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The association between blood pressure variability and hip or vertebral fracture risk: a population-based study

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Abstract

Background: The present study evaluated the association between blood pressure variability and the risk of hip/vertebral fractures in middle aged and elderly patients.

Methods: This was a retrospective observational study of patients attending family medicine outpatient clinics, recruited from 1st January 2000 to 31st December 2003 and were followed up until 31st December 2019. Standard deviation (SD), root mean square (RMS), coefficient of variation (CV) and a variability score (defined as the number of changes in blood pressure (diastolic and systolic) of 5 mmHg or more) were used as measures of blood pressure variability. The primary outcome was a composite of new onset hip or vertebral fractures.

Results: A total of 57810 patients were included. Over a median follow-up of 5894 days (interquartile range: 3505-6487), 3285 patients (5.68%) developed new onset hip/vertebral fractures. The crude incidence rates were 4.95%, 5.31%, and 7.2% for diastolic blood pressure-CV and 5.0%, 5.28%, and 7.08% for systolic blood pressure-CV in the first, second, and third tertiles, respectively. Survival analysis demonstrated differences in hip/vertebral fracture amongst the tertiles of systolic and diastolic blood pressure variability ($P < 0.0001$).

Conclusions: Measures of blood pressure variability were significantly associated with incident hip/vertebral fractures. They can be incorporated into existing clinical scores to improve risk stratification.

Key words: hip fracture; vertebral fracture; blood pressure variability; association

Introduction

Osteoporosis is an increasingly important pathological condition in the face of the ageing population around the world. It is the most common metabolic bone disease and the leading cause of hip and vertebral fractures. [1] Globally, one in three women and one in five men over age 50 will experience an osteoporotic fracture. [2] Whilst the fracture itself may not be immediately lethal, the sequelae of the fracture often drastically impair the patient's functionality, mobility and quality of life, ultimately placing more strain on the healthcare system. [3] Therefore, identifying risks for hip and vertebral fractures is of critical importance to allow early intervention for an improvement in patient prognosis.

In addition to the disease burden of osteoporosis itself, fall and fracture prevention in elderlies is complicated by their multi-comorbidities. For example, cardiovascular diseases itself, and their treatments, are often risk factors for osteoporosis. Over the past decade, large-scale clinical studies have reported an increased osteoporotic fracture risk amongst type 2 diabetes mellitus patients. [4, 5] Antihypertensives have been known to show modulatory effects on bone mineral density, with loop diuretics presenting with adverse effects and thiazide to be bone-protective.[6, 7] Atherosclerosis is associated with osteoporosis through aging and shared biochemical processes. [8] Over the past decade, blood pressure variability has been associated with cardiovascular outcomes and mortality. [9, 10] However, little has been explored on its prognostic value towards osteoporotic fractures. Recently, visit-to-visit blood pressure variability has been associated with the development of hip fractures amongst type 2 diabetic patients. [11] In this study, we evaluated the association between blood pressure variability and the risk of hip/vertebral fractures in middle aged and elderly patients.

Methods

Study Population

The analysis was based on a wider study on antihypertensives and adverse outcomes that was approved by The Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. The patients were identified from the Clinical Data Analysis and Reporting System (CDARS), a territory-wide database that centralizes patient information from individual local hospitals to establish comprehensive medical data, including clinical characteristics, disease diagnosis, laboratory results, and medication prescription details. The system has been previously used by both our team and other teams in Hong Kong to conduct studies on comparative drug action [12], specific diseases [13-15], model development [16] or visit-to-visit variability in metabolic parameters [17, 18] or blood pressure [19].

The inclusion criteria were patients with a first attendance at family medicine clinics managed by the Hospital authority of Hong Kong between 1st January 2000 and 31st December 2003, and above the age of 50 years old. The exclusion criteria were those with a history of hip fracture, accidental fall, bone tumor, and those without at least three records of blood pressure measurements, and those missing covariate data.

Patients' demographics include sex and age of initial blood pressure test (baseline). Prior comorbidities before initial blood pressure test were extracted, including cardiovascular diseases, respiratory diseases, renal diseases, diabetes mellitus, hypertension, gastrointestinal diseases, acute myocardial infarction (AMI), dementia, anxiety disorder and depression, atrial fibrillation (AF), intracranial hemorrhage (ICH), chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), ischemic heart disease (IHD), cancer, congestive heart failure (CHF), gastrointestinal bleeding, transient ischemic attack (TIA), ischemic stroke, osteopenia, osteoporosis, history of falls, liver diseases, rheumatoid arthritis and other inflammatory polyarthropathies (RAOIP), based on the comorbidities data from 1st January 2000 to 31st December 2003. The Charlson comorbidity index was also calculated. Mortality was recorded using the International Classification of Diseases Tenth Edition (ICD-10) coding, whilst the secondary outcomes, exclusion criteria and comorbidities were

documented in CDARS under ICD-9 codes. **Supplementary Table 1** displays the ICD codes used to search for patient outcomes and comorbidities.

Medication use was also extracted, including 1) antihypertensives: angiotensinogen-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), calcium channel blockers, beta-blockers, diuretics, nitrates; 2) anti-diabetic drugs: insulin, sulphonylurea, meglitinide, alpha-glucosidase inhibitors; 3) antihyperlipidemic/lipid-lowering drugs: statins and fibrates; 4) anticoagulants. Baseline biochemical data, defined as complete blood count, liver function tests, glycemic and lipid profile measured from 1st January, 2000 to 31st December, 2003, were extracted. Complete blood count includes mean corpuscular volume (MCV), basophil, eosinophil, lymphocyte, blast, metamyelocyte, monocyte, neutrophil, white blood count, mean corpuscular hemoglobin (MCH), myelocyte, platelet, reticulocyte, red blood count, and hematocrit (HCT). Liver function tests include potassium, urate, albumin, sodium, urea, protein, creatinine, alkaline phosphatase (ALP), aspartate transaminase, alanine aminotransferase (ALT), and bilirubin. Glycemic and lipid profiles include HbA1c, cholesterol, fasting blood glucose, and triglycerides.

Primary outcomes and statistical analysis

Hip/vertebral fracture

The primary outcome was new onset hip or vertebral fractures (**Figure 1**). Patients with outcome events such as an open hip fracture (ICD-9-CM 820.1, 820.10-820.12, 820.19, 820.9, 820.13, 820.22, 820.3, and 820.30-820.32), and pathological fracture (ICD-9-CM 733.14 and 733.15) were not considered to ascertain the primary hip fracture events. Patients with prior composite outcome of hip or vertebral fractures were excluded. In addition, fractures that were recorded with a traumatic event (ICD-9-CM E800-E848) were regarded as censoring events and were not included as outcome events to exclude possible cases of traumatic fractures. Only a maximum of one hip fracture (initial hip

fracture) per patient was included, and repeated hip fracture was not considered in the present study. The endpoint date of interest for eligible patients who met the primary outcome was event presentation date, and the endpoint for those without primary outcome presentation was mortality date or until 31st December 2019.

Descriptive statistics were used to summarize patients' characteristics of the primary outcome. Continuous variables were presented as median (95% confidence interval [CI] or interquartile range [IQR]) and categorical variables were presented as count (%). The Mann-Whitney U test was used to compare continuous variables. The Kruskal-Wallis test was used to determine whether more than two continuous variables have a different distribution. The $\chi 2$ test with Yates' correction was used for 2×2 contingency data.

Blood pressure variability

Baseline/maximum/minimum values of diastolic blood pressure (DBP) and systolic blood pressure (SBP) are extracted, and the temporal variability of DBP and SBP was examined through the following approaches: 1) mean, 2) median, 3) standard deviation (SD), 4) root mean square (RMS) by first squaring all blood pressure values then performing square root of the mean of the squares, 5) coefficient of variation (CV) by dividing the blood pressure standard deviation by the mean blood pressure then multiplying by 100, and 6) a variability score (from 0 [low] to 100 [high]) defined as the number of changes in blood pressure of 5 mmHg or more. To examine the effect of blood pressure variability on patient outcomes, the patients were divided into subgroups and compared based on tertiles of DBP-CV and SBP-CV levels.

Univariate Cox hazard proportional models were used to identify the factors that were associated with the risk of developing new onset hip/vertebral fracture. Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) and P-values were reported accordingly. The

associations between baseline/latest/mean/median of blood pressure and time-to-death for all-cause mortality were modeled using the generalized additive model, with 95% CIs displayed. Kaplan-Meier curves were plotted against the time-to-event for hip fracture presentation and were stratified by patient gender. All statistical tests were two-tailed and considered statistically significant if P values < 0.05. Data analyses were performed using RStudio software (Version: 1.1.456) and Python (Version: 3.6).

Results

Clinical and Biochemical Characteristics

A total of 77970 patients at or above the age 50 was identified initially. Those with a history of hip fracture, accidental fall, bone tumor, and those without more than three records of blood pressure measurements were excluded. A total of 67728 persons fulfilled the eligibility criteria. We further excluded persons with missing covariate data. A total of 57810 persons (43.07% males, median age of initial blood pressure test: 67.5 years old, IQR: 58.8-74.7, max: 103.9 years old) were included (**Figure 1**). After a median follow-up period of 5894 days (IQR: 3505-6487, max: 7474 days), 3285 patients (5.68%) suffered from new onset hip or vertebral fractures. The crude incidence rates were 4.95%, 5.31%, and 7.2% for DBP-CV and 5.0%, 5.28%, and 7.08% for SBP-CV in the first, second, and third tertiles, respectively. Kaplan-Meier survival curves of primary outcome according to the tertile subgroups of DBP-CV and SBP-CV are presented in the top and bottom panels of **Figure 2**, respectively. A significant intergroup difference in hip or vertebral fractures was identified (P< 0.0001).

The baseline characteristics according to the tertile subgroups of DBP-CV are presented in **Table 1**, with significant differences across demographics, comorbidities and medications prescribed (P-value < 0.05). The tertile subgroup with higher DBP CV has higher levels of neutrophil, creatinine, alkaline phosphatase, aspartate transaminase, and triglyceride, but has lower levels of lymphocyte, platelet, red blood count, alanine transaminase, low-density lipoprotein, total cholesterol, and HbA1c.

The baseline characteristics according to the tertile subgroups of SBP-CV are presented in **Supplpementary Table 3**, with significant differences across demographics, comorbidities and medications prescribed (P-value < 0.05). The third tertile SBP-CV subgroup has higher levels of neutrophil, white blood count, platelet, red blood count, albumin, sodium, urea tests, but have lower levels of lymphocyte, protein, creatinine, low-density lipoprotein, high-density lipoprotein, total cholesterol, HbA1c, and fasting glucose.

Significant risk factors of new onset hip or vertebral fractures

Univariate Cox regression models were conducted to identify the significant risk factors of new onset hip or vertebral fractures in the tertile subgroups of DBP-CV (**Table 2**) and SBP-CV (**Table 3**). Higher baseline levels of neutrophil and alkaline phosphatase, and lower baseline levels of lymphocyte, red blood count, potassium, albumin, urea, protein, alanine transaminase, and HbA1c were significantly associated with the development of new onset hip or vertebral fractures. Higher values of most DBP measures and most SBP measures demonstrated the highest association strength for new onset hip or vertebral fractures (HR>1, P <0.05). The third tertile subgroup of both DBP-CV and SBP-CV has the highest incidence rate of new onset composite of hip or vertebral fractures: 7.2% and 7.08%, respectively.

The nonlinear associations of the time-to-event of hip or vertebral fractures with DBP or SBP measures are depicted in **Supplementary Figures 1 and 2**, respectively. The linear fitting results of the association between DBP/SBP measures and the duration to event presentation are shown in **Supplementary Figures 3 and 4**, respectively, where the fitted functions with coefficients of R^2, p value, and the variable distributions (lines) were also presented. With the first tertile subgroup as a reference, the results of both unadjusted and adjusted HRs show that higher CV in third tertiles of

DBP-CV and SBP-CV provide significant association strength for new onset hip or vertebral fractures (HR>1, P value<0.0001) in five models adjusted by increasing number of confounders (**Table 4**).

Discussion

The main finding of this population-based study is that higher systolic or diastolic blood pressure variability is associated with higher rates of incident hip/vertebral fractures even after adjusting for potential confounders.

Blood pressure variability is a complex phenomenon and results from interactions between the extrinsic environment, behavioral factors and intrinsic cardiovascular regulatory mechanisms. [20] The significant difference in the demographic, comorbidities, and medications prescribed between patients of high and low blood pressure variability in the present study demonstrates the multifactorial nature underlying the hip fracture risk in elderly patients.

Previous studies have shown an association with blood pressure variability and adverse cardiovascular outcomes but not with osteoporosis or osteoporotic fractures. [21-23] Recently, Li *et al*. demonstrated that blood pressure variability could increase hip fracture risk in elderly patients with type 2 diabetes mellitus. [11] This could be a consequence of multiple factors including vascular abnormalities that lead to stroke, neuropathy, or retinopathy that can affect a person's balance and vision. Increased oxidative stress and inflammation can cause blood pressure variability, which can also influence bone mass. In addition, blood pressure variability may be more common in patients with multiple comorbidities on multiple drugs that could influence blood pressure. Findings from the present study support this claim. Besides from the third tertile subgroup of both DBP-CV and SBP-CV having the largest incidence rate of new onset composite of hip or vertebral fractures, a higher Charlson's score, cardiovascular comorbidities and medications were significantly associated iwth

incident fractures. Finally, blood pressure variability can be associated with autonomic nervous system dysfunction that predisposes to falls and fracture [24].

Whilst neither particular class of antihypertensive nor antihypertensive polypharmacy has been reported as a risk factor for increased falls, the period of initiation or intensification of antihypertensive treatment have been reported to significantly increase elderlies' short term fall risk, which often results in severe injuries such as hip fractures. [25-27] Moreover, cognitive impairment is associated with both low bone mineral density and decreases in bone mineral density over time. [28], which may be related to reduced vitamin D and calcium intake. [29, 30] In patients who have received the appropriate medication, efficacy may be reduced in patients with dementia due to factors such as medical comorbidities, polypharmacy, poor compliance, substance abuse, delirium and inadequate social support. [31]

Limitations

As in other observational studies using administrative data, this study is limited by potential under-coding of comorbidities, missing data, and coding errors. Additionally, the duration of the complications and the prescribed treatments were not accounted for, which could affect the interpretation of blood pressure value and variability measurements. In addition, this study is conducted based on a Hong Kong cohort, and it is expected that external validity through comparisons with studies from other countries could be conducted for further confirmation.

Conclusion

Measures of blood pressure variability are significantly associated with the development of incident hip/vertebral fractures. Further study is needed to elucidate the underlying pathogenic

mechanisms and to explore incorporating these variables into existing clinical scores to improve risk stratification for hip/vertebral fractures amongst older adults.

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Table 1. Comparisons of baseline characteristics according to tertiles of DBP-CV
* for p≤ 0.05, ** for p ≤ 0.01, *** for p ≤ 0.001

Characteristics	DBP-CV<7.48 (N=28903) Median (IQR);Max;N or Count(%)	7.48≤DBP-CV≤12.13 (N=14453) Median (IQR);Max;N or Count(%)	DBP-CV>12.13 (N=14454) Median (IQR);Max;N or Count(%)	P value
SBP-CV<7.36	5250(18.16%)	1048(7.25%)	8774(60.70%)	<0.0001***
7.36≤SBP-CV≤11.83	18576(64.27%)	6211(42.97%)	4924(34.06%)	<0.0001***
SBP-CV>11.83	5077(17.56%)	7194(49.77%)	756(5.23%)	<0.0001***
Event	1432(4.95%)	768(5.31%)	1041(7.20%)	<0.0001***
Mortality	11583(40.07%)	8199(56.72%)	6793(46.99%)	<0.0001***
Demographics				
Male	12414(42.95%)	5877(40.66%)	6613(45.75%)	<0.0001***
Baseline age, year	65.95(57.47-73.19);103.9	70.87(63.53-77.01);100.44	66.71(57.48-74.36);101.63	<0.0001***
Past comorbidities				
Charlson score	2.0(1.0-3.0);11.0	3.0(2.0-3.0);12.0	2.0(1.0-3.0);12.0	<0.0001***
Cardiovascular	1337(4.62%)	796(5.50%)	763(5.27%)	0.0002**
Respiratory	1534(5.30%)	848(5.86%)	963(6.66%)	<0.0001***
Renal	235(0.81%)	148(1.02%)	144(0.99%)	0.0459*
Diabetes mellitus	251(0.86%)	145(1.00%)	169(1.16%)	0.0113*
Hypertension	2150(7.43%)	1367(9.45%)	1138(7.87%)	<0.0001***
Gastrointestinal	1222(4.22%)	629(4.35%)	708(4.89%)	0.0083*
Acute myocardial infarction	101(0.34%)	56(0.38%)	62(0.42%)	0.4406
Dementia	98(0.33%)	92(0.63%)	76(0.52%)	<0.0001***
Anxiety disorder and depression	121(0.41%)	46(0.31%)	57(0.39%)	0.2837
Atrial fibrillation	239(0.82%)	189(1.30%)	184(1.27%)	<0.0001***
Intracranial hemorrhage	32(0.11%)	16(0.11%)	20(0.13%)	0.7033

Chronic obstructive pulmonary disease	196(0.67%)	124(0.85%)	160(1.10%)	<0.0001***
Peripheral vascular disease	40(0.13%)	17(0.11%)	28(0.19%)	0.2087
Ischemic heart disease	669(2.31%)	414(2.86%)	372(2.57%)	0.0032*
Cancer	408(1.41%)	222(1.53%)	274(1.89%)	0.0008**
Congestive heart failure	218(0.75%)	188(1.30%)	163(1.12%)	<0.0001***
Gastrointestinal bleeding	212(0.73%)	136(0.94%)	120(0.83%)	0.075
Transient ischemic attack	129(0.44%)	71(0.49%)	68(0.47%)	0.8037
Ischemic stroke	108(0.37%)	60(0.41%)	66(0.45%)	0.4312
Osteopenia	1(0.00%)	1(0.00%)	0(0.00%)	0.6065
Osteoporosis	13(0.04%)	8(0.05%)	5(0.03%)	0.7075
History of falls	222(0.76%)	101(0.69%)	194(1.34%)	<0.0001***
Liver diseases	16(0.05%)	10(0.06%)	19(0.13%)	0.0254*
RAOIP	13(0.04%)	5(0.03%)	13(0.08%)	0.085
Medications				
ACEI	3371(11.66%)	2600(17.98%)	1839(12.72%)	<0.0001***
ARB	101(0.34%)	97(0.67%)	55(0.38%)	<0.0001***
Calcium channel blockers	6300(21.79%)	4358(30.15%)	3323(22.99%)	<0.0001***
Beta blockers	5607(19.39%)	3539(24.48%)	2904(20.09%)	<0.0001***
Diuretics for heart failure	821(2.84%)	728(5.03%)	647(4.47%)	<0.0001***
Diuretics for hypertension	3010(10.41%)	1919(13.27%)	1733(11.98%)	<0.0001***
Nitrates	2438(8.43%)	1785(12.35%)	1379(9.54%)	<0.0001***
Statins and fibrates	2999(10.37%)	2018(13.96%)	1626(11.24%)	<0.0001***
Insulin	186(0.64%)	167(1.15%)	112(0.77%)	<0.0001***
Acarbose	167(0.57%)	101(0.69%)	64(0.44%)	0.0164*
Sulphonylurea	1064(3.68%)	771(5.33%)	332(2.29%)	<0.0001***
Meglitinide	216(0.74%)	152(1.05%)	76(0.52%)	<0.0001***
Alpha-Glucosidase Inhibitors	167(0.57%)	101(0.69%)	64(0.44%)	0.0164*

Anticoagulants	80(0.27%)	88(0.60%)	81(0.56%)	<0.0001***
Complete blood count				
Mean corpuscular volume, fL	90.1(86.9-93.2);129.5;n=5760	90.2(86.8-93.4);122.0;n=3798	90.2(86.7-93.3);127.8;n=3651	0.7331
Basophil, x10^9/L	0.01(0.005-0.04);0.34;n=2125	0.025(0.01-0.04);0.6;n=1577	0.01(0.0-0.04);0.32;n=1362	0.0221*
Eosinophil, x10^9/L	0.1(0.1-0.2);7.2;n=2520	0.1(0.08-0.2);9.25;n=1817	0.1(0.06-0.2);5.9;n=1607	0.9781
Lymphocyte, x10^9/L	1.68(1.2-2.2);24.49;n=2572	1.58(1.1-2.1);7.3;n=1840	1.5(1.1-2.1);5.4;n=1637	<0.0001***
Blast, x10^9/L	0.0(0.0-0.0);1.9;n=417	0.0(0.0-0.0);0.3;n=268	0.0(0.0-0.01);0.64;n=266	0.7045
Metamyelocyte, x10^9/L	0.13(0.08-0.48);2.04;n=32	0.1(0.08-0.28);1.3;n=17	0.16(0.07-0.4);3.0;n=27	0.7135
Monocyte, x10^9/L	0.5(0.4-0.67);4.5;n=2554	0.5(0.4-0.7);3.0;n=1831	0.5(0.4-0.7);16.5;n=1627	0.113
Neutrophil, x10^9/L	4.8(3.6-6.9);37.22;n=2548	5.0(3.66-7.2);27.8;n=1830	5.1(3.7-7.63);32.9;n=1621	0.0004**
White blood count, x10^9/L	7.3(6.0-9.2);43.3;n=5767	7.45(6.1-9.3);34.5;n=3803	7.4(5.9-9.5);6100.0;n=3656	0.0743
Mean cell haemoglobin, pg	30.7(29.4-31.9);45.0;n=5760	30.7(29.3-31.9);42.8;n=3798	30.7(29.4-31.9);41.8;n=3651	0.544
Myelocyte, x10^9/L	0.25(0.11-0.38);2.85;n=25	0.2(0.12-0.45);1.25;n=17	0.2(0.13-0.55);1.04;n=23	0.9437
Platelet, x10^9/L	233.0(192.0-283.0);2300.0;n=3654	235.0(193.0-281.0);1040.0;n=5766	229.0(188.0-275.0);1296.0;n=3802	0.0006**
Reticulocyte, x10^9/L	55.1(37.9-86.3);371.68;n=149	55.8(38.62-73.88);236.98;n=115	50.4(38.33-78.88);247.5;n=112	0.6378
Red blood count, x10^12/L	4.33(3.93-4.73);7.02;n=3649	4.37(4.01-4.73);7.15;n=5755	4.26(3.89-4.66);7.23;n=3794	<0.0001***
Hematocrit, L/L	0.39(0.36-0.42);0.56;n=1084	0.39(0.36-0.41);0.55;n=714	0.39(0.35-0.42);0.55;n=555	0.1139
Biochemical tests				
Potassium, mmol/L	4.2(3.9-4.5);10.0;n=12047	4.2(3.9-4.54);8.9;n=6858	4.2(3.84-4.5);8.4;n=7074	0.1174
Urate, mmol/L	0.4(0.32-0.49);1.4;n=2527	0.4(0.33-0.49);1.08;n=1534	0.41(0.33-0.49);1.08;n=1501	0.3739
Albumin, g/L	41.4(39.0-43.7);58.0;n=7818	41.0(39.0-43.0);56.0;n=4938	41.0(38.4-43.33);54.0;n=4801	0.2342
Sodium, mmol/L	141.0(139.0-142.0);181.0;n=12073	141.0(139.0-142.0);156.0;n=6878	140.1(138.36-142.0);169.0;n=7080	0.4612
Urea, mmol/L	5.9(4.9-7.2);53.4;n=12057	6.1(5.0-7.6);57.5;n=6871	6.0(4.9-7.4);49.93;n=7063	0.2661

Protein, g/L	74.0(70.0-77.0);147.0;n=7759	73.75(70.0-77.0);114.4;n=4899	74.0(70.0-78.0);109.0;n=4772	0.0614
Creatinine, umol/L	89.0(76.0-105.0);1274.0;n=7128	88.0(76.0-104.0);1957.0;n=12157	91.0(78.0-109.0);1191.0;n=6915	<0.0001***
Alkaline phosphatase, U/L	78.0(65.0-96.0);3275.0;n=6014	79.0(65.0-98.0);1422.0;n=3927	80.0(66.0-98.0);2028.0;n=3446	0.0014*
Aspartate transaminase, U/L	21.0(18.0-27.0);5110.0;n=1976	21.0(18.0-28.0);3304.0;n=1301	23.0(18.0-30.0);1787.0;n=1018	0.0010**
Alanine transaminase, U/L	20.0(14.0-29.0);1836.0;n=5310	19.0(14.0-27.0);2279.0;n=3676	19.0(14.0-28.0);1959.0;n=2928	<0.0001***
Bilirubin, umol/L	9.9(7.0-13.0);360.8;n=5992	9.3(7.0-13.0);281.7;n=3908	10.0(7.0-13.0);305.0;n=3433	0.0739
Glycemic and lipid profile				
Triglyceride, mmol/L	1.35(0.95-1.93);19.45;n=4536	1.37(0.98-1.93);31.63;n=13072	1.38(1.0-1.97);22.9;n=5342	0.0363*
Low-density lipoprotein, mmol/L	3.12(2.52-3.76);7.72;n=3610	3.05(2.48-3.66);8.23;n=11705	2.98(2.4-3.62);8.67;n=4549	<0.0001***
High-density lipoprotein, mmol/L	1.3(1.1-1.58);3.38;n=3712	1.3(1.1-1.57);4.1;n=11859	1.29(1.07-1.56);4.14;n=4619	0.0028*
Total cholesterol, mmol/L	5.24(4.59-5.94);11.86;n=4506	5.18(4.52-5.85);12.6;n=13024	5.1(4.48-5.83);13.84;n=5311	<0.0001***
HbA1c, g/dL	13.1(11.8-14.1);19.0;n=2674	13.2(12.2-14.2);19.5;n=4542	12.9(11.8-13.9);19.1;n=3089	<0.0001***
Fasting glucose, mmol/L	5.9(5.2-7.3);23.8;n=2867	5.98(5.14-7.5);26.3;n=2578	5.8(5.1-7.4);26.7;n=5076	0.1708
DBP measures				
Baseline, mmHg	80.0(71.0-90.0);232.0	80.0(69.0-107.0);240.0	83.0(71.0-130.0);221.0	<0.0001***
Latest, mmHg	71.0(61.0-100.0);238.0	78.0(70.0-90.0);244.0	79.0(68.0-124.0);224.0	<0.0001***
Maximum, mmHg	84.0(76.0-95.0);244.0	94.0(84.0-158.0);232.0	95.0(86.0-130.0);267.0	<0.0001***
Minimal, mmHg	55.0(49.0-78.0);165.0	66.0(57.0-103.0);172.0	72.0(66.0-82.0);222.0	<0.0001***
Mean, mmHg	72.7(66.83-102.0);188.0	78.3(71.36-87.69);231.5	78.5(71.0-130.1);200.6	<0.0001***
Median, mmHg	72.0(66.0-100.0);191.0	78.5(71.0-88.5);231.5	79.0(70.5-129.5);201.0	<0.0001***

Variance	24.57(12.92-37.62);312.5	72.0(51.67-148.59);840.5	129.22(94.19-283.09);5618.0	<0.0001***
SD	4.96(3.59-6.13);17.68	8.49(7.19-12.19);28.99	11.37(9.71-16.83);74.95	<0.0001***
RMS	73.5(67.56-103.24);189.56	78.39(71.49-87.85);231.84	78.87(71.37-130.75);201.98	<0.0001***
CV, %	5.62(3.85-6.67);7.48	9.78(8.73-10.87);12.13	13.99(12.92-15.61);37.87	<0.0001***
Variability score	50.0(33.33-57.14);92.31	64.29(52.83-73.44);96.55	66.67(58.93-76.27);97.06	<0.0001***
SBP measures				
Baseline, mmHg	126.0(83.0-147.0);238.0	134.0(113.0-150.0);232.0	135.0(99.0-154.0);251.0	<0.0001***
Latest, mmHg	123.0(76.0-140.0);240.0	126.0(92.0-143.0);261.0	132.0(112.0-147.0);235.0	<0.0001***
Maximum, mmHg	147.0(124.0-160.0);235.0	151.0(95.0-168.0);268.0	164.0(119.0-181.0);261.0	<0.0001***
Minimal, mmHg	103.0(75.0-115.0);196.0	104.0(61.0-118.0);212.0	120.0(105.0-134.0);221.0	<0.0001***
Mean, mmHg	129.5(77.18-141.12);213.33	133.76(94.73-143.5);215.8	134.75(116.0-146.24);225.0	<0.0001***
Median, mmHg	129.0(77.0-140.5);214.0	133.0(94.0-143.0);219.0	134.5(115.0-146.0);225.0	<0.0001***
Variance	81.33(34.92-156.52);5618.0	124.38(63.74-211.66);3444.5	226.41(121.01-376.73);4802.0	<0.0001***
SD	9.02(5.91-12.51);74.95	11.15(7.98-14.55);58.69	15.05(11.0-19.41);69.3	<0.0001***
RMS	130.1(77.57-141.82);213.34	134.82(95.7-144.68);217.18	135.09(116.25-146.64);225.04	<0.0001***
CV, %	6.65(4.37-8.7);38.46	9.68(8.07-11.39);32.01	12.11(10.0-14.45);32.23	<0.0001***
Variability score	51.78(50.0-66.67);94.74	66.67(56.1-75.0);96.43	72.58(62.9-80.0);96.97	<0.0001***

SBP: systolic blood pressure; DBP: diastolic blood pressure; SD: standard deviation; RMS: root mean square; CV: coefficient of variation; RAOIP: rheumatoid arthritis and other inflammatory polyarthropathies; ACEI: angiotensinogen-converting enzyme inhibitor; ARB: angiotensin receptor blocker

Table 2. Significant predictors of the primary outcome stratified by tertiles of DBP-CV using univariate Cox regression.
* for p≤ 0.05, ** for p ≤ 0.01, *** for p ≤ 0.001

Characteristics	DBP-CV<7.48 (N=28903) HR [95% CI]	P value	7.48≤DBP-CV≤12.13 (N=14453) HR [95% CI]	P value	DBP-CV>12.13 (N=14454) HR [95% CI]	P value
Demographics						
Male	0.43[0.38, 0.48]	<0.0001***	0.42[0.35, 0.50]	<0.0001***	0.39[0.34, 0.45]	<0.0001***
Baseline age, year	1.09[1.08, 1.10]	<0.0001***	1.08[1.07, 1.09]	<0.0001***	1.08[1.08, 1.09]	<0.0001***
Past comorbidities						
Charlson score	1.77[1.70, 1.83]	<0.0001***	1.67[1.58, 1.76]	<0.0001***	1.67[1.61, 1.74]	<0.0001***
Cardiovascular	1.56[1.25, 1.96]	0.00011***	1.18[0.85, 1.65]	0.321	1.66[1.29, 2.15]	0.0001***
Respiratory	1.66[1.34, 2.05]	<0.0001***	1.87[1.41, 2.47]	<0.0001***	1.87[1.49, 2.35]	<0.0001***
Renal	0.99[0.50, 1.99]	0.985	0.69[0.22, 2.15]	0.524	3.26[2.04, 5.20]	<0.0001***
Diabetes mellitus	1.52[0.92, 2.54]	0.104	1.22[0.58, 2.56]	0.607	1.80[1.13, 2.87]	0.0132*
Hypertension	1.30[1.07, 1.57]	0.0089**	1.13[0.87, 1.46]	0.354	1.54[1.24, 1.90]	<0.0001***
Gastrointestinal	1.37[1.08, 1.73]	0.0101*	1.05[0.73, 1.53]	0.783	1.82[1.44, 2.30]	<0.0001***
Acute myocardial infarction	1.20[0.50, 2.88]	0.687	1.88[0.71, 5.03]	0.207	1.29[0.54, 3.11]	0.57
Dementia	3.07[1.38, 6.85]	0.0062**	4.40[2.36, 8.23]	<0.0001***	3.49[1.66, 7.36]	0.001**
Anxiety disorder and depression	0.79[0.33, 1.90]	0.601	0.37[0.05, 2.66]	0.326	0.70[0.23, 2.18]	0.539
Atrial fibrillation	2.41[1.47, 3.94]	0.0005***	1.20[0.57, 2.52]	0.634	1.61[0.86, 3.00]	0.137
Intracranial hemorrhage	2.11[0.53, 8.44]	0.292	1.76[0.25, 12.47]	0.574	2.32[0.58, 9.28]	0.235
Chronic obstructive pulmonary disease	1.57[0.75, 3.29]	0.236	1.34[0.50, 3.57]	0.565	2.28[1.22, 4.25]	0.0098**
Peripheral vascular disease	3.19[1.03, 9.90]	0.0449*	3.28[0.46, 23.30]	0.236	5.13[2.13, 12.36]	0.0003***
Ischemic heart disease	1.55[1.14, 2.10]	0.0055**	0.78[0.46, 1.33]	0.366	1.59[1.10, 2.28]	0.0128*
Cancer	1.29[0.81, 2.06]	0.279	1.63[0.94, 2.82]	0.0822.	1.67[1.07, 2.60]	0.0233*

Congestive heart failure	2.20[1.22, 3.99]	0.0092**	1.00[0.41, 2.41]	0.999	2.57[1.45, 4.54]	0.0012**
Gastrointestinal bleeding	1.41[0.80, 2.49]	0.235	0.34[0.08, 1.36]	0.126	2.82[1.75, 4.56]	<0.0001***
Transient ischemic attack	1.73[0.90, 3.33]	0.102	1.70[0.71, 4.10]	0.236	0.89[0.33, 2.37]	0.81
Ischemic stroke	1.93[0.97, 3.88]	0.0629.	0.88[0.22, 3.52]	0.855	1.51[0.63, 3.63]	0.362
Osteopenia	17.65[2.48, 125.40]	0.0041**	34.44[4.84, 245.10]	0.0004***	-	-
Osteoporosis	9.79[3.15, 30.39]	<0.0001***	2.64[0.37, 18.79]	0.331	6.72[0.95, 47.81]	0.0569.
History of falls	6.23[4.53, 8.57]	<0.0001***	6.45[4.09, 10.18]	<0.0001***	4.08[2.89, 5.78]	<0.0001***
Liver diseases	2.34[0.33, 16.60]	0.396	-	-	1.12[0.16, 7.93]	0.912
RAOIP	3.45[0.86, 13.80]	0.0802.	-	-	1.30[0.18, 9.21]	0.795
Medications						
ACEI	1.60[1.39, 1.84]	<0.0001***	1.33[1.12, 1.59]	0.00107**	1.25[1.04, 1.49]	0.0163*
ARB	1.89[0.98, 3.63]	0.0576.	0.59[0.19, 1.85]	0.368	2.93[1.57, 5.47]	0.0007***
Calcium channel blockers	1.48[1.32, 1.66]	<0.0001***	1.38[1.19, 1.60]	<0.0001***	1.37[1.19, 1.57]	<0.0001***
Beta blockers	0.98[0.86, 1.12]	0.796	0.90[0.77, 1.07]	0.235	1.04[0.89, 1.20]	0.631
Diuretics for heart failure	2.54[1.97, 3.28]	<0.0001***	2.06[1.55, 2.75]	<0.0001***	2.33[1.78, 3.05]	<0.0001***
Diuretics for hypertension	1.58[1.36, 1.82]	<0.0001***	1.27[1.05, 1.54]	0.0153*	1.25[1.05, 1.49]	0.0109*
Nitrates	1.67[1.42, 1.95]	<0.0001***	1.32[1.08, 1.61]	0.0072**	1.46[1.20, 1.78]	0.0002***
Statins and fibrates	1.15[0.98, 1.35]	0.0844.	0.96[0.79, 1.18]	0.722	0.95[0.78, 1.15]	0.58
Insulin	1.93[1.14, 3.27]	0.0144*	2.00[1.22, 3.28]	0.0061**	2.47[1.40, 4.37]	0.0019**
Acarbose	1.81[1.05, 3.12]	0.0336*	0.73[0.27, 1.96]	0.536	1.98[0.82, 4.76]	0.129
Sulphonylurea	1.42[1.12, 1.80]	0.0034**	1.21[0.90, 1.61]	0.202	1.72[1.20, 2.47]	0.0035**
Meglitinide	1.55[0.93, 2.58]	0.0902.	1.05[0.52, 2.10]	0.898	1.93[0.92, 4.05]	0.0841.
Alpha glucosidase inhibitors	1.81[1.05, 3.12]	0.0336*	0.73[0.27, 1.96]	0.536	1.98[0.82, 4.76]	0.129
Anticoagulants	1.83[0.76, 4.39]	0.18	0.48[0.12, 1.93]	0.304	1.60[0.72, 3.58]	0.25

Complete blood count						
Mean corpuscular volume, fL	1.00[0.99, 1.01]	0.785	1.00[0.98, 1.02]	0.944	1.01[1.00, 1.03]	0.107
Basophil, x10^9/L	47.24[2.90, 768.60]	0.0068**	0.10[0.00, 10.33]	0.326	0.54[0.01, 30.07]	0.765
Eosinophil, x10^9/L	0.88[0.43, 1.78]	0.719	0.53[0.17, 1.68]	0.283	0.96[0.54, 1.72]	0.902
Lymphocyte, x10^9/L	0.77[0.63, 0.93]	0.0073**	0.90[0.71, 1.15]	0.398	0.69[0.55, 0.87]	0.0015**
Blast, x10^9/L	13.81[4.18, 45.62]	<0.0001***	-	-	0.07[0.00, 2029]	0.615
Metamyelocyte, x10^9/L	-	-	1.14[0.01, 189.10]	0.961	10.60[0.03, 3256.00]	0.419
Monocyte, x10^9/L	1.09[0.67, 1.77]	0.722	1.41[0.77, 2.56]	0.268	0.89[0.52, 1.52]	0.669
Neutrophil, x10^9/L	1.04[1.00, 1.07]	0.0445*	1.02[0.97, 1.08]	0.384	1.07[1.03, 1.10]	0.0007***
White blood count, x10^9/L	1.06[1.03, 1.08]	<0.0001***	1.03[0.99, 1.07]	0.117	1.000[0.998, 1.001]	0.775
Mean cell haemoglobin, pg	0.99[0.96, 1.02]	0.63	0.99[0.95, 1.02]	0.487	1.03[0.99, 1.07]	0.123
Platelet, x10^9/L	1.000[0.998, 1.001]	0.575	1.001[0.999, 1.002]	0.309	0.999[0.998, 1.001]	0.325
Reticulocyte, x10^9/L	1.00[0.99, 1.01]	0.853	0.98[0.94, 1.02]	0.255	1.00[0.98, 1.02]	0.802
Red blood count, x10^12/L	0.47[0.40, 0.55]	<0.0001***	0.55[0.46, 0.67]	<0.0001***	0.58[0.49, 0.69]	<0.0001***
Hematocrit, L/L	0.00[0.00, 0.06]	0.0009***	0.00[0.00, 0.26]	0.0164*	0.01[0.00, 1.54]	0.0751.
Biochemical tests						
Potassium, mmol/L	0.84[0.73, 0.97]	0.0198*	0.84[0.70, 1.01]	0.0578.	0.80[0.68, 0.94]	0.006**
Urate, mmol/L	2.04[0.56, 7.41]	0.28	0.32[0.05, 2.13]	0.238	1.10[0.22, 5.64]	0.906
Albumin, g/L	0.94[0.91, 0.96]	<0.0001***	0.93[0.91, 0.96]	<0.0001***	0.91[0.89, 0.93]	<0.0001***
Sodium, mmol/L	0.97[0.95, 1.00]	0.0282*	0.99[0.96, 1.02]	0.437	0.98[0.96, 1.00]	0.102
Urea, mmol/L	1.08[1.06, 1.10]	<0.0001***	1.05[1.02, 1.08]	0.0011**	1.08[1.05, 1.10]	<0.0001***
Protein, g/L	0.995[0.979, 1.012]	0.571	0.98[0.96, 1.00]	0.0739.	0.97[0.95, 0.98]	0.0002***

Creatinine, umol/L	1.002[1.001, 1.003]	0.000137***	1.000[0.997, 1.004]	0.881	1.001[1.000, 1.003]	0.136
Alkaline phosphatase, U/L	1.001[1.001, 1.002]	<0.0001***	1.002[0.999, 1.004]	0.265	1.002[1.002, 1.003]	<0.0001***
Aspartate transaminase, U/L	0.998[0.993, 1.004]	0.556	1.000[0.999, 1.001]	0.944	1.001[1.000, 1.003]	0.156
Alanine transaminase, U/L	0.986[0.978, 0.994]	0.0007***	0.996[0.988, 1.003]	0.234	0.99[0.98, 0.99]	0.0022**
Bilirubin, umol/L	0.984[0.965, 1.003]	0.0889.	0.98[0.96, 1.01]	0.126	0.99[0.97, 1.01]	0.333
Glycemic and lipid profile						
Triglyceride, mmol/L	1.02[0.96, 1.09]	0.48	1.04[0.93, 1.16]	0.465	0.98[0.89, 1.09]	0.756
Low-density lipoprotein, mmol/L	1.00[0.89, 1.12]	0.944	1.01[0.84, 1.22]	0.897	0.95[0.82, 1.10]	0.465
High-density lipoprotein, mmol/L	1.15[0.89, 1.50]	0.288	1.15[0.74, 1.78]	0.528	1.18[0.84, 1.65]	0.343
Total cholesterol, mmol/L	1.07[0.97, 1.17]	0.17	1.08[0.93, 1.24]	0.311	1.04[0.92, 1.17]	0.544
HbA1c, g/dL	0.76[0.72, 0.80]	<0.0001***	0.81[0.76, 0.87]	<0.0001***	0.86[0.81, 0.91]	<0.0001***
Fasting glucose, mmol/L	1.05[1.00, 1.10]	0.0448*	1.08[1.01, 1.16]	0.0226*	1.04[0.99, 1.10]	0.146
DBP measures						
Baseline, mmHg	1.036[1.034, 1.038]	<0.0001***	1.034[1.031, 1.037]	<0.0001***	1.041[1.034, 1.042]	<0.0001***
Latest, mmHg	1.036[1.034, 1.038]	<0.0001***	1.036[1.033, 1.039]	<0.0001***	1.042[1.04, 1.05]	<0.0001***
Maximum, mmHg	1.035[1.033, 1.037]	<0.0001***	1.032[1.029, 1.035]	<0.0001***	1.041[1.04, 1.043]	<0.0001***
Minimal, mmHg	1.035[1.033, 1.038]	<0.0001***	1.032[1.028, 1.036]	<0.0001***	1.043[1.04, 1.05]	0.0003***
Mean, mmHg	1.034[1.032, 1.036]	<0.0001***	1.03[1.026, 1.034]	<0.0001***	1.042[1.04, 1.045]	<0.0001***

Median, mmHg	1.034[1.032, 1.036]	<0.0001***	1.03[1.026, 1.034]	<0.0001***	1.042[1.04, 1.043]	<0.0001***
Variance	1.046[1.045, 1.047]	<0.0001***	1.048[1.047, 1.048]	<0.0001***	1.042[1.04, 1.05]	<0.0001***
SD	0.96[0.94, 0.98]	<0.0001***	0.98[0.96, 1]	<0.0001***	0.98[0.96, 1.01]	<0.0001***
RMS	1.03[1.03, 1.04]	<0.0001***	1.03[1.026, 1.034]	<0.0001***	1.042[1.04, 1.045]	<0.0001***
CV, %	1.07[1.03, 1.11]	0.291	1.05[1.02, 1.08]	0.973	0.96[0.93, 0.99]	<0.0001***
Variability score	1.03[1.03, 1.03]	<0.0001***	1.03[1.03, 1.04]	<0.0001***	1.042[1.04, 1.05]	0.0001***
SBP measures						
Baseline, mmHg	1.011[1.009, 1.012]	<0.0001***	1.009[1.007, 1.011]	<0.0001***	1.007[1.004, 1.009]	<0.0001***
Latest, mmHg	1.012[1.011, 1.014]	<0.0001***	1.011[1.009, 1.013]	<0.0001***	1.006[1.004, 1.009]	<0.0001***
Maximum, mmHg	1.009[1.007, 1.010]	<0.0001***	1.008[1.006, 1.010]	<0.0001***	1.004[1.002, 1.006]	<0.0001***
Minimal, mmHg	1.018[1.016, 1.020]	<0.0001***	1.019[1.016, 1.022]	<0.0001***	1.010[1.008, 1.013]	<0.0001***
Mean, mmHg	1.015[1.013, 1.017]	<0.0001***	1.016[1.013, 1.019]	<0.0001***	1.008[1.005, 1.010]	<0.0001***
Median, mmHg	1.015[1.013, 1.017]	<0.0001***	1.016[1.013, 1.019]	<0.0001***	1.008[1.005, 1.010]	<0.0001***
Variance	1.001[1.001, 1.002]	<0.0001***	1.001[1.000, 1.001]	<0.0001***	1.001[1.000, 1.001]	<0.0001***
SD	1.06[1.05, 1.07]	<0.0001***	1.04[1.03, 1.05]	<0.0001***	1.02[1.01, 1.03]	0.0003***
RMS	1.015[1.013, 1.017]	<0.0001***	1.02[1.01, 1.02]	<0.0001***	1.008[1.005, 1.010]	<0.0001***
CV, %	0.97[0.96, 0.99]	0.007**	0.99[0.97, 1.02]	0.585	0.98[0.96, 1.00]	0.0378*
Variability score	0.999[0.995, 1.003]	0.651	1.001[0.996, 1.007]	0.607	0.99[0.99, 1.00]	0.0002***

SBP: systolic blood pressure; DBP: diastolic blood pressure; SD: standard deviation; RMS: root mean square; CV: coefficient of variation; RAOIP: rheumatoid arthritis and other inflammatory polyarthropathies; ACEI: angiotensinogen-converting enzyme inhibitor; ARB: angiotensin receptor blocker

Table 3. Significant predictors of the primary outcome stratified by tertiles of SBP-CV using univariate Cox regression.
* for p≤ 0.05, ** for p ≤ 0.01, *** for p ≤ 0.001

Characteristics	**SBP-CV≤7.36 (N=29711) HR [95% CI]**	**P value**	**7.36≤SBP-CV≤11.83 (N=13027) HR [95% CI]**	**P value**	**SBP-CV≥11.83 (N=15072) HR [95% CI]**	**P value**
Demographics						
Male	0.43[0.38, 0.49]	<0.0001***	0.43[0.35, 0.51]	<0.0001***	0.38[0.33, 0.44]	<0.0001***
Baseline age, year	1.09[1.08, 1.09]	<0.0001***	1.08[1.07, 1.09]	<0.0001***	1.09[1.08, 1.09]	<0.0001***
Past comorbidities						
Charlson score	1.79[1.72, 1.85]	<0.0001***	1.58[1.50, 1.67]	<0.0001***	1.72[1.65, 1.79]	<0.0001***
Cardiovascular	1.62[1.29, 2.04]	<0.0001***	1.11[0.80, 1.55]	0.539	1.60[1.24, 2.06]	0.0003***
Respiratory	1.83[1.48, 2.25]	<0.0001***	1.58[1.18, 2.11]	0.0021**	1.83[1.46, 2.30]	<0.0001***
Renal	2.06[1.21, 3.48]	0.0073**	0.88[0.37, 2.13]	0.78	1.73[0.93, 3.23]	0.0844.
Diabetes mellitus	1.65[1.02, 2.67]	0.0395*	1.48[0.70, 3.13]	0.299	1.50[0.91, 2.45]	0.109
Hypertension	1.28[1.05, 1.55]	0.0152*	1.19[0.93, 1.53]	0.165	1.48[1.19, 1.83]	0.0003***
Gastrointestinal	1.42[1.13, 1.79]	0.0025**	1.21[0.85, 1.73]	0.286	1.67[1.30, 2.14]	<0.0001***
Acute myocardial infarction	0.96[0.36, 2.55]	0.927	1.82[0.68, 4.87]	0.231	1.60[0.71, 3.56]	0.254
Dementia	2.50[1.04, 6.02]	0.0411*	5.06[2.86, 8.97]	<0.0001***	3.21[1.44, 7.17]	0.0045**
Anxiety disorder and depression	1.02[0.46, 2.28]	0.96	0.29[0.04, 2.04]	0.212	0.51[0.13, 2.03]	0.338

Atrial fibrillation	2.47[1.48, 4.11]	0.0005***	1.18[0.56, 2.49]	0.663	1.54[0.85, 2.78]	0.157
Intracranial hemorrhage	-	0.98	3.58[1.15, 11.13]	0.0276*	2.26[0.56, 9.05]	0.249
Chronic obstructive pulmonary disease	1.47[0.66, 3.28]	0.345	1.71[0.76, 3.82]	0.192	2.06[1.07, 3.97]	0.0315*
Peripheral vascular disease	5.14[1.93, 13.72]	0.0011**	6.77[2.17, 21.05]	0.001**	1.89[0.47, 7.58]	0.368
Ischemic heart disease	1.36[0.98, 1.89]	0.0699.	0.92[0.57, 1.49]	0.733	1.69[1.20, 2.40]	0.0029**
Cancer	1.54[1.02, 2.32]	0.041*	1.95[1.19, 3.20]	0.0085**	1.20[0.68, 2.11]	0.539
Congestive heart failure	2.32[1.28, 4.21]	0.005**	0.96[0.40, 2.32]	0.931	2.43[1.38, 4.30]	0.0022**
Gastrointestinal bleeding	1.52[0.88, 2.63]	0.131	0.89[0.37, 2.16]	0.804	2.00[1.16, 3.46]	0.0128*
Transient ischemic attack	1.40[0.66, 2.93]	0.38	1.20[0.45, 3.21]	0.714	1.62[0.77, 3.40]	0.205
Ischemic stroke	1.88[0.89, 3.94]	0.0971.	0.70[0.17, 2.80]	0.614	1.86[0.83, 4.14]	0.131
Osteopenia	-	-	20.19[5.04, 80.92]	<0.0001***	-	-
Osteoporosis	7.42[1.85, 29.68]	0.005**	11.39[2.84, 45.66]	0.0006***	2.07[0.29, 14.70]	0.467
History of falls	6.37[4.49, 9.05]	<0.0001***	6.51[4.29, 9.87]	<0.0001***	3.89[2.79, 5.42]	<0.0001***
Liver diseases	4.53[1.13, 18.12]	0.0328*	-	-	-	-
RAOIP	3.45[0.86, 13.79]	0.0803.	-	-	1.42[0.20, 10.11]	0.725
Medications						
ACEI	1.54[1.35, 1.77]	<0.0001***	1.35[1.12, 1.64]	0.00207**	1.28[1.08, 1.53]	0.0049**
ARB	2.07[1.17, 3.65]	0.0123*	0.92[0.30, 2.87]	0.89	1.65[0.78, 3.47]	0.187
Calcium channel blockers	1.48[1.33, 1.66]	<0.0001***	1.52[1.30, 1.78]	<0.0001***	1.27[1.11, 1.46]	0.0007***
Beta blockers	0.96[0.85, 1.09]	0.567	0.96[0.81, 1.15]	0.655	1.03[0.88, 1.19]	0.728

Diuretics for heart failure	2.90[2.31, 3.65]	<0.0001***	1.89[1.36, 2.62]	0.0002***	1.99[1.52, 2.62]	<0.0001***
Diuretics for hypertension	1.48[1.28, 1.70]	<0.0001***	1.33[1.08, 1.63]	0.00782**	1.33[1.12, 1.57]	0.0011**
Nitrates	1.52[1.30, 1.78]	<0.0001***	1.45[1.17, 1.80]	0.0007***	1.49[1.24, 1.79]	<0.0001***
Statins and fibrates	1.01[0.87, 1.18]	0.868	1.13[0.91, 1.42]	0.269	1.01[0.84, 1.21]	0.909
Insulin	2.03[1.27, 3.22]	0.00294**	2.09[1.18, 3.70]	0.0114*	2.21[1.25, 3.91]	0.0062**
Acarbose	1.31[0.68, 2.51]	0.426	1.30[0.62, 2.74]	0.491	1.88[0.84, 4.18]	0.125
Sulphonylurea	1.40[1.12, 1.74]	0.00281**	1.29[0.92, 1.79]	0.134	1.54[1.08, 2.21]	0.0174*
Meglitinide	1.43[0.86, 2.38]	0.167	0.89[0.37, 2.16]	0.803	1.92[1.03, 3.57]	0.0406*
Alpha-Glucosidase Inhibitors	1.31[0.68, 2.51]	0.426	1.30[0.62, 2.74]	0.491	1.88[0.84, 4.18]	0.125
Anticoagulants	1.69[0.80, 3.55]	0.167	0.90[0.22, 3.61]	0.883	0.96[0.36, 2.56]	0.934
Complete blood count tests						
Mean corpuscular volume, fL	1.00[0.99, 1.01]	0.769	1.00[0.98, 1.02]	0.935	1.01[0.99, 1.02]	0.298
Basophil, x10^9/L	3.00[0.15, 61.85]	0.476	4.37[0.07, 267.80]	0.482	2.73[0.07, 113.10]	0.597
Eosinophil, x10^9/L	0.84[0.41, 1.71]	0.632	0.98[0.55, 1.74]	0.934	0.74[0.32, 1.73]	0.487
Lymphocyte, x10^9/L	0.75[0.62, 0.90]	0.0023**	0.97[0.75, 1.26]	0.828	0.70[0.56, 0.88]	0.0023**
Blast, x10^9/L	2.22[0.00, 4751.00]	0.839	19.46[4.39, 86.24]	<0.0001***	0.12[0.00, 1861.00]	0.671
Metamyelocyte, x10^9/L	-	-	-	-	3.02[0.01, 1094.00]	0.713
Monocyte, x10^9/L	1.11[0.71, 1.73]	0.641	2.20[1.19, 4.06]	0.0114*	0.62[0.33, 1.16]	0.134
Neutrophil, x10^9/L	1.04[1.00, 1.07]	0.0324*	1.04[0.99, 1.09]	0.172	1.06[1.02, 1.10]	0.0046**
White blood count, x10^9/L	1.04[1.02, 1.07]	0.0009***	1.06[1.02, 1.09]	0.0022**	1.000[0.998, 1.001]	0.786
Mean cell haemoglobin, pg	1.01[0.98, 1.04]	0.698	0.99[0.95, 1.04]	0.686	1.01[0.97, 1.04]	0.731

Platelet, x10^9/L	1.000[0.999, 1.001]	0.852	1.001[1.000, 1.003]	0.171	0.999[0.998, 1.000]	0.143
Reticulocyte, x10^9/L	0.99[0.98, 1.01]	0.426	1.01[0.99, 1.04]	0.294	1.00[0.98, 1.02]	0.849
Red blood count, x10^12/L	0.51[0.44, 0.59]	<0.0001***	0.59[0.47, 0.73]	<0.0001***	0.52[0.44, 0.61]	<0.0001***
Hematocrit, L/L	0.00[0.00, 0.05]	0.0006***	0.02[0.00, 16.60]	0.25	0.00[0.00, 0.14]	0.0064**
Biochemical tests						
Potassium, mmol/L	0.84[0.73, 0.96]	0.0126*	0.88[0.72, 1.08]	0.227	0.78[0.67, 0.92]	0.0029**
Urate, mmol/L	1.11[0.30, 4.10]	0.873	2.12[0.31, 14.26]	0.441	0.72[0.15, 3.55]	0.689
Albumin, g/L	0.93[0.91, 0.95]	<0.0001***	0.94[0.91, 0.97]	0.0003***	0.91[0.89, 0.93]	<0.0001***
Sodium, mmol/L	0.97[0.95, 1.00]	0.0179*	0.98[0.95, 1.01]	0.142	0.99[0.96, 1.01]	0.387
Urea, mmol/L	1.08[1.06, 1.10]	<0.0001***	1.05[1.02, 1.09]	0.0029**	1.06[1.03, 1.09]	<0.0001***
Protein, g/L	0.99[0.97, 1.00]	0.117	0.99[0.97, 1.02]	0.541	0.97[0.95, 0.99]	0.0006***
Creatinine, umol/L	1.002[1.001, 1.003]	<0.0001***	1.002[0.999, 1.005]	0.193	1.001[0.998, 1.003]	0.629
Alkaline phosphatase, U/L	1.002[1.001, 1.002]	<0.0001***	1.002[1.000, 1.005]	0.0908.	1.002[1.001, 1.003]	<0.0001***
Aspartate transaminase, U/L	0.999[0.995, 1.003]	0.619	1.000[0.998, 1.002]	0.96	1.001[1.000, 1.003]	0.0317*
Alanine transaminase, U/L	0.980[0.972, 0.989]	<0.0001***	0.999[0.994, 1.003]	0.554	0.989[0.981, 0.998]	0.0126*
Bilirubin, umol/L	0.986[0.969, 1.003]	0.117	0.99[0.96, 1.01]	0.301	0.98[0.96, 1.01]	0.127
Glycemic and lipid profile						
Triglyceride, mmol/L	1.03[0.96, 1.10]	0.458	1.07[0.96, 1.18]	0.211	0.96[0.86, 1.06]	0.401
Low-density lipoprotein, mmol/L	1.04[0.92, 1.17]	0.539	0.88[0.73, 1.06]	0.17	0.98[0.85, 1.14]	0.799
High-density lipoprotein, mmol/L	1.16[0.89, 1.52]	0.277	1.00[0.65, 1.52]	0.992	1.37[0.98, 1.91]	0.0625.

Total cholesterol, mmol/L	1.06[0.96, 1.16]	0.241	1.02[0.89, 1.17]	0.786	1.09[0.97, 1.23]	0.131
HbA1c, g/dL	0.78[0.74, 0.82]	<0.0001***	0.84[0.77, 0.91]	<0.0001***	0.82[0.78, 0.87]	<0.0001***
Fasting glucose, mmol/L	1.05[1.00, 1.10]	0.0695.	1.09[1.02, 1.17]	0.0153*	1.05[0.99, 1.11]	0.0938.
DBP measures						
Baseline, mmHg	1.035[1.033, 1.037]	<0.0001***	1.035[1.033, 1.038]	<0.0001***	1.041[1.038, 1.044]	<0.0001***
Latest, mmHg	1.037[1.034, 1.039]	<0.0001***	1.037[1.034, 1.04]	<0.0001***	1.042[1.039, 1.045]	<0.0001***
Maximum, mmHg	1.034[1.032, 1.036]	<0.0001***	1.035[1.033, 1.038]	<0.0001***	1.039[1.037, 1.042]	<0.0001***
Minimal, mmHg	1.037[1.034, 1.039]	<0.0001***	1.037[1.033, 1.04]	<0.0001***	1.044[1.041, 1.047]	0.0002***
Mean, mmHg	1.033[1.031, 1.035]	<0.0001***	1.034[1.031, 1.037]	<0.0001***	1.041[1.038, 1.044]	<0.0001***
Median, mmHg	1.033[1.031, 1.035]	<0.0001***	1.035[1.032, 1.038]	<0.0001***	1.041[1.038, 1.044]	<0.0001***
Variance	1.046[1.045, 1.047]	<0.0001***	1.047[1.046, 1.048]	<0.0001***	1.049[1.048, 1.05]	0.0638.
SD	1.01[1, 1.03]	<0.0001***	1.02[1, 1.03]	<0.0001***	1.08[1.03, 1.09]	0.0051**
RMS	1.033[1.031, 1.035]	<0.0001***	1.03[1.03, 1.04]	<0.0001***	1.041[1.038, 1.044]	<0.0001***
CV, %	1.026[1.009, 1.045]	0.0108*	1.02[1, 1.04]	0.00273**	1.029[1.011, 1.047]	0.0207*
Variability score	1.034[1.031, 1.037]	<0.0001***	1.03[1.03, 1.04]	<0.0001***	1.045[1.042, 1.047]	<0.0001***
SBP measures						
Baseline, mmHg	1.012[1.010, 1.013]	<0.0001***	1.008[1.006, 1.010]	<0.0001***	1.006[1.004, 1.009]	<0.0001***

Latest, mmHg	1.012[1.011, 1.014]	<0.0001***	1.009[1.007, 1.011]	<0.0001***	1.008[1.006, 1.010]	<0.0001***
Maximum, mmHg	1.009[1.007, 1.011]	<0.0001***	1.007[1.006, 1.009]	<0.0001***	1.004[1.002, 1.007]	0.000194***
Minimal, mmHg	1.021[1.018, 1.023]	<0.0001***	1.017[1.014, 1.019]	<0.0001***	1.012[1.009, 1.015]	<0.0001***
Mean, mmHg	1.016[1.014, 1.018]	<0.0001***	1.013[1.010, 1.016]	<0.0001***	1.008[1.005, 1.011]	<0.0001***
Median, mmHg	1.016[1.014, 1.018]	<0.0001***	1.013[1.010, 1.016]	<0.0001***	1.008[1.005, 1.010]	<0.0001***
Variance	1.004[1.004, 1.005]	<0.0001***	1.001[1.001, 1.001]	<0.0001***	1.001[1.000, 1.002]	0.214
SD	1.14[1.12, 1.15]	<0.0001***	1.06[1.05, 1.07]	<0.0001***	0.99[0.97, 1.01]	0.51
RMS	1.016[1.014, 1.018]	<0.0001***	1.01[1.01, 1.02]	<0.0001***	1.008[1.005, 1.011]	<0.0001***
CV, %	1.001[1.01, 1.036]	0.0014**	1.07[1.04, 1.10]	<0.0001***	1.01[1.0, 1.04]	<0.0001***
Variability score	1.006[1.002, 1.010]	0.0046**	1.004[0.998, 1.010]	0.245	1.004[1.001, 1.006]	<0.0001***

SBP: systolic blood pressure; DBP: diastolic blood pressure; SD: standard deviation; RMS: root mean square; CV: coefficient of variation; RAOIP: rheumatoid arthritis and other inflammatory polyarthropathies; ACEI: angiotensinogen-converting enzyme inhibitor; ARB: angiotensin receptor blocker

Table 4. The hazard ratios (HRs) of hip fracture according to tertiles of DBP-CV and SBP-CV using different multivariate models.

* for $p \leq 0.05$, ** for $p \leq 0.01$, *** for $p \leq 0.001$

	DBP-CV			SBP-CV		
	1st tertile ≤7.48	2nd tertile [7.48, 12.13]	3rd tertile ≥12.13	1st tertile ≤7.36	2nd tertile [7.36, 11.83]	3rd tertile ≥11.83
N	28903	14453	14454	29711	13027	15072
Cases	1432	768	1041	1486	688	1067
IR	4.95%	5.31%	7.20%	5.00%	5.28%	7.08%
New onset hip or vertebral fracture composite HR [95% CI], p value						
Model 1	1.00	0.99[0.91, 1.07], 0.776	1.52[1.41, 1.63], <0.0001***	1.00	1.02[0.94, 1.11], 0.585	1.50[1.39, 1.61], <0.0001***
Model 2	1.00	0.72[0.67, 1.01], 0.512	1.70[1.58, 1.83], <0.0001***	1.00	0.78[0.71, 1.01], 0.101	1.62[1.5, 1.74], <0.0001***
Model 3	1.00	0.74 [0.68, 1.05], 0.419	1.67[1.55, 1.80], <0.0001***	1.00	0.78[0.72, 0.85], 0.782	1.58[1.47, 1.71], <0.0001***
Model 4	1.00	0.71 [0.65, 0.77], 0.901	1.71[1.58, 1.84], <0.0001***	1.00	0.77[0.71, 0.84], 0.623	1.61[1.49, 1.73], <0.0001***
Model 5	1.00	0.56 [0.43, 1.01], 0.231	1.86[1.45,2.38], <0.0001***	1.00	0.68[0.51,0.91], 0.782	1.59[1.25,2.02], <0.0001***

IR: incidence rate.
Model 1 adjusted for none.
Model 2 adjusted for age and gender.
Model 3 adjusted for age, gender, Charlson score, cardiovascular, respiratory, renal, diabetes mellitus, hypertension, gastrointestinal, AMI, dementia and Alzheimer, anxiety disorder and depression, AF, ICH, SCD, COPD, PVD, IHD, Cancer, CHF, gastrointestinal bleeding, HF, TIA, ischemic stroke, osteopenia, osteoporosis, history of falls, liver diseases, and RAOIP.
Model 4 adjusted for ACEI, ARB, calcium channel blockers, beta blockers, diuretics for heart failure, diuretics for hypertension, nitrates, antihypertensive drugs, antidiabetic drugs, statins and fibrates, insulin, acarbose, antihyperlipidemic/lipid-lowering drugs, sulphonylurea, meglitinide, alpha-glucosidase inhibitors, and anticoagulants in model 3.
Model 5 adjusted for baseline fasting glucose, baseline HbA1c, baseline SBP, and baseline DBP in model 4.

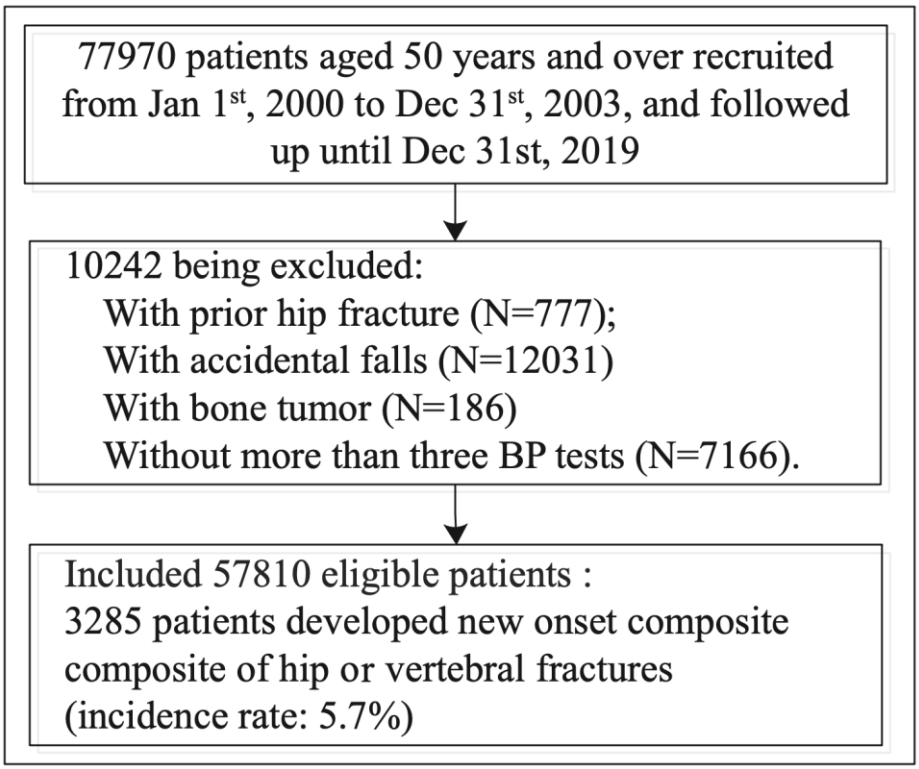

Figure 1. Procedures of data processing

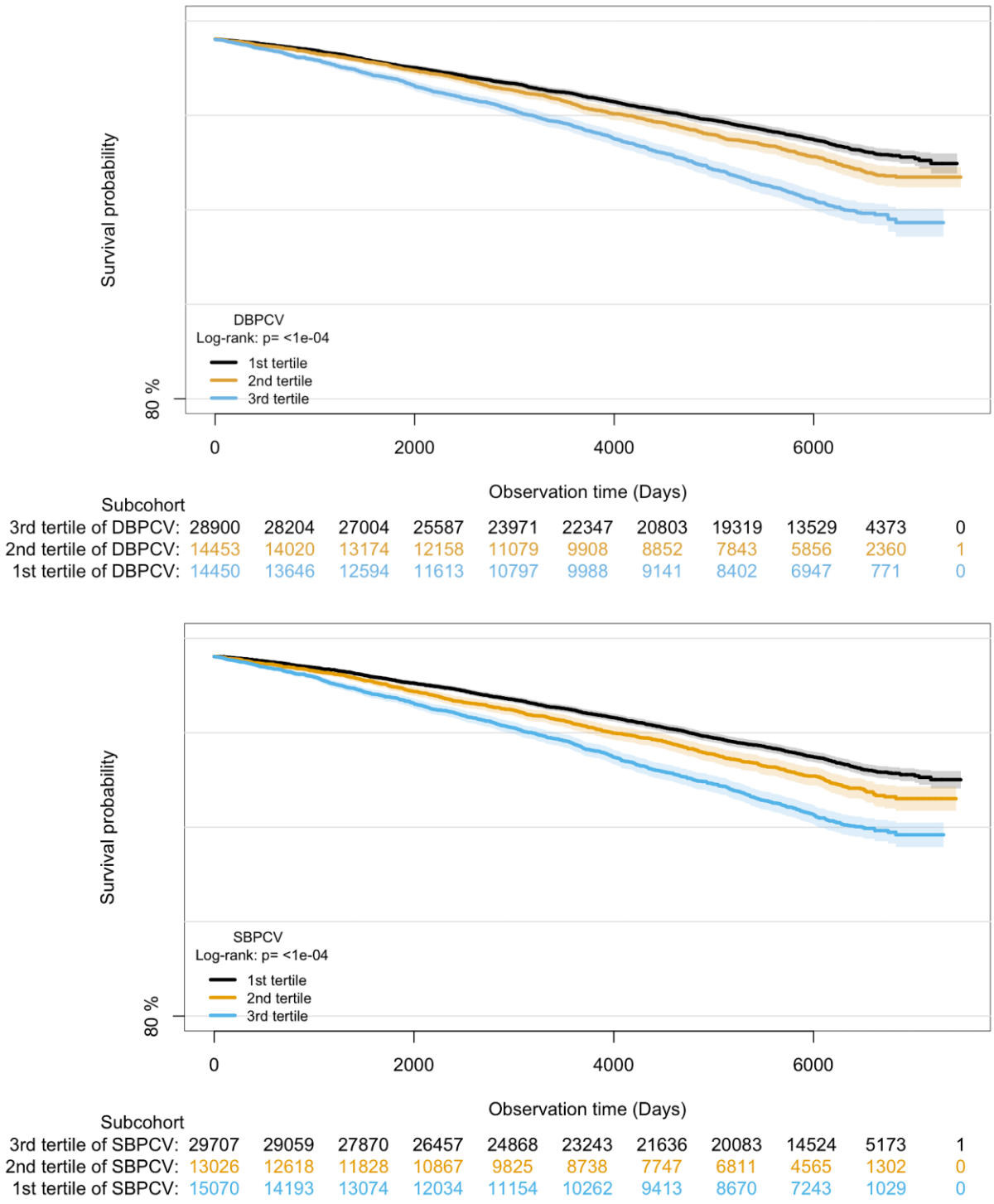

Figure 2. Kaplan-Meier survival curves of new onset hip/vertebral fracture outcome stratified by DBP-CV (top) or SBP-CV (bottom) tertiles.