-H, Luo Q, Yu X-Q, Li Y, Xu J-S, Huang S-M, Wang L-N, Huang W, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol*. 2006;17:2937–2944. DOI: 10.1681/ASN.2006040368.
- Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. John Wiley & Sons; 2004.
- San H, Lewington S. Lexis expansion-age-at-risk adjustment for survival analysis. *Brussels: Statistics and Pharmacokinetics Pharmaceutical Users Software Exchange conference*. 2013.
- Plummer M. Improved estimates of floating absolute risk. *Stat Med*. 2004;23:93–104. DOI: 10.1002/sim.1485.
- Lacey B, Lewington S, Clarke R, Kong XL, Chen Y, Guo Y, Yang L, Bennett D, Bragg F, Bian Z. Age-specific association between blood pressure and vascular and non-vascular chronic diseases in 0.5 million adults in China: a prospective cohort study. *Lancet Glob Health*. 2018;6:e641–e649.
- Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.
- Collaboration. Blood pressure and cardiovascular disease in the Asia Pacific region. *J Hypertens*. 2003;21:707–716.
- Durrleman S, Simon R. Flexible regression models with cubic splines. *Stat Med*. 1989;8:551–561. DOI: 10.1002/sim.4780080504.
- Rosner B, Willett W, Spiegelman D. Correction of logistic regression relative risk estimates and confidence intervals for systematic

- within-person measurement error. *Stat Med*. 1989;8:1051–1069. DOI: 10.1002/sim.4780080905.
35. Ohkuma T, Woodward M, Jun M, Muntner P, Hata J, Colagiuri S, Harrap S, Mancia G, Poulter N, Williams B, et al. Prognostic value of variability in systolic blood pressure related to vascular events and premature death in type 2 diabetes mellitus: the ADVANCE-ON study. *Hypertension*. 2017;70:461–468. DOI: 10.1161/HYPERTENSIONAHA.117.09359.
  36. Hsieh YT, Tu ST, Cho TJ, Chang SJ, Chen JF, Hsieh MC. Visit-to-visit variability in blood pressure strongly predicts all-cause mortality in patients with type 2 diabetes: a 5.5-year prospective analysis. *Eur J Clin Invest*. 2012;42:245–253. DOI: 10.1111/j.1365-2362.2011.02574.x.
  37. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ*. 2010;340:b5087. DOI: 10.1136/bmj.b5087.
  38. 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. DOI: 10.1093/eurheartj/ehx760.
  39. Hata J, Arima H, Rothwell PM, Woodward M, Zoungas S, Anderson C, Patel A, Neal B, Glasziou P, Hamet P. Effects of visit-to-visit variability in systolic blood pressure on macrovascular and microvascular complications in patient with type 2 diabetes: the ADVANCE trial. *Circulation*. 2013;128:1325–1334.
  40. Krakoff LR. Fluctuation: does blood pressure variability matter? *Circulation*. 2012;126:525–527. DOI: 10.1161/CIRCULATIONAHA.112.124750.
  41. Wijsman LW, de Craen AJ, Muller M, Sabayan B, Stott D, Ford I, Trompet S, Jukema JW, Westendorp RG, Mooijaart SP. Blood pressure lowering medication, visit-to-visit blood pressure variability, and cognitive function in old age. *Am J Hypertens*. 2016;29:311–318.
  42. Hong K, Muntner P, Kronish I, Shilane D, Chang TI. Medication adherence and visit-to-visit variability of systolic blood pressure in African Americans with chronic kidney disease in the AASK trial. *J Hum Hypertens*. 2016;30:73. DOI: 10.1038/jhh.2015.26.
  43. Kronish IM, Lynch AI, Oparil S, Whittle J, Davis BR, Simpson LM, Krousel-Wood M, Cushman WC, Chang TI, Muntner P. The association between antihypertensive medication nonadherence and visit-to-visit variability of blood pressure: findings from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Hypertension*. 2016;68:39–45. DOI: 10.1161/HYPERTENSIONAHA.115.06960.
  44. Muntner P, Whittle J, Lynch AI, Colantonio LD, Simpson LM, Einhorn PT, Levitan EB, Whelton PK, Cushman WC, Louis GT, et al. 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.
  45. Shiga Y, Miura S-I, Adachi S, Suematsu Y, Sugihara M, Iwata A, Yahiro E, Nishikawa H, Ogawa M, Saku K. Visit-to-visit variability and seasonal variation in blood pressure with single-pill fixed-dose combinations of angiotensin II receptor blocker/calcium channel blocker and angiotensin II receptor blocker/diuretic in hypertensive patients. *J Clin Med Res*. 2015;7:802. DOI: 10.14740/jocmr2292w.

# **SUPPLEMENTAL MATERIAL**

## Data S1.

### Supplemental Methods

#### Usual variability SBP using mixed effects model

Given a dataset with  $N$  individuals and  $n_i$  SBP measurements from the  $i^{\text{th}}$  individual,  $i = 1, \dots, N$ , let  $Y_{ij}, j = 1, \dots, n_i$ , be the  $j^{\text{th}}$  measurement of individual  $i$  taken at measurement time  $t_{ij}$ .

Consider a standard linear mixed effects model

$$Y_{ij} = \beta^T X_{ij} + b_i^T Z_{ij} + \varepsilon_{ij}$$

where  $X_{ij}$  is a covariate vector for the fixed effects  $\beta$  and  $Z_{ij}$  is a covariate vector for the random effects  $b_i$ , assumed normally distributed  $b_i \sim N(0, \Sigma_b)$ . The residual errors  $\varepsilon_{ij}$  are assumed independent and normally distributed,  $\varepsilon_{ij} \sim N(0, \sigma^2)$ . We can allow variability in the repeated measurements to differ between individuals by replacing the residual SD  $\sigma$  with an individual-specific residual SD  $\sigma_i$  and assuming that the  $\sigma_i$  are randomly distributed. We assume a log-normal distribution for the residual SD distribution, ensuring positivity of the SDs,  $\sigma_i \sim \text{logN}(\mu_\sigma, \tau_\sigma^2)$ . The choice of log-normal distribution also allows a natural extension of the model to incorporate correlation between the usual level and the residual SD by assuming a multivariate normal distribution for the random effects and log residual SD

$$\varepsilon_{ij} \sim N(0, \sigma_i^2), \quad \begin{pmatrix} b_i \\ \log \sigma_i \end{pmatrix} \sim N \left( \begin{pmatrix} 0 \\ \mu_\sigma \end{pmatrix}, \begin{pmatrix} \Sigma_b & \Sigma_{b\sigma} \\ \Sigma_{b\sigma}^T & \tau_\sigma^2 \end{pmatrix} \right)$$

where  $\Sigma_{b\sigma}$  is a vector of covariances between the random effects and the random residual errors. The details of the models have been described elsewhere in the literature [12]. For this study, the model was

$$\begin{pmatrix} b_i \\ \log \sigma_i \end{pmatrix} \sim N \left( \begin{pmatrix} 0 \\ \mu_\sigma \end{pmatrix}, \begin{pmatrix} \tau_0^2 & \rho \tau_0 \tau_\sigma \\ \rho \tau_0 \tau_\sigma & \tau_\sigma^2 \end{pmatrix} \right)$$

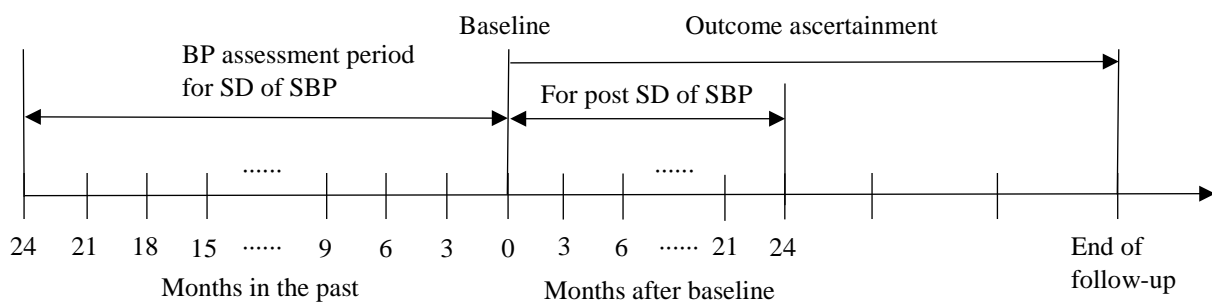
For the Bayesian estimation, we used diffuse uniform prior distributions  $U[0, 100]$  for SDs, uniform  $U[-1, 1]$  prior distributions for correlation parameters, and diffuse normal prior distributions  $N(0, 100^2)$  for all other parameters. Priors were specified for the bivariate and trivariate normal distributions by expressing them as two and three conditional univariate normal distributions, respectively. In the current study, we used a burn-in of 1000 Markov Chain Monte Carlo updates for the mixed effects models. The posterior means (95% credible interval) for usual SBP and SBP variability were 137.1 (112.9, 160.3) and 12.7 (7.1, 20.9), respectively.

### Rosner's regression method

Rosner's regression method is used to calculate the regression dilution ratio to evaluate the association between systolic blood pressure (SBP) variability and event outcomes in sensitivity analysis 1. The detailed method is shown as below.

First, the standard deviation (SD) of SBP as the variability measurement was calculated based on the measurements of SBP at 9 visits (baseline, every 3 months in the past). To deal with random errors in this SBP variability measurement, regression dilution ratio was applied to the analyses based on Rosner's regression method [34], employing the measurements of SBP at 8 visits unit 2 years after baseline (every 3 months after baseline). The timeline for the measurement of SBP and outcome ascertainment of this method shown in the Figure below. Regression dilution ratio was calculated as the coefficient relating to the post measurement to the baseline measurement. Finally, continuous hazard ratios for baseline measurement were multiplied by the ratio to estimate the association for SBP variability. For example, regression dilution ratio of 4 for SD of SBP. If an hazard ratio for baseline SD of SBP of 1.1 was calculated, the hazard ratio for SBP was calculated as  $e^{(4 \times \ln(1.1))} = 1.5$ .

Figure. Study design for sensitivity analysis 1.



In current study, the mean of SD of SBP at post SD of SBP was 12.1mmHg (SD: 4.8mmHg). Applying the Rosner's regression method, the regression dilution ratio was 4.13. To evaluate the association between SBP variability and event outcomes, multivariable Cox proportional hazards regressions adjusted with baseline characteristics, usual SBP and regression dilution ratio. The results were shown in **Figure S5**.

**Table S1. Definition of the diseases.**

Event	ICPC-2 codes	ICD-9-CM codes
DM	T89, T90	NA
CHD	K74-K76	410-414
Heart Failure	K77	428
Stroke	K89-K91	430-438

ICPC-2 = the International Classification of Primary Care-2; ICD-9-CM = the International Classification of Diseases, Ninth Edition, Clinical Modification; HT = Hypertension; DM = Diabetes Mellitus; CHD = Coronary heart disease

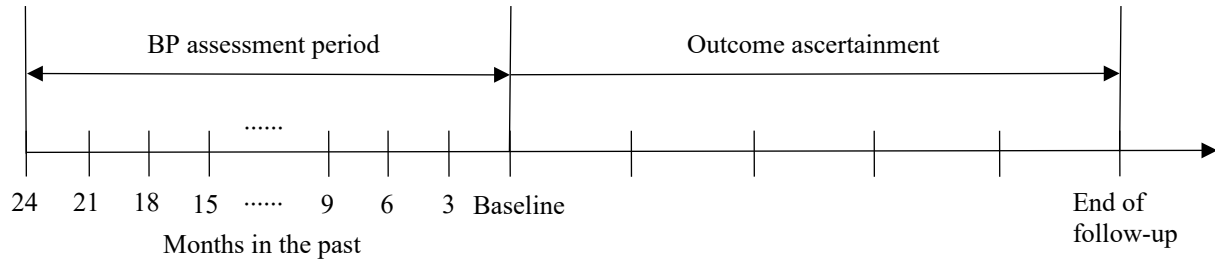


**Table S2. Data completion rate of the baseline characteristics in studied patients.**

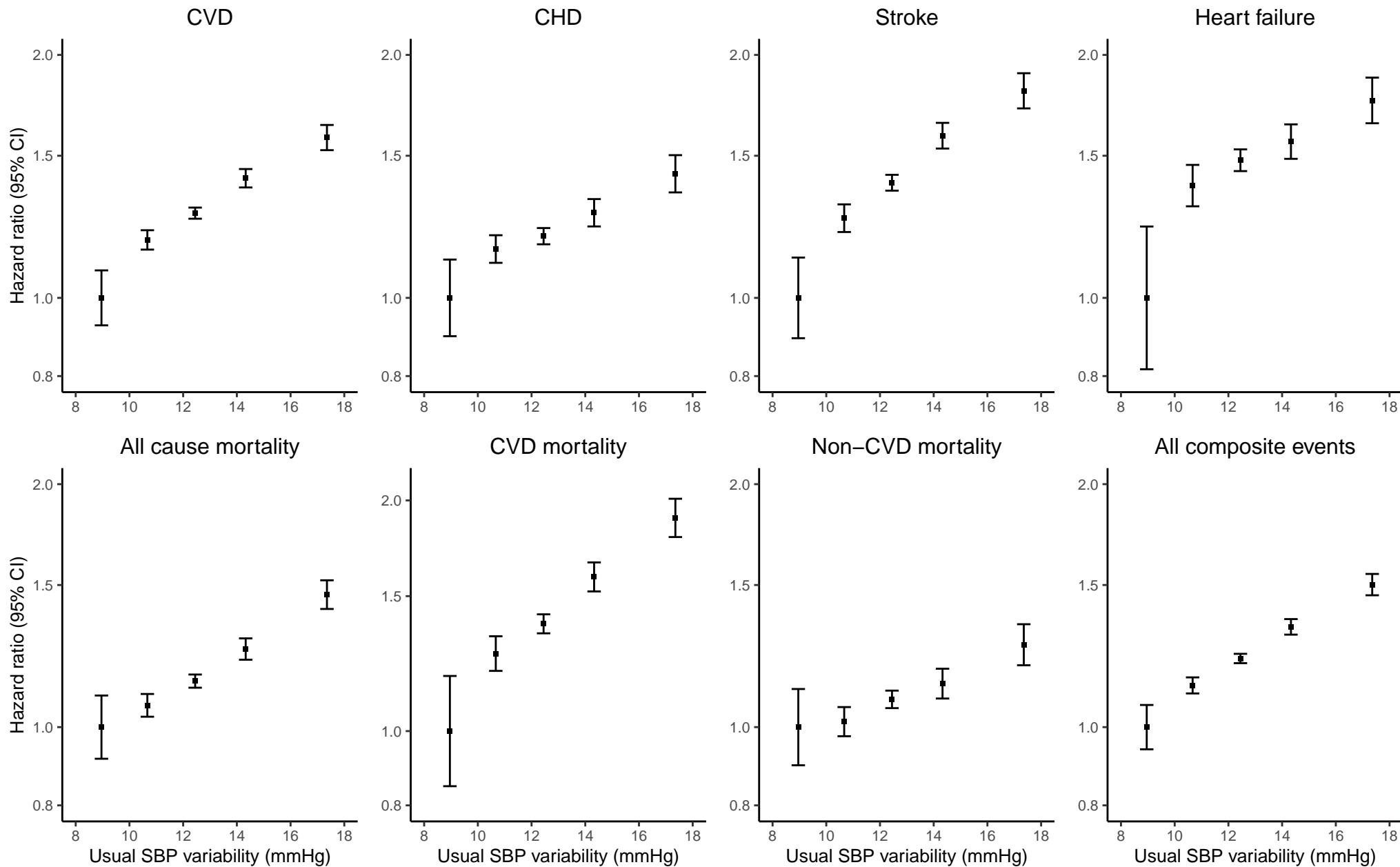
	Total (N = 155,982)
Age	100.0% (155,982)
Sex	100.0% (155,982)
Smoking status	97.4% (151,991)
BMI	64.6% (100,753)
SBP	100.0% (155,982)
DBP	100.0% (155,982)
HbA1c	84.3% (131,493)
LDL-C	63.6% (99,236)
eGFR	77.1% (120,190)
Charlson Index	100.0% (155,982)
Use of oral anti-diabetic drugs	100.0% (155,982)
Use of insulin	100.0% (155,982)
Use of ACEI/ARB	100.0% (155,982)
Use of $\beta$ -blocker	100.0% (155,982)
Use of CCB	100.0% (155,982)
Use of Diuretic	100.0% (155,982)
Use of other anti-hypertensive drugs	100.0% (155,982)
Use of lipid-lowering agents	100.0% (155,982)

Other anti-hypertensive drugs included Acarbose, Glucagon-like peptide-1 agonist, Meglitinides. BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HbA1c = Haemoglobin A1c; LDL-C = Low-density Lipoprotein-Cholesterol; eGFR = Estimated Glomerular Filtration Rate; ACEI = Angiotensin Converting Enzyme Inhibitor; ARB = Angiotensin Receptor Blocker; CCB = Calcium Channel Blocker

**Figure S1. Study design for the investigation of the association visit-to-visit in systolic blood pressure (SBP) and cardiovascular diseases and all-cause mortality.** The measurements of SBP at 9 visits (baseline, each 3 months in the past) were used to calculate usual mean and variability of SBP. The median follow-up period was 9.7 years after baseline

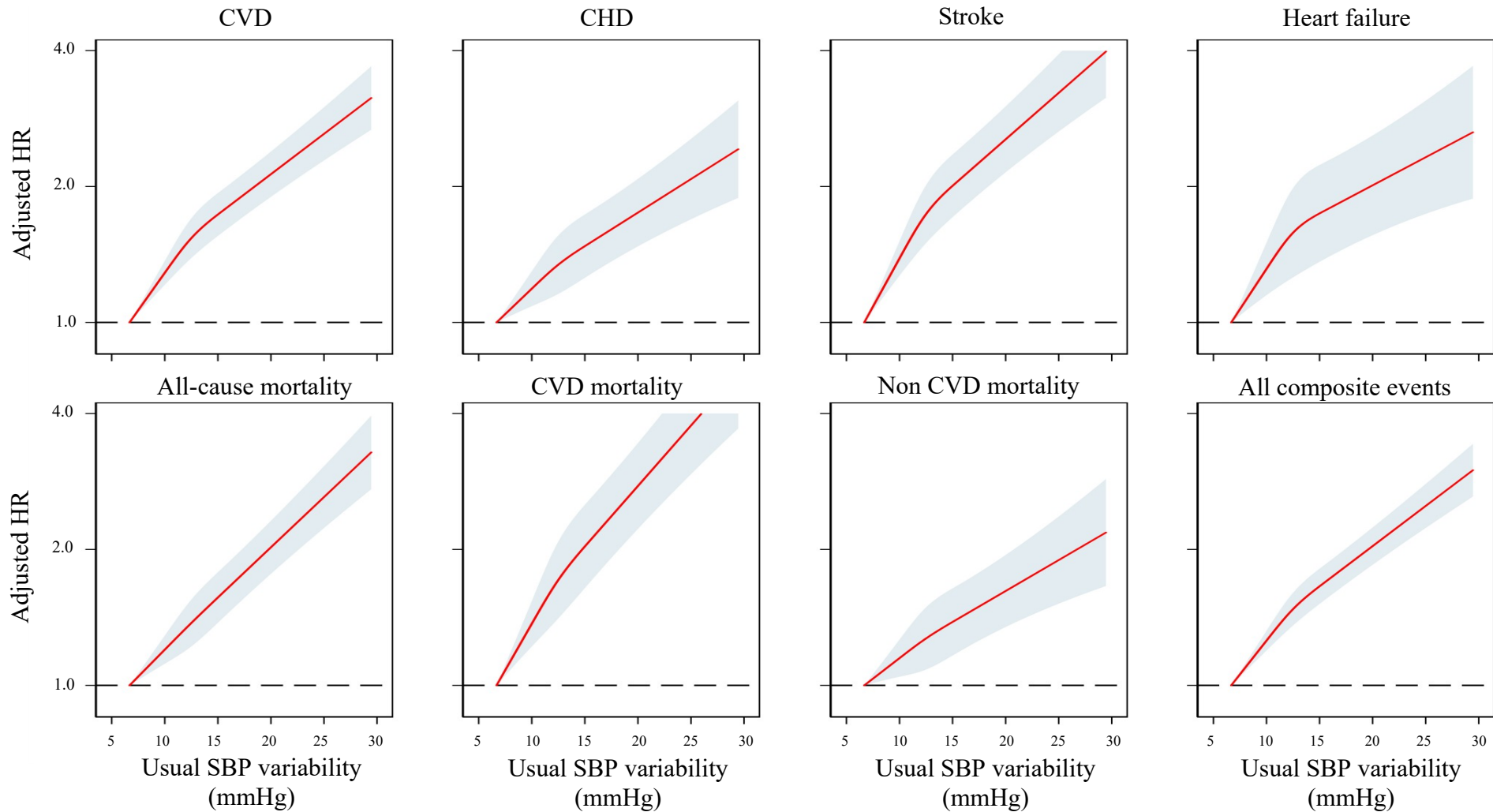


**Figure S2. Adjusted Hazard ratio for incidence of CVD, CHD, Stroke, Heart failure, all-cause mortality, CVD mortality, non-CVD mortality and their composite with increasing usual SBP variability by multivariable Cox regressions.**



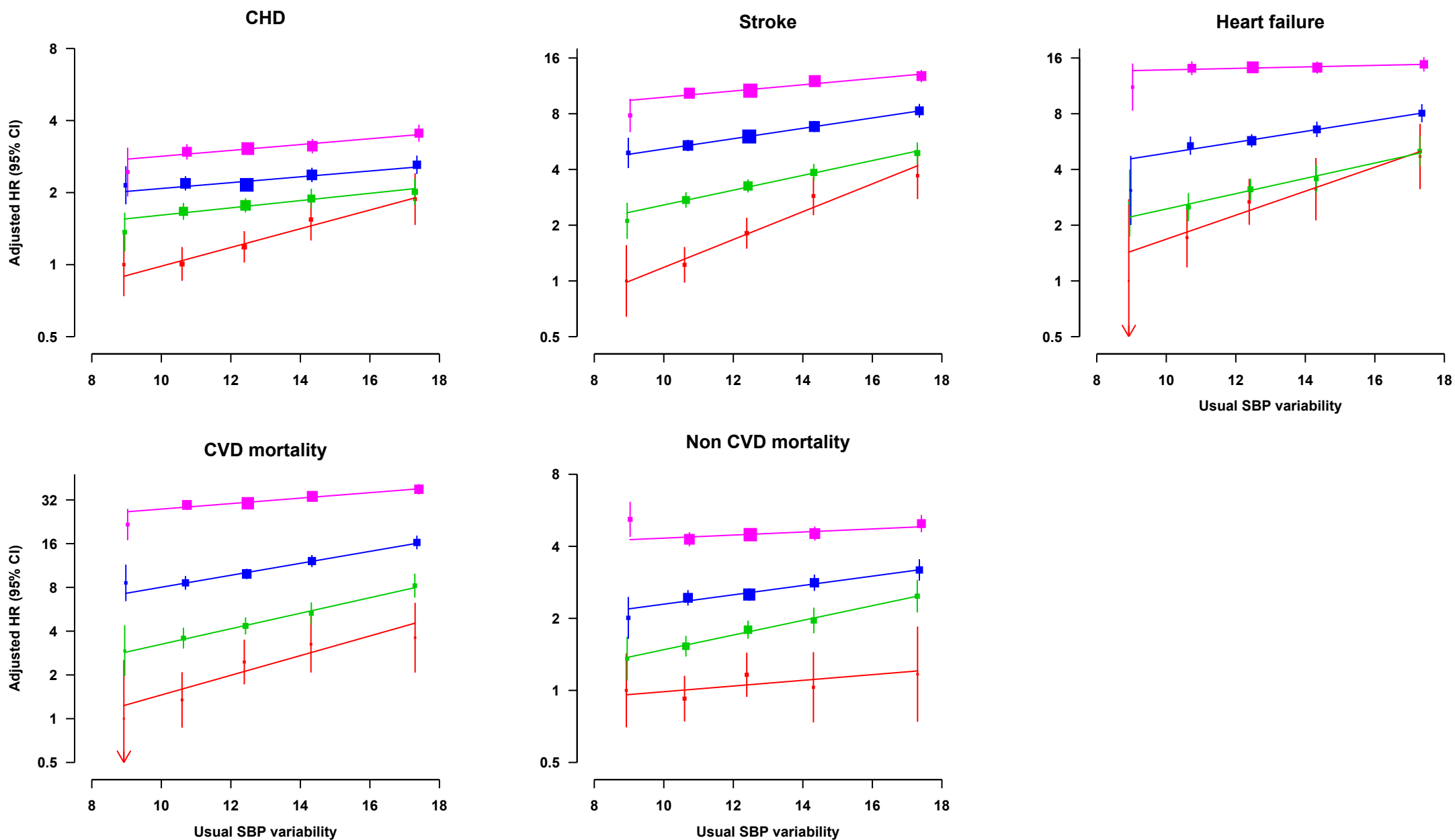
Hazard ratio was adjusted by age at risk, gender, smoking status, body mass index, SBP, diastolic blood pressure, haemoglobin A1c, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of oral anti-diabetic drugs, insulin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker,  $\beta$ -blocker, calcium channel blocker, diuretic, other anti-hypertensive drugs, lipid-lowering agent, Charlson's index and usual SBP. CIs are displayed as floating absolute risks. SD=Standard deviation; SBP=Systolic blood pressure; CVD=Cardiovascular disease; CHD=Coronary heart disease.

Figure S3. Adjusted Hazard ratio for incidence of CVD, CHD, Stroke, Heart failure, all-cause mortality, CVD mortality, non-CVD mortality and their composite with increasing usual SBP variability by multivariable Cox regressions with restricted cubic spline.



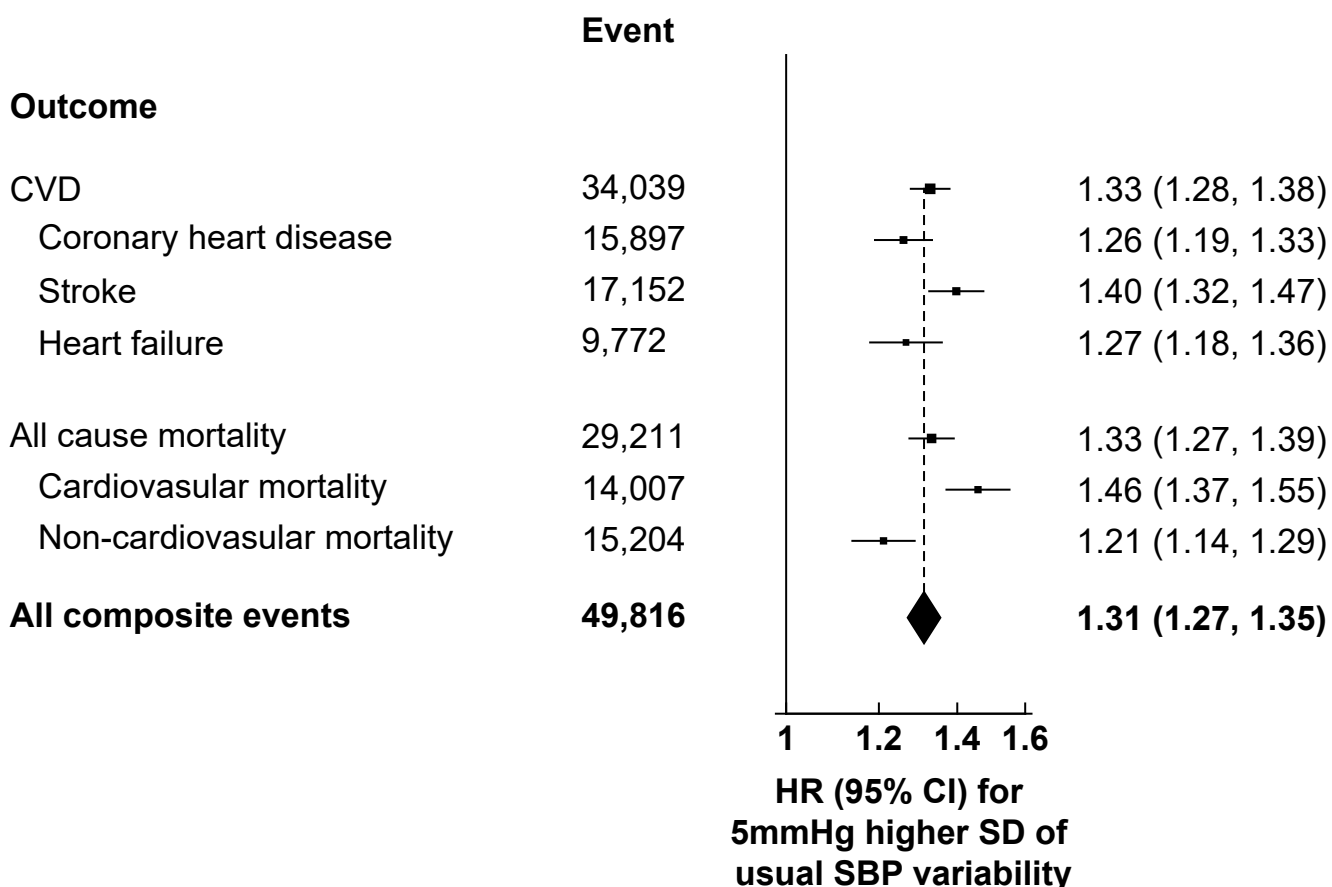
Hazard ratio was adjusted by age at risk, sex, smoking status, body mass index, SBP, diastolic blood pressure, haemoglobin A1c, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of oral anti-diabetic drugs, insulin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker,  $\beta$ -blocker, calcium channel blocker, diuretic, other anti-hypertensive drugs, lipid-lowering agent, Charlson's index and usual SBP. Shaded region represents 95% confidence intervals. SBP=Systolic blood pressure; CVD=Cardiovascular disease; CHD=Coronary heart disease;

Figure S4. Age-specific adjusted hazard ratios for the risk of CVD, coronary heart disease, stroke, heart failure, CVD mortality and non-CVD mortality with increasing usual SBP variability by multivariable Cox re-gressions.



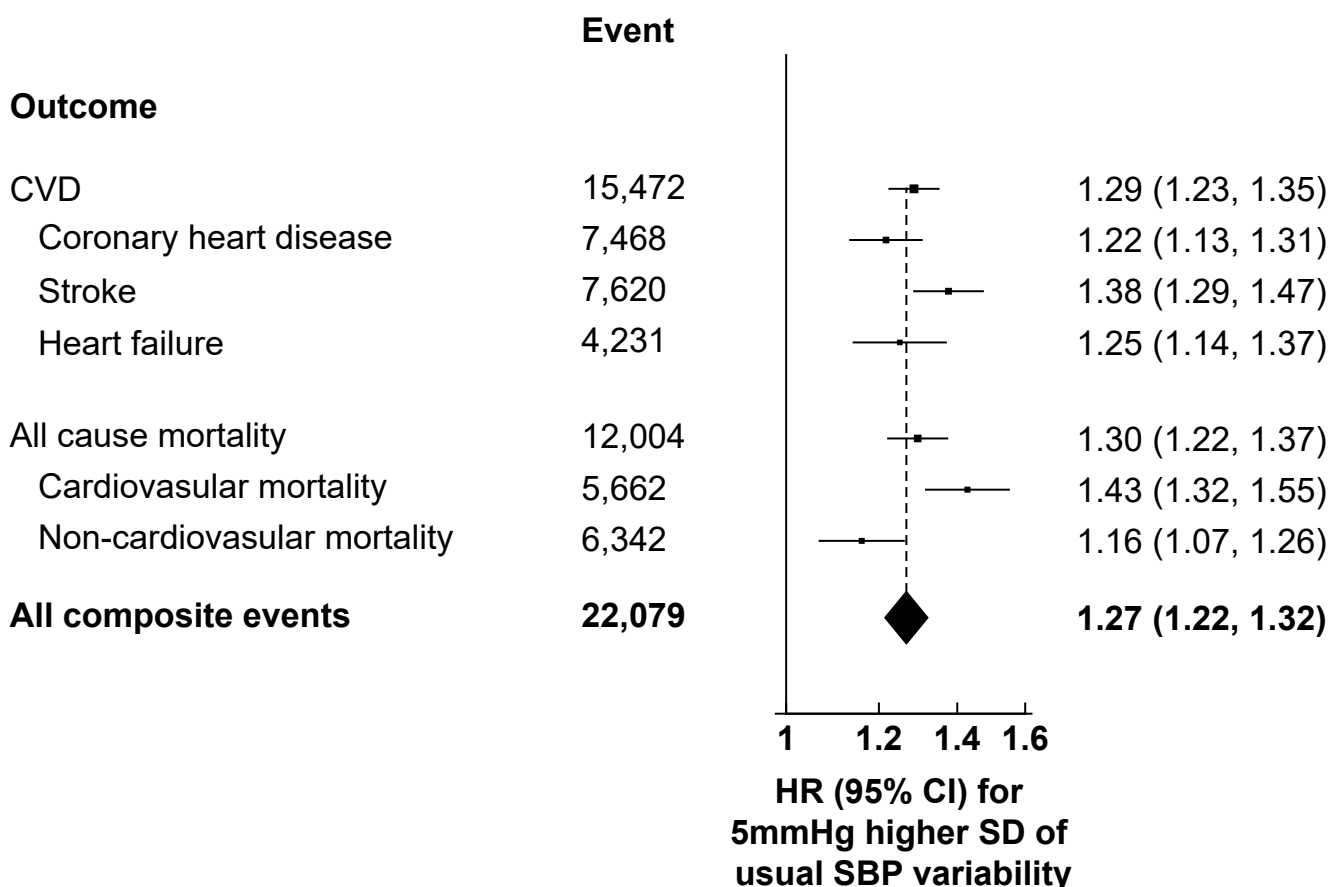
HR was adjusted by age at risk, sex, smoking status, body mass index, SBP, diastolic blood pressure, haemoglobin A1c, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of oral anti-diabetic drugs, insulin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker,  $\beta$ -blocker, calcium channel blocker, diuretic, other anti-hypertensive drugs, lipid-lowering agent, Charlson's index and usual SBP. Red, green, blue and pink line were 45-54, 55-64, 65-74 and 75-84 age at risk group. The area of each square was inversely proportional to the variance of the category-specific log risk. CIs are displayed as floating absolute risks. SBP=Systolic blood pressure; CVD=Cardiovascular disease; HR=Hazard ratio; CI=Confidence interval.

**Figure S5. Adjusted hazard ratios for the risk of CVD, coronary heart disease, stroke, heart failure, all cause mortality, CVD mortality, non-CVD mortality and their composite with each 5mmHg increasing usual SBP variability using multivariable Cox regressions based on Rosner's regression method (Sensitivity analysis 1).**



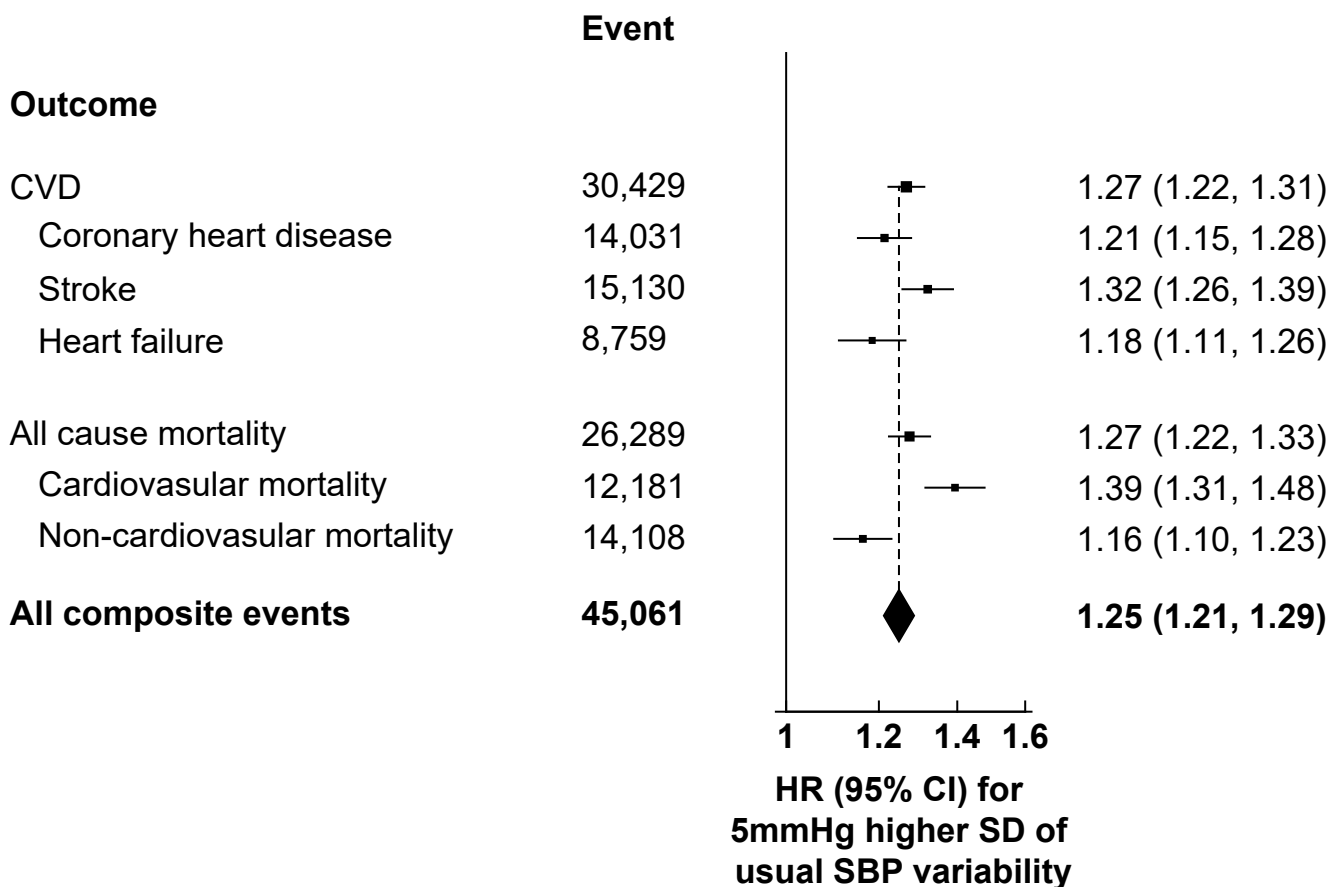
Applying the Rosner's regression method, the regression dilution ratio was 4.13. HR was adjusted by age at risk, gender, smoking status, body mass index, SBP, diastolic blood pressure, haemoglobin A1c, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of oral anti-diabetic drugs, insulin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker,  $\beta$ -blocker, calcium channel blocker, diuretic, other anti-hypertensive drugs, lipid-lowering agent, Charlson's index, usual SBP and regression dilution ratio. SD=Standard deviation; SBP=Systolic blood pressure; CVD=Cardiovascular disease; HR=Hazard ratio.

**Figure S6. Adjusted hazard ratios for the risk of CVD, coronary heart disease, stroke, heart failure, all cause mortality, CVD mortality, non-CVD mortality and their composite with each 5mmHg increasing usual SBP variability using multivariable Cox regressions based on complete case analysis (Sensitivity analysis 2).**



HR was adjusted by age at risk, sex, smoking status, body mass index, SBP, diastolic blood pressure, haemoglobin A1c, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of oral anti-diabetic drugs, insulin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker,  $\beta$ -blocker, calcium channel blocker, diuretic, other anti-hypertensive drugs, lipid-lowering agent, Charlson's index and usual SBP. SD=Standard deviation; SBP=Systolic blood pressure; CVD=Cardiovascular disease; HR=Hazard ratio.

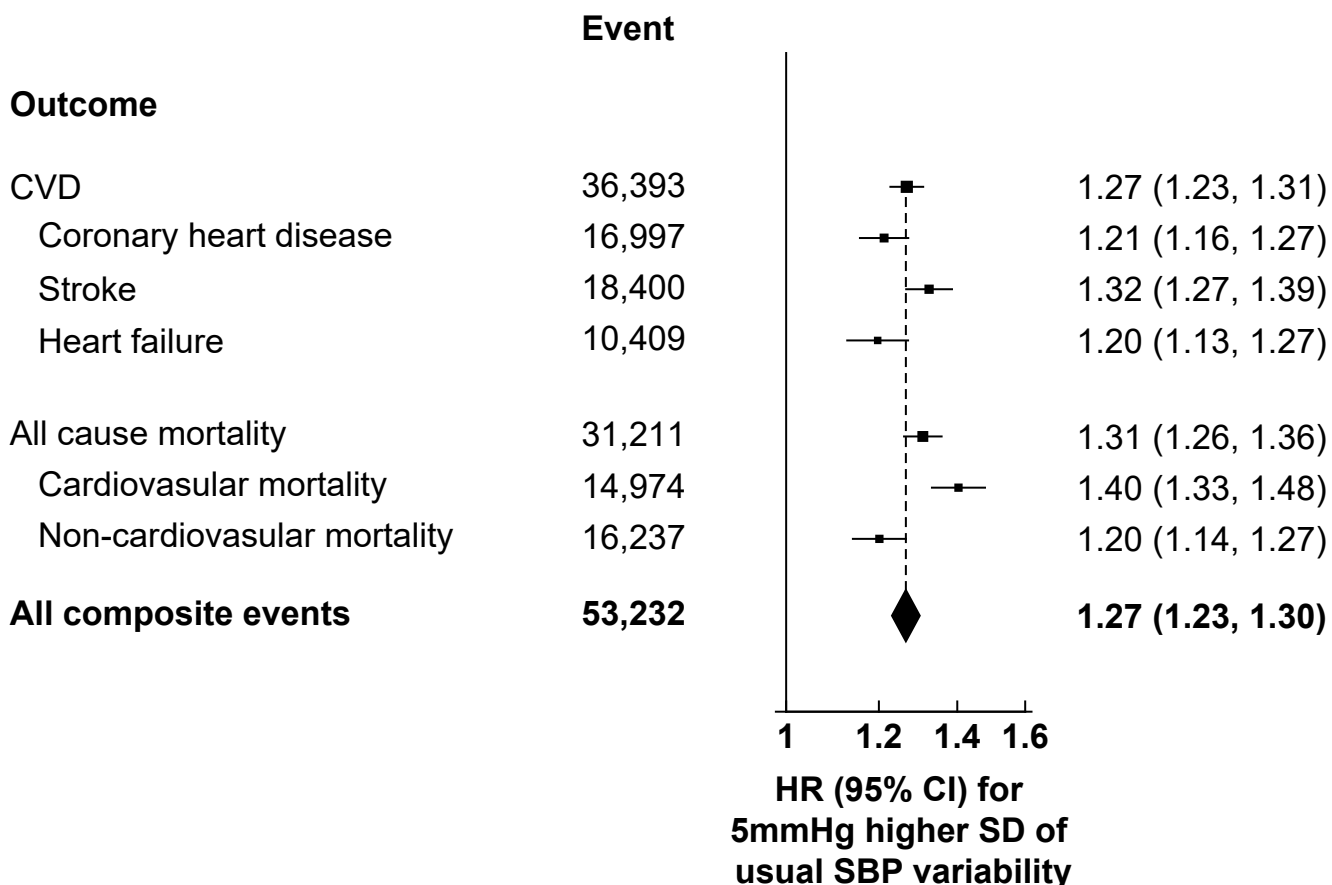
**Figure S7. Adjusted hazard ratios for the risk of CVD, coronary heart disease, stroke, heart failure, all cause mortality, CVD mortality, non-CVD mortality and their composite with each 5mmHg increasing usual SBP variability using multivariable Cox regressions based on patients with at least 12 months follow-up period (Sensitivity analysis 3).**



HR was adjusted by age at risk, sex, smoking status, body mass index, SBP, diastolic blood pressure, haemoglobin A1c, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of oral anti-diabetic drugs, insulin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker,  $\beta$ -blocker, calcium channel blocker, diuretic, other anti-hypertensive drugs, lipid-lowering agent, Charlson's index and usual SBP. SD=Standard deviation; SBP=Systolic blood pressure; CVD=Cardiovascular disease; HR=Hazard ratio.

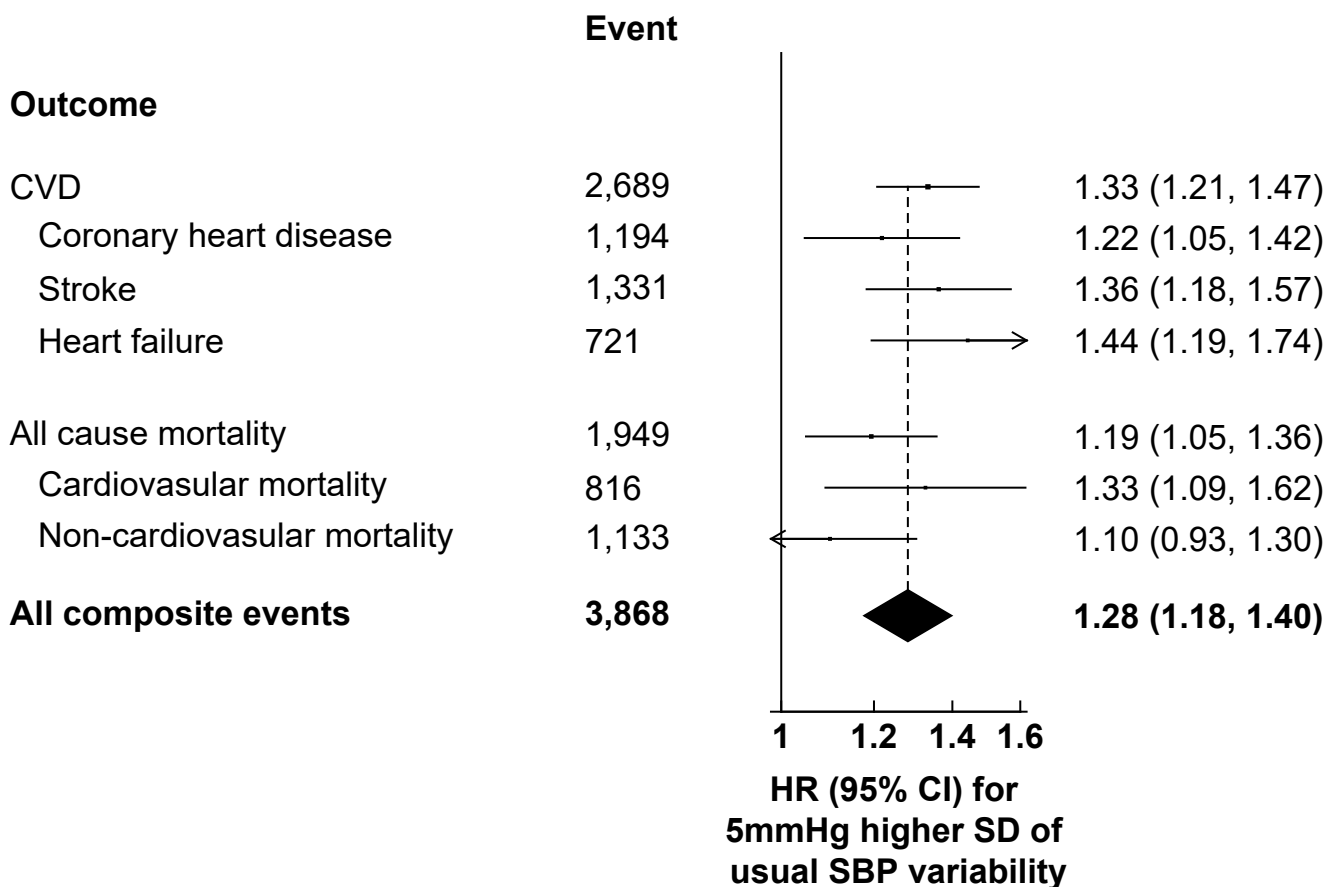


**Figure S8. Adjusted hazard ratios for the risk of CVD, coronary heart disease, stroke, heart failure, all cause mortality, CVD mortality, non-CVD mortality and their composite with each 5mmHg increasing usual SBP variability using multivariable Cox regressions based on patients with at least 2 SBP measurements on or before baseline (Sensitivity analysis 4).**



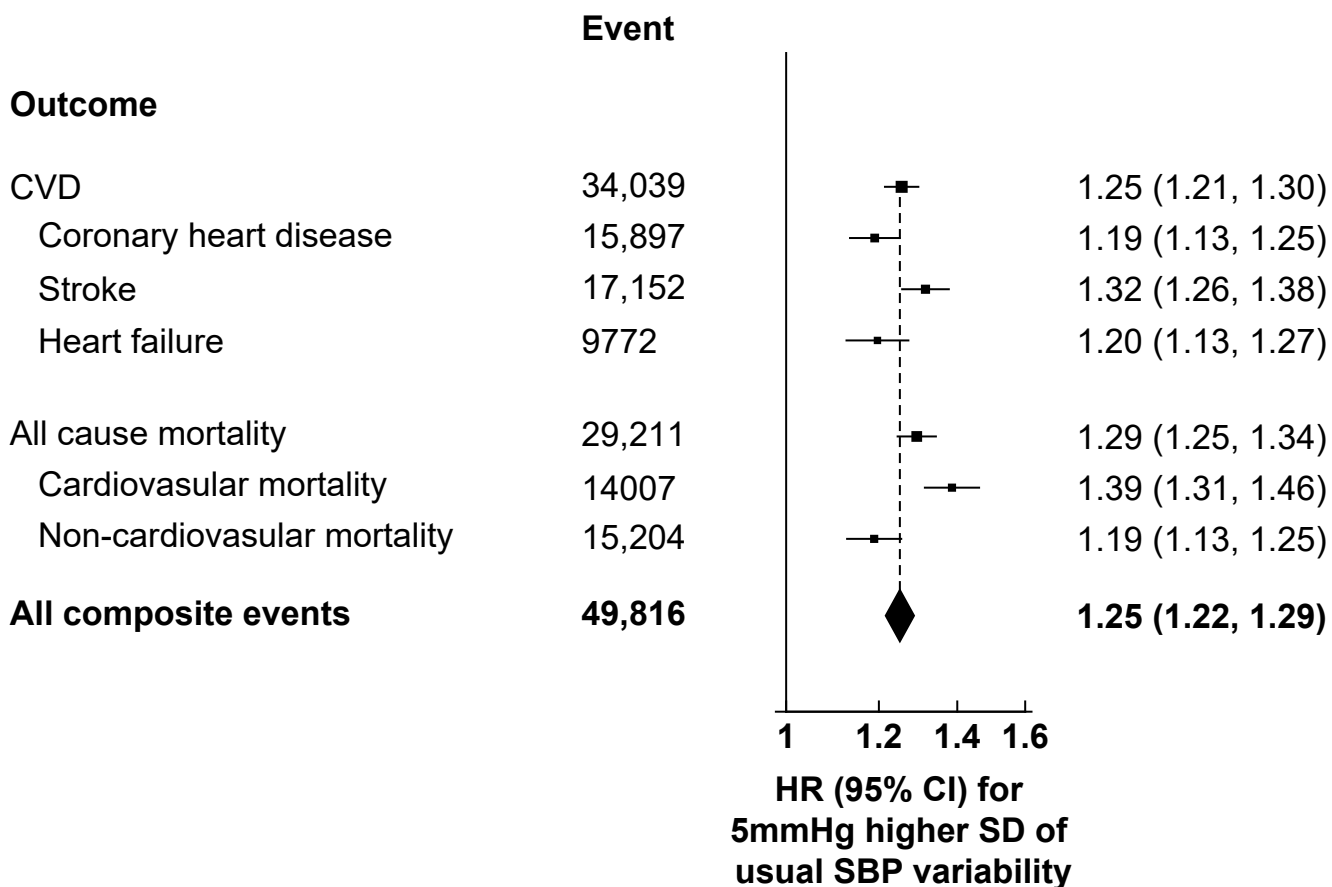
HR was adjusted by age at risk, sex, smoking status, body mass index, SBP, diastolic blood pressure, haemoglobin A1c, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of oral anti-diabetic drugs, insulin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker,  $\beta$ -blocker, calcium channel blocker, diuretic, other anti-hypertensive drugs, lipid-lowering agent, Charlson's index and usual SBP. SD=Standard deviation; SBP=Systolic blood pressure; CVD=Cardiovascular disease; HR=Hazard ratio.

**Figure S9. Adjusted hazard ratios for the risk of CVD, coronary heart disease, stroke, heart failure, all cause mortality, CVD mortality, non-CVD mortality and their composite with each 5mmHg increasing usual SBP variability using multivariable Cox regressions based on patients with at least 7 SBP measurements on or before baseline (Sensitivity analysis 4).**



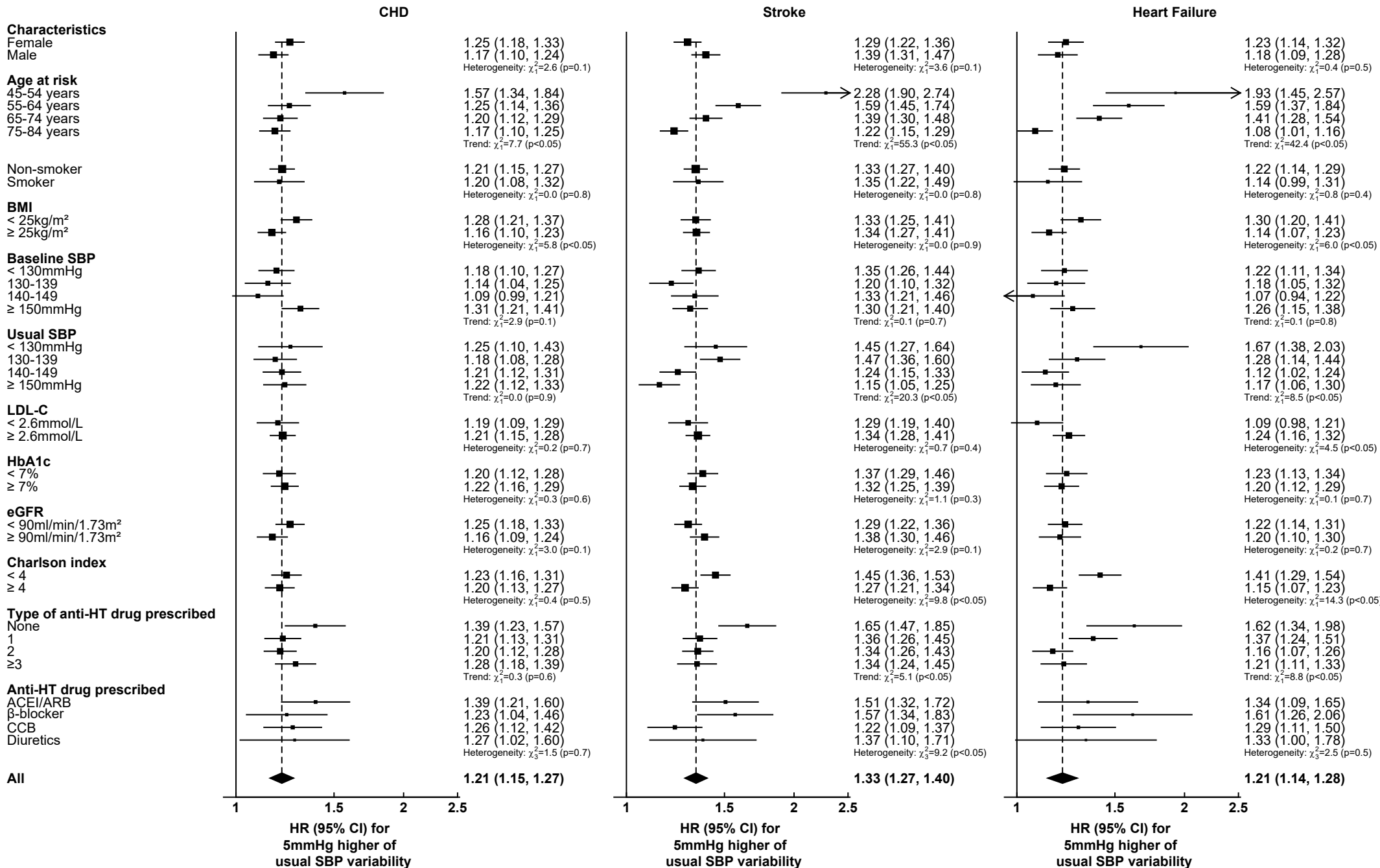
HR was adjusted by age at risk, sex, smoking status, body mass index, SBP, diastolic blood pressure, haemoglobin A1c, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of oral anti-diabetic drugs, insulin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker,  $\beta$ -blocker, calcium channel blocker, diuretic, other anti-hypertensive drugs, lipid-lowering agent, Charlson's index and usual SBP. SD=Standard deviation; SBP=Systolic blood pressure; CVD=Cardiovascular disease; HR=Hazard ratio.

**Figure S10. Adjusted hazard ratios for the risk of CVD, coronary heart disease, stroke, heart failure, all cause mortality, CVD mortality, non-CVD mortality and their composite with each 5mmHg increasing usual SBP variability using multivariable Cox regressions with additional adjustment for patients with the usage of aspirin on or before baseline (Sensitivity analysis 5).**



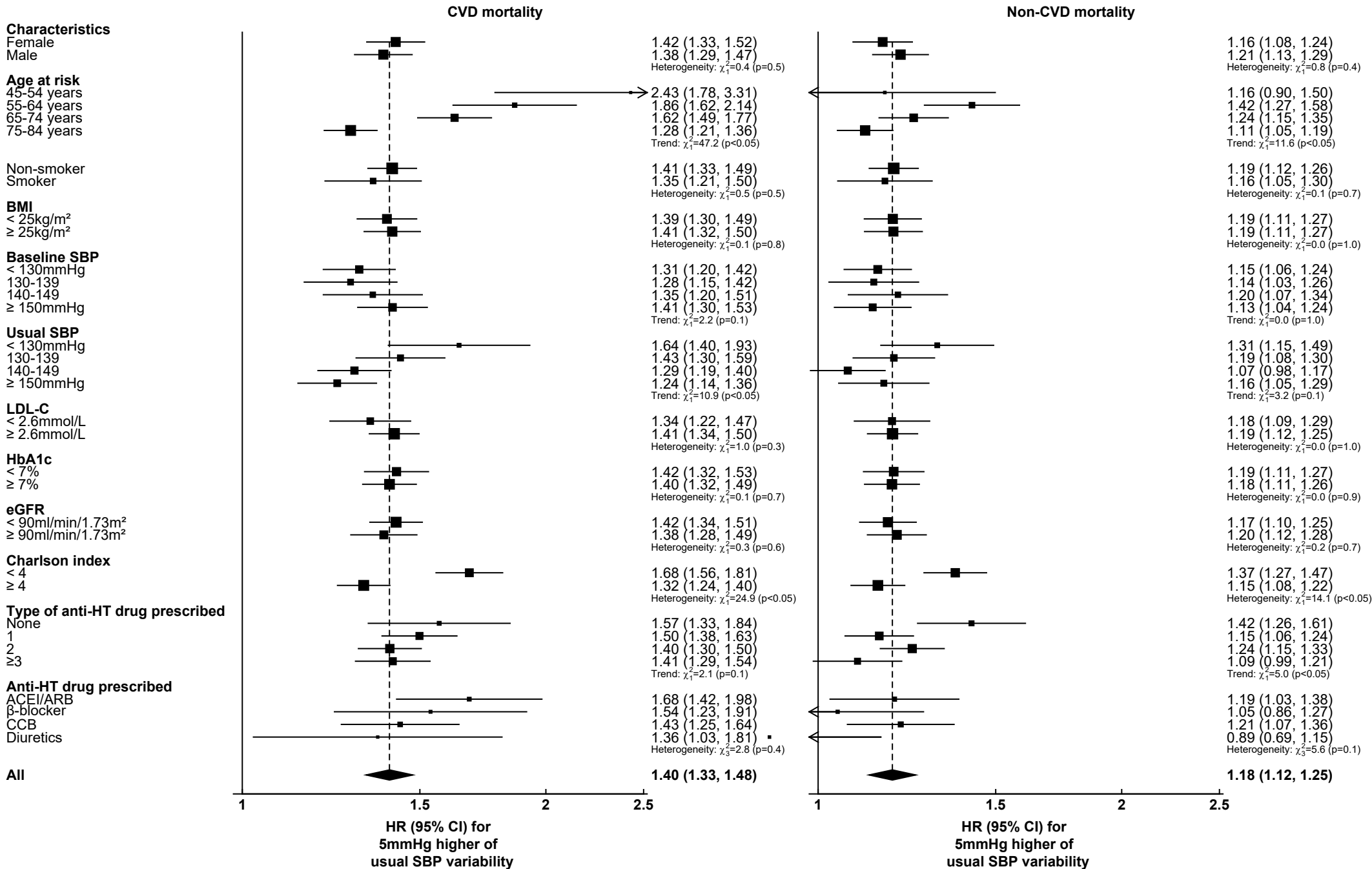
HR was adjusted by age at risk, sex, smoking status, body mass index, SBP, diastolic blood pressure, haemoglobin A1c, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of oral anti-diabetic drugs, insulin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker,  $\beta$ -blocker, calcium channel blocker, diuretic, other anti-hypertensive drugs, lipid-lowering agent, aspirin, Charlson's index and usual SBP. SD=Standard deviation; SBP=Systolic blood pressure; CVD=Cardiovascular disease; HR=Hazard ratio.

**Figure S11. Adjusted hazard ratios for the risk of coronary heart disease, stroke and heart failure with each 5mmHg increasing usual SBP variability by stratifying patient's characteristics at baseline using multivariable Cox regressions.**



HR was adjusted by age at risk, sex, smoking status, BMI, SBP, diastolic blood pressure, HbA1c, LDL-C, estimated glomerular filtration rate, the usages of oral anti-diabetic drugs, insulin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, β-blocker, calcium channel blocker, diuretic, other anti-hypertensive drugs, lipid-lowering agent, Charlson's index and usual SBP. SBP=Systolic blood pressure; CHD=Coronary heart disease; BMI=Body Mass Index; LDL-C=Low-density lipoprotein-cholesterol; HbA1c=Haemoglobin A1c; HR=Hazard ratio; eGFR=estimated glomerular filtration rate; HT=Hypertensive; ACEI = Angiotensin Converting Enzyme Inhibitor; ARB = Angiotensin Receptor Blocker; CCB = Calcium Channel Blocker; CI=Confidence interval.

**Figure S12. Adjusted hazard ratios for the risk of CVD mortality and non-CVD mortality with each 5mmHg increasing usual SBP variability by stratifying patient's characteristics at baseline using multivariable Cox regressions.**



HR was adjusted by age at risk, sex, smoking status, BMI, SBP, diastolic blood pressure, HbA1c, LDL-C, estimated glomerular filtration rate, the usages of oral anti-diabetic drugs, insulin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, β-blocker, calcium channel blocker, diuretic, other anti-hypertensive drugs, lipid-lowering agent, Charlson's index and usual SBP. SBP=Systolic blood pressure; CVD=Cardiovascular disease; BMI=Body Mass Index; LDL-C=Low-density lipoprotein-cholesterol; HbA1c=Haemoglobin A1c; HR=Hazard ratio; eGFR=estimated glomerular filtration rate; HT=Hypertensive; ACEI = Angiotensin Converting Enzyme Inhibitor; ARB = Angiotensin Receptor Blocker; CCB = Calcium Channel Blocker; CI=Confidence interval.