DO WE NEED A PATIENT-CENTRED TARGET FOR SYSTOLIC BLOOD PRESSURE IN HYPERTENSIVE PATIENTS WITH TYPE 2 DIABETES MELLITUS?

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Abstract

The current trend on diabetes management advocates replacing the paradigm from a uniform to an individualized patient-centered systolic blood pressure, but there is no consensus on the achieved treatment goals of systolic blood pressure level. The study aimed at evaluating the association between systolic blood pressure and the risk of cardiovascular diseases and all-cause mortality for diabetic patients to identify patient-centered treatment targets. A retrospective study was conducted on 95,086 Chinese adult primary care patients with type 2 diabetes mellitus and hypertension. Using the average of the annual systolic blood pressure records('updated systolic blood pressure') over a median follow-up of 5.9 years, the risks of overall cardiovascular diseases, all-cause mortality and their composite associated with systolic blood pressure were evaluated using Cox proportional hazards regression. Subgroup analysis was performed on the incidence of cardiovascular diseases by stratifying patient's baseline characteristics. The systolic blood pressure range for the lowest risk of cardiovascular diseases and all-cause mortality was 130-134mmHg among type 2 diabetes mellitus population. A J-shaped curvilinear relationship was identified between systolic blood pressure and risk of cardiovascular diseases and all-cause mortality, irrespective of patients' characteristics. The findings showed that all patients with systolic blood pressure<125mmHg or ≥140mmHg had an increased risk of cardiovascular diseases and mortality. This large territory wide study showed the level of achieved systolic blood pressure of 125-139mmHg

in pharmacological therapy, irrespective of patients' characteristics, suggested the systolic blood pressure treatment goal of <140mmHg and individualized systolic blood pressure target may not be necessary in diabetic management.

Keywords: Systolic blood pressure; Cardiovascular diseases; Type 2 diabetes mellitus; Hypertension; Mortality, Primary care

Manuscript Text

Introduction

The risks of cardiovascular diseases (CVD) and all-cause mortality in patients with Diabetes Mellitus (DM) are thought to be related to suboptimal blood pressure (BP) control over a period of time, but the achieved target for pharmacologic BP lowering remains unclear. As one of the key goals of diabetes management is to minimize the risk of events [1-7], knowledge of the optimum achieved BP range in preventing CVD and all-cause mortality is important to help inform clinical practice and policy planning.

Many international guidelines provide a systolic blood pressure (SBP) target as one of the goals for diabetic management. However, there is currently no consensus on the optimal SBP target varying from 130mmHg to 140mmHg [1-7]. The discrepancy results across several randomized controlled trials (RCTs) showed that the benefits of intensive SBP control on CVD or mortality was still a matter of prolonged controversy [8-10]. Inconsistent associations between SBP and risk of CVD and mortality have been found in several epidemiological studies, with some suggesting a positive linear, J-shaped or U-shaped relationship [11-16]. Due to the heterogeneity of diabetic populations, a few studies also advocated that the aggressive treatment may not be appropriate for all patients and a rigid and uniform target should be replaced to a more flexible and patient-centered target for diabetic patients [4]. These

conflicting evidences leave clinicians with a high level of uncertainty to the optimal SBP target. Furthermore, the global trend is towards shifting delivery of diabetic care away from hospitals to primary care [17], and most of results from previous studies under RCTs or hospital-based settings may not be fully transferable to diabetic patient managed in real-world primary care setting. Understanding the relationship between SBP and the incidences of CVD and all-cause mortality among hypertensive and diabetic patients with different characteristics in primary care, the risk reduction that can be achieved through controlling SBP and the achieved treatment goals of SBP level in pharmacological therapy can assist clinicians in setting evidence-based SBP targets and recommendations for intervention.

The aim of this study was to investigate the association between SBP with the incidence of CVD events and all-cause mortality in treated patients with hypertension and Type 2 DM (T2DM), and explore the variation of the relationship among different characteristics such as gender, age, smoking status, duration of DM, body mass index (BMI), kidney function, severity of comorbidities and treatment modalities.

Methods

Study Design

This was a territory-wide retrospective cohort study that included all Chinese patients aged 18 or above, who were clinically diagnosed with T2DM and hypertension and without prior history of CVD before baseline and received DM management in primary care. Clinical data were collected from the administrative database of the Hong Kong Hospital Authority (HA) for patients who had received primary care services from any of the 74 general out-patient clinics of the HA between 1 January 2009 and 31 December 2010. The HA is the governing body of all public-sector hospitals and primary care clinics in Hong Kong. Due to large subsidized public health care system managing in Hong Kong, the HA provides care for at least 90% of the diagnosed local diabetic patients [18]. The date of the first prescription of anti-hypertensive drugs between 1 January 2009 and 31 December 2010 was defined as baseline. Each patient was followed-up until the date of diagnosis of an outcome event, death or last follow-up as of the censoring date of 30 November 2015, whichever occurred first.

Clinical diagnosis of T2DM and hypertension were identified using the International Classification of Primary Care-2 (ICPC-2) code of ‘T90’ and ‘K86’/’K87’, respectively. The primary outcomes of interest was incidence of composite of all-cause mortality and CVD, including coronary heart disease (CHD), stroke and heart failure. The secondary outcomes were CVD, each subtype of CVD and all-cause mortality. CHD including ischaemic heart

disease, myocardial infarction, coronary death and sudden death was identified by ICPC-2 of K74 to K76 or International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) of 410.x, 411.x to 414.x, 798.x. Heart failure was identified by ICPC-2 of K77 or ICD-9-CM of 428.x. Stroke including fatal and non-fatal was identified by ICPC-2 of K89 to K91 or ICD-9-CM of 430.x to 438.x. Although there was no validation study performed to assess the accuracy and completeness of the coding, a previous study showed that only 1.5% and 5.5% of records were miscoded or lacked coding, respectively, for the diagnosis of DM using ICPC-2 in the clinical management system of HA [19]. Moreover, in routine clinical practice, clinicians in clinical and hospital settings provide ICPC-2 and ICD-9-CM codes, respectively, for each episode of attendance [20, 21]. Another study also demonstrated reliability of the administrative database of HA to capture demographics and use of anti-diabetic drugs with an almost perfect level of data completeness regarding demographics (100%) and drug prescription (99.98%) [20]. Furthermore, due to heavily subsidized health care system in Hong Kong, patients with chronic diseases and serious complication, e.g. myocardial infarction, were mostly treated in the HA public health care system. Therefore, the cohort in the present study should have captured nearly all CVD outcomes of DM patients who are managed in the HA primary care setting. In term of mortality data, the records were extracted from the Hong Kong Death Registry, which is a population-based government official registry covering all registered deaths for the residents

of Hong Kong. These mortality data have been used widely in governmental departments; and thus should be highly reliable.

Consent of participants was not necessary as all data were anonymous and were extracted through the computerized administrative system of the Hospital Authority. Ethics approval was received from all the regional Institutional Review Boards (IRB) of the Hong Kong Hospital Authority. This study complies with the Declaration of Helsinki AND Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001.

Updated BP and Measurements

The guideline for obtaining and documenting SBP readings in diabetic patients during baseline and follow-up were standardized amongst all general outpatient clinics [22]. SBP was measured multiple times at each single visit, with an interval of at least 1 minute, after at least 5 minutes without any distractions in seated position, using a standardized semi-automated oscillometric devices (UA-853, Tokyo, Japan; or EDAN M3A, Shenzhen, China). If the difference between the two readings exceeded 5mmHg, an additional measurement was performed. The record of each SBP measurement was defined as the average of these readings.

The ‘updated’ SBP value was defined as the average of all annual SBP measurements. For instance, if the follow-up period was 2 years, then the updated mean value was calculated by averaging the baseline, one-year and two-year SBP measurements. This approach has been widely used to investigate the association between clinical parameter and the incidences of morbidity and mortality [12, 23, 24]. The average number of SBP readings recorded was 6.0, and at least 93.0% had at least three SBP records until last follow-up among our subjects.

Baseline covariates consisted of patient’s socio-demographics, clinical parameters, disease characteristics and treatment modalities. Socio-demographics included gender, age and smoking status. Clinical parameters included hemoglobin A1c (HbA1c), BMI, diastolic blood pressure (DBP), lipid profile (low-density lipoprotein-cholesterol (LDL-C) and total cholesterol to high-density lipoprotein-cholesterol ratio (TC/HDL-C ratio)), triglyceride (TG) and estimated glomerular filtration rate (eGFR). Disease characteristics included self-reported duration of diabetes mellitus. Co-morbidity was measured using the Charlson’s comorbidity index [25, 26]. Treatment modalities composed of the usages of anti-hypertensive drug (e.g. angiotensin converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB), β-blocker, calcium channel blocker (CCB), diuretics and others (hydralazine, methyldopa and prazosin)), oral anti-diabetic drugs, insulin and lipid-lowering agents. 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.

Data Analysis

Multiple imputation was used to handle missing data for baseline covariates (except SBP) [27]. In this study, each missing value was imputed five times by the chained equation method. For each of the five imputed datasets, the same analysis was performed with the five sets of results combined based on Rubin's rules [28]. All subjects were categorized as one of ten groups according to the updated SBP value (< 120mmHg, 120-124mmHg, 125-129mmHg, 130-134mmHg, 135-139mmHg, 140-144mmHg, 145-149mmHg, 150-154mmHg, 155-159mmHg and ≥ 160mmHg). Descriptive statistics were shown after multiple imputation for each subgroup of SBP. The incidence rate was estimated by an exact 95% confidence interval (CI) based on a Poisson distribution [29]. The SBP groups associated with the incidence of CVD were examined using multivariable Cox proportional hazards regressions, adjusted by all baseline covariates. Moreover, the nonlinear association between updated SBP and CVD for each outcomes were assessed by the restricted cubic splines with three knots in Cox models [30]. The proportional hazards assumption was checked by examining plots of the scaled Schoenfeld residuals against time for the covariates. Presence of multi-collinearity was

also checked by examining the variance inflation factor. Analysis of the data showed that all models fulfilled proportional hazards assumption and no multi-collinearity existed. To eliminate the potential bias from the imbalance number of patients in current groups, the main analyses were repeated by dividing the cohort into decile group of updated SBP levels. Four scenarios on the exclusion of patients either with follow-up period less than or equal to 1 year after baseline or with history of lung disease, cancer or chronic kidney disease on or before baseline, and with complete data were subsequently performed as sensitivity analyses to avoid potential bias due to severe disease at baseline.

Subgroup analysis was performed on the incidence of composite of CVD and all-cause mortality by stratifying gender, age groups (< 50 years, 50-64 years, 65-79 years, ≥ 80 years), duration of DM (< 2 years, ≥ 2 years), smoking status (non-smoker, smoker), BMI groups (< 23kg/m^2; 23kg/m^2-24.9kg/m^2; BMI ≥ 25kg/m^2), SBP (≤ 129mmHg;:129-141mmHg; 141-153mmHg; ≥ 153mmHg), eGFR (< 60ml/min/1.73m^2, ≥ 60ml/min/1.73m^2), Charlson's Index (< 5, ≥ 5), number of types of anti-hypertensive drugs used (1 kind, 2 kinds, ≥ 3 kinds) and usages of ACEI/ARB, β-blocker, CCB and diuretic at baseline.

All significance tests were two-tailed and those with a p-value less than 0.05 were considered statistically significant. The statistical analysis was performed in Stata Version 13.0.

Results

There were a total of 106,101 Chinese patients with T2DM aged 18 or above with valid SBP measurements and received DM care in one of the primary care clinics of HA between 1 January 2009 and 31 December 2010. A total of 95,086 diabetic patients were included in the data analysis after excluding 10,981 patients with CVD history and 34 patients without follow-up after baseline. Data completion rates for most baseline factors were greater than 85%.

The baseline characteristics for overall cohort and each SBP group after multiple imputation are summarized in **Table 1**. As a whole, 42.8% were male; mean age was 66.7 years (Standard Deviation (SD): 11.0 years); Updated SBP was 137.6mmHg (SD: 10.7mmHg). The number and unadjusted incidence rates of the four outcome events for each SBP group are shown in **Table 2**. During a median follow-up period of 51.5-81.5 months, the incidence rates of CVD were between 19.5 and 105.5 per 1,000 person-years among SBP groups. Multivariable Cox proportional hazards regressions were also performed and the corresponding hazard ratios for the marginal effects of SBP are shown and plotted in **Figure 1** and **Figure S1** with and without restricted cubic spline. After adjusting for all baseline characteristics, the J-shaped associations between SBP level and incidence for each outcome

were preserved. In terms of SBP, group 4 (130-134mmHg), the reference group, had the lowest risk of CVD and mortality and patients with SBP <125mmHg or ≥140mmHg had significantly higher risk. Repeated analysis by dividing the cohort into decile group of updated SBP levels in **Tables S2, S3 and Figure S2** demonstrated similar J-shaped association between SBP level and the outcomes. Four different sensitivity analyses were performed by considering exclusion of 1) patients with follow-up period less than or equal to 1 year after baseline; 2) patients with history of lung disease, cancer or chronic kidney disease on or before baseline; 3) both (1) and (2), and; 4) with complete data. The results obtained were almost identical to the main analysis of a J-shaped curvilinear relationship between SBP level and CVD incidence with an optimal SBP range between 130-134mmHg for each outcome. Similar J-shaped pattern (**Figure S3**) was observed on the risk of CVD by stratifying gender, age group, duration of DM, smoking status, SBP, BMI, eGFR, Charlson's index and usages of different anti-hypertensive drugs at baseline.

Discussion

This population-based cohort study is the first to examine the effect of SBP on the risks of CVD and all-cause mortality amongst Chinese hypertensive patients with T2DM managed in primary care. A key finding from this study identified the optimal level of achieved SBP of 125-139mmHg for the lowest risk of having all-cause mortality and CVD event including

CHD, stroke and heart failure, which supports the SBP target of 140mmHg in several international guidance in diabetic management. The current findings also demonstrated a J-shaped curvilinear relationship between SBP and incidence of CVD and all-cause mortality among diabetic population, irrespective of patients' characteristics, and thus lower BP is not always better and may even be potentially hazardous. While the J-curve pattern was shifted slightly to the right in patients with age ≥ 65 years, similar results were obtained that patients with SBP < 125mmHg or ≥ 140mmHg had an increased risk of CVD and mortality. Hence, the individualized SBP target may not be necessary in diabetic management.

Our findings were consistent with the results of previous clinical trials and observational studies which have also found a J-shape relationship between BP and cardiovascular outcomes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD), Cochrane review and two meta-analyses also concluded that lower BP targets (SBP < 120mmHg for ACCORD; SBP < 130mmHg for other) do not reduce macrovascular complications and mortality, but can increase the risk of adverse events attributed to hypertensive therapy [8-10, 31]. While ACCORD illustrated the advantage of the treatment SBP goal below 120mmHg on stroke in RCT [31], a post-hoc analysis from ACCORD showed that achieving SBP <120mmHg cannot attenuate the risk of all-cause mortality, overall CVD, myocardial

infarction and stroke compared to achieving SBP 120-140mmHg [32, 33]. A cohort study conducted in the US found similar results with the current study that SBP < 110mmHg was associated with increased risks of CHD, stroke and heart failure [11-13]. Two observational studies conducted in the UK also found an increased incidence of mortality at SBP < 125mmHg [15, 16]. A meta-analysis also demonstrated that antihypertensive treatment evaluated the risk of mortality caused by CVD at SBP < 140mmHg [34]. There is still no consensus on why low BP levels are associated with higher risks of CVD and all-cause mortality [35, 36]. Possible reason may be attributable to underperfusion, some unmeasured variables such as frailty and undiagnosed heart failure [15, 37].

Conversely, the United Kingdom Prospective Diabetes Study (UKPDS) identified a positive linear relationship between SBP and macrovascular complications and mortality, concluding that diabetic patients with SBP < 120mmHg had the lowest risk of events [14]. The Systolic Blood Pressure Intervention Trial (SPRINT) also reached the same conclusion with UKPDS among patients at high risk for CVD but without diabetes [38]. In comparing this current study's findings to earlier studies, our study had a much larger sample size of subjects with SBP < 120mmHg and is better powered to examine the outcomes of patients with lower SBP. On the other hand, the unattended automated office BP measurements, which aims to minimise the white coat effect, was used in SPRINT [38], and thus the BP values in SPRINT

may underestimate conventional office BP measurements by ranging from 5mmHg to 16mmHg [39]. Several concern groups pointed out that caution should be taken when translating the SPRINT targets into the real world clinical practices [40-42] as same targets applied in routine practices may fall into the left side of the J-curve.

Of interest, the findings from the present study showed the J-curve pattern was shifted slightly to the right in older patients but patients with SBP ≥140mmHg had an increased risk of CVD and mortality, irrespective of patients' age. A few updated international guidelines advocated a looser treatment SBP for elderly patients [1, 5]. For example, the Eighth Joint National Committee (JNC 8) Report and the International Diabetes Federation advocated treatment goal for SBP of < 150mmHg for patients aged ≥ 60 and ≥ 80 years, respectively [1, 5]. Nevertheless, two landmark randomized controlled trials, SHEP (Systolic Hypertension in Elderly Program) for persons aged ≥ 60 years and HYVET (Hypertension in the Very Elderly Trial) for persons aged ≥ 80 years, showed the benefit of treating hypertension for SBP to around 140 mmHg on health outcomes including mortality, stroke and heart failure [43, 44]. A recent prospective cohort study conducted in the general population aged 65 to 94 years from Australia also provided evidence that there was a direct positive association between SBP and CVD throughout the SBP ranging from 145 to 170mmHg, even at 85-94

years [45]. Our results indicated that this increased risk for CVD event and mortality extends to patients with SBP >140 mmHg regardless their age.

This study consisted of a large number of diabetic patients, and thus a greater number of events allowed a more precise estimate on the strength of association. A multiple repeated measurement for SBP, regression and stratified analyses were able to evaluate the association between SBP and outcome events comprehensively. Clinical characteristics were closely captured by the HA's computerised administrative database allowing accurate access to relevant baseline covariates such as laboratory results, disease characteristics and treatment modalities. Multiple imputations were used to replace the missing data to avoid biased results.

There were also several limitations to this study. Firstly, our design was a retrospective cohort study which evaluates associations but not causation. To confirm the association between BP and CVD and all-cause mortality among Chinese diabetic patients, a more convincing study design like RCT would be required. Nonetheless, the common limitations of RCTs like UKPDS included high attrition rates, low number of incident events, short follow-up times and strict subject's inclusion criteria that reduce the applicability to diabetic patients in clinical practices, with building evidence to supported the value of observational

studies in producing similar results to RCTs [46-48]. In addition, the probability of reverse causation was low in the current study as all our patients were without previous CVD at baseline, and the results were very similar in sensitivity analysis after excluding patients with follow-up period less than or equal to 1 year or with history of lung disease, cancer or chronic kidney disease. The current results were also adjusted with Charlson's comorbidity index and the subgroup analysis by stratifying Charlson's comorbidity index found similar results. Secondly, lifestyle interventions such as regular exercise and diet modification which may contribute to CVD risk were not taken into account in the analysis. However, the disease characteristics such as duration of T2DM and the severity of chronic kidney disease and some key clinical parameters like BMI, waist circumference, HbA1c, BP, and lipid, to a certain extent, reflect the intensity of disease severity and lifestyle modification, have been considered. Thirdly, this study highlighted the relationship between low BP level and the increased risks of CVD and all-cause mortality. However, this pattern of association between BP and outcomes excluded cluster effect across clinics and thus may differ in the general population and other Chinese diabetic populations from other regions. The relationship may be subject to temporal changes and modifications in unmeasured risk factors or interventions. Researchers should be cautious when adopting the study findings in other settings. Lastly, the long-term effects on BP on CVD and all-cause mortality are uncertain among Chinese diabetic patients. Further longitudinal studies with longer follow-up period are warranted to

reappraise the association between low BP and incidence CVD events and mortality to confirm the reasons contributing to the excess mortality at lower BP.

Perspectives

This large territory wide naturalistic primary care study showed a J-shaped pattern between SBP and risks of all-cause mortality and CVD events including CHD, stroke and heart failure. The increased risk associated with low levels of SBP (< 125mmHg) should make clinicians cautious against overtreatment of Chinese hypertensive T2DM patients without existing complications. The level of achieved SBP of 125-139mmHg in pharmacological therapy, irrespective of gender, age, smoking status, duration of DM, BMI, kidney function, severity of comorbidities and treatment modalities, support the SBP treatment goal of < 140mmHg and the individualized SBP target may not be necessary in diabetic management.

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E.Y.F.W. and C.S.C.F. 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. E.Y.T.Y. contributed to the study design, contributed to the statistical analysis and interpretation of the results, supervision and critical revision. W.Y.C., D.Y.T.F. and A.K.C.C. contributed to the interpretation of the results and wrote the manuscript. C.L.K.L.

contributed to the study design, supervision and acquisition of the data. All authors reviewed and edited the manuscript.

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Conflict of Interest

None.

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Novelty and Significance

What Is New?

This first large territory wide naturalistic primary care study showed that the systolic blood pressure range for the lowest risk of cardiovascular diseases and all-cause mortality was 130-134mmHg amongst Chinese patients with type 2 diabetes mellitus and hypertension managed in primary care. The current findings also demonstrated a J-shaped curvilinear relationship between systolic blood pressure and cardiovascular diseases incidence and all-cause mortality among diabetic population, irrespective of patients' characteristics.

What Is Relevant?

Our findings contribute to improve the knowledge on the effect of systolic blood pressure on cardiovascular diseases and all-cause mortality for Chinese diabetic patients.

Summary

Lower blood pressure is not always better and may even be harmful, irrespective of patients' characteristics, and thus the individualized systolic blood pressure target may not be necessary in diabetic management.

Figure Legends

Figure 1. Adjusted hazard ratios for incidence of (A) cardiovascular diseases, (B) coronary heart disease, (C) stroke, (D) heart failure, (E) all-cause mortality and (F) composite of cardiovascular disease and mortality among all subjects by multivariable Cox proportional hazards regressions. Hazard ratios were adjusted by age, gender, smoking status, BMI, haemoglobin A1c, diastolic blood pressure, triglyceride, total cholesterol to high-density lipoprotein cholesterol ratio, low-density lipoprotein cholesterol, eGFR, duration of DM, the usages of ACEI/ARB, β-blocker, CCB, diuretic, other anti-hypertensive drugs, oral-diabetic drugs, insulin and lipid-lowering agent, and Charlson's Index at baseline.

Tables

Table 1. Baseline characteristics among subjects, stratified by systolic blood pressure

Characteristic	Total (N=95,086)	SBP Group 1 (<120mm Hg) (N=3,314)	SBP Group 2 (120-124 mmHg) (N=6,183)	SBP Group 3 (125-129 mmHg) (N=12,140)	SBP Group 4 (130-134 mmHg) (N=17,765)	SBP Group 5 (135-139 mmHg) (N=19,271)	SBP Group 6 (140-144 mmHg) (N=15,683)	SBP Group 7 (145-149 mmHg) (N=9,893)	SBP Group 8 (150-154 mmHg) (N=5,402)	SBP Group 9 (155-159 mmHg) (N=2,698)	SBP Group 10 (≥160mm Hg) (N=2,737)	P-value
Socio-demographics												
Male	42.8%	43.5%	42.9%	43.5%	43.6%	43.6%	42.7%	41.6%	41.3%	39.6%	40.0%	<0.001*
Age, years	66.66±10.	65.97±11.	65.00±11.	64.75±10.	65.25±10.	66.24±10.	67.42±10.	68.68±10.	69.70±10.	70.18±11.	70.85±11.	<0.00

	98	71	27	94	85	72	66	57	65	01	26	1*
Current smoker	8.7%	11.0%	9.2%	9.1%	9.0%	8.7%	8.5%	8.2%	7.8%	8.0%	8.1%	<0.001*
Clinical parameters												
HbA1c, %	7.35±1.42	7.04±1.25	7.13±1.25	7.19±1.29	7.27±1.32	7.35±1.35	7.43±1.39	7.49±1.52	7.54±1.49	7.64±1.74	7.79±1.75	<0.001*
BMI, kg/m^2	25.83±6.02	25.53±4.44	25.69±4.43	25.85±4.03	25.97±5.34	25.87±4.31	25.86±4.72	25.79±6.16	25.72±4.88	25.66±4.55	25.59±5.68	<0.001*
Baseline SBP, mmHg	141.49±17.59	118.42±12.35	126.26±13.42	131.48±13.70	136.95±14.03	141.85±14.07	146.38±14.26	150.66±14.68	155.19±14.97	159.63±16.24	169.12±18.92	<0.001*
Mean SBP, mmHg	137.62±1	115.82±3.	122.69±1.	127.63±1.	132.52±1.	137.38±1.	142.28±1.	147.16±1.	152.12±1.	157.08±1.	167.91±8.	<0.00

	0.74	95	44	44	43	44	43	42	42	41	61	1*
DBP, mmHg	75.76±11.04	68.83±10.13	72.06±10.35	73.93±10.55	75.40±10.69	76.17±10.68	76.90±10.82	77.16±10.95	77.97±11.33	78.55±11.70	81.49±12.78	<0.001*
LDL-C, mmol/L	3.16±1.29	3.13±1.03	3.14±0.95	3.15±1.03	3.15±0.93	3.15±1.01	3.16±0.96	3.17±1.03	3.20±1.14	3.20±1.05	3.24±1.03	<0.001*
TC/HDL-C ratio	4.52±1.81	4.48±1.50	4.51±1.66	4.53±1.59	4.51±1.40	4.51±1.85	4.51±1.84	4.52±1.57	4.55±1.87	4.59±1.52	4.62±2.08	0.019*
Triglyceride, mmol/L	1.77±1.35	1.73±1.33	1.79±1.33	1.78±1.58	1.78±1.24	1.76±1.24	1.75±1.28	1.75±1.37	1.75±1.57	1.80±1.40	1.79±1.51	0.195
eGFR < 60ml/min/1.73m^2	18.2%	18.7%	16.7%	15.2%	15.6%	16.8%	18.8%	21.1%	23.7%	25.9%	30.6%	<0.001*
Disease characteristics												

Duration of DM, years	7.71±7.11	7.61±6.63	7.24±6.31	7.18±6.51	7.34±6.55	7.63±7.68	7.88±6.91	8.32±7.64	8.36±7.85	8.44±7.62	8.86±7.99	<0.001*
Treatment modalities												
Charlson's Index	4.10±1.07	4.04±1.17	3.95±1.13	3.93±1.10	3.97±1.08	4.06±1.06	4.17±1.04	4.28±1.02	4.36±1.01	4.38±1.00	4.44±1.05	<0.001*
Use of ACEI/ARB	46.6%	41.2%	41.8%	42.6%	45.3%	47.2%	48.3%	49.3%	50.4%	51.6%	53.7%	<0.001*
Use of β-blocker	37.4%	40.4%	38.5%	37.9%	36.7%	36.2%	36.8%	37.6%	38.2%	39.1%	40.8%	<0.001*
Use of CCB	54.1%	61.5%	57.7%	55.7%	53.3%	52.5%	51.8%	53.9%	55.8%	56.8%	55.0%	<0.001*
Use of Diuretic	15.9%	14.7%	14.4%	14.9%	15.0%	16.1%	16.9%	16.8%	17.0%	16.3%	16.4%	<0.001

												1*
Use of other anti-hypertensive drugs	13.6%	12.8%	10.7%	11.6%	11.8%	13.4%	14.5%	15.7%	17.7%	18.1%	18.9%	<0.001*
Oral anti-diabetic drug used	85.0%	81.9%	82.4%	82.8%	84.4%	85.1%	86.0%	86.9%	87.6%	87.7%	87.6%	<0.001*
Insulin used	0.8%	1.3%	0.5%	0.7%	0.7%	0.6%	0.8%	1.0%	1.3%	1.3%	1.5%	<0.001*
Lipid-lowering agents used	7.3%	7.2%	7.7%	7.6%	7.5%	7.2%	7.1%	6.6%	7.1%	7.6%	8.0%	0.081

HbA1c = Haemoglobin A1c; BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; LDL-C = Low-density Lipoprotein-Cholesterol; TC = Total Cholesterol; HDL-C = High-density Lipoprotein-Cholesterol; ACR = Albumin/Creatinine

Ratio; eGFR = Estimated Glomerular Filtration Rate; DM = Diabetes Mellitus; ACEI = Angiotensin Converting Enzyme Inhibitor; ARB = Angiotensin Receptor Blocker; CCB = Calcium Channel Blocker

Notes:

All parameters are expressed in either percentage or mean ± sd.

* Significant difference ($P < 0.05$) by ANOVA or chi-square test, as appropriate

Table 2. Number, incidence rate and hazard ratio of cardiovascular diseases events and all-cause mortality, stratified by systolic blood pressure

Outcome	SBP Group 1 (<120mmHg) (N=3,314)	SBP Group 2 (120-124mmHg) (N=6,183)	SBP Group 3 (125-129mmHg) (N=12,140)	SBP Group 4 (130-134mmHg) (N=17,765)	SBP Group 5 (135-139mmHg) (N=19,271)	SBP Group 6 (140-144mmHg) (N=15,683)	SBP Group 7 (145-149mmHg) (N=9,893)	SBP Group 8 (150-154mmHg) (N=5,402)	SBP Group 9 (155-159mmHg) (N=2,698)	SBP Group 10 (≥160mmHg) (N=2,737)
CVD										
Cumulative cases with event	727	925	1,455	2,144	2,491	2,495	2,068	1,454	863	1,199
Cumulative Incidence Rate	21.9%	15.0%	12.0%	12.1%	12.9%	15.9%	20.9%	26.9%	32.0%	43.8%
Person-years	17,558	36,715	74,471	109,494	118,567	94,348	56,992	29,220	13,567	11,363

Median follow-up (Months)	80.5	81.5	81.5	81.5	81.5	81.5	81.5	80.5	75.5	51.5
Incidence rate (95% CI)†	41.40 (38.50,44.53)	25.19 (23.62,26.87)	19.54 (18.56,20.57)	19.58 (18.77,20.43)	21.01 (20.20,21.85)	26.44 (25.43,27.50)	36.29 (34.76,37.88)	49.76 (47.27,52.39)	63.61 (59.51,68.00)	105.52 (99.71,111.66)
Hazard ratio‡ (95% CI)	2.06* (1.89,2.24)	1.31* (1.21,1.41)	1.02 (0.96,1.10)	Reference group	1.02 (0.97,1.08)	1.22* (1.15,1.29)	1.56* (1.47,1.66)	2.05* (1.92,2.19)	2.54* (2.35,2.76)	4.15* (3.86,4.47)
CHD										
Cumulative cases with event	356	455	728	1,044	1,163	1,152	950	655	408	559
Cumulative Incidence Rate	10.7%	7.4%	6.0%	5.9%	6.0%	7.3%	9.6%	12.1%	15.1%	20.4%

Person-years	18,842	38,000	76,450	112,364	121,804	97,906	60,257	31,730	15,055	13,715
Median follow-up (Months)	81.5	81.5	81.5	81.5	81.5	81.5	81.5	81.5	80.5	74.5
Incidence rate (95% CI)†	18.89 (17.03,20.96)	11.97 (10.92,13.13)	9.52 (8.86,10.24)	9.29 (8.74,9.87)	9.55 (9.01,10.11)	11.77 (11.11,12.47)	15.77 (14.79,16.80)	20.64 (19.12,22.29)	27.10 (24.59,29.86)	40.76 (37.52,44.28)
Hazard ratio‡ (95% CI)	1.89* (1.68,2.14)	1.28* (1.15,1.43)	1.04 (0.95,1.14)	Reference group	0.99 (0.91,1.08)	1.17* (1.08,1.28)	1.48* (1.36,1.62)	1.87* (1.69,2.06)	2.38* (2.12,2.67)	3.52* (3.16,3.91)
Stroke										
Cumulative cases with event	311	364	615	917	1,067	1,064	867	606	348	519
Cumulative	9.4%	5.9%	5.1%	5.2%	5.5%	6.8%	8.8%	11.2%	12.9%	19.0%

Incidence Rate										
Person-years	18,828	38,184	76,529	112,286	121,905	97,792	60,116	31,379	15,035	13,305
Median follow-up (Months)	81.5	81.5	81.5	81.5	81.5	81.5	81.5	81.5	80.5	72.5
Incidence rate (95% CI)†	16.52 (14.78,18.46)	9.53 (8.60,10.56)	8.04 (7.43,8.70)	8.17 (7.65,8.71)	8.75 (8.24,9.29)	10.88 (10.25,11.55)	14.42 (13.49,15.41)	19.31 (17.83,20.91)	23.15 (20.84,25.71)	39.01 (35.79,42.51)
Hazard ratio‡ (95% CI)	1.96* (1.72,2.23)	1.18* (1.04,1.33)	1.01 (0.91,1.12)	Reference group	1.02 (0.93,1.11)	1.20* (1.10,1.31)	1.47* (1.34,1.62)	1.87* (1.69,2.08)	2.16* (1.91,2.45)	3.53* (3.16,3.94)
Heart Failure										
Cumulative cases with event	197	262	386	572	733	790	727	534	332	463

Cumulative Incidence Rate	5.9%	4.2%	3.2%	3.2%	3.8%	5.0%	7.3%	9.9%	12.3%	16.9%
Person-years	19,367	38,615	77,349	113,522	123,154	98,924	61,017	32,000	15,322	14,059
Median follow-up (Months)	81.5	81.5	81.5	81.5	81.5	81.5	81.5	81.5	80.5	77.5
Incidence rate (95% CI)†	10.17 (8.85,11.70)	6.78 (6.01,7.66)	4.99 (4.52,5.51)	5.04 (4.64,5.47)	5.95 (5.54,6.40)	7.99 (7.45,8.56)	11.91 (11.08,12.81)	16.69 (15.33,18.16)	21.67 (19.46,24.13)	32.93 (30.06,36.07)
Hazard ratio‡ (95% CI)	1.76* (1.50,2.07)	1.33* (1.15,1.55)	1.02 (0.89,1.16)	Reference group	1.10 (0.99,1.23)	1.37* (1.23,1.53)	1.82* (1.63,2.03)	2.36* (2.09,2.66)	2.96* (2.58,3.40)	4.34* (3.82,4.93)
All-cause Mortality										
Cumulative cases	665	712	1,113	1,537	1,727	1,707	1,304	920	584	765

with event										
Cumulative Incidence Rate	20.1%	11.5%	9.2%	8.7%	9.0%	10.9%	13.2%	17.0%	21.6%	28.0%
Person-years	19,883	39,193	78,176	114,635	124,538	100,552	62,610	33,224	16,118	15,191
Median follow-up (Months)	81.5	81.5	81.5	81.5	81.5	81.5	81.5	81.5	81.5	80.5
Incidence rate (95% CI)†	33.45 (31.00,36.09)	18.17 (16.88,19.55)	14.24 (13.42,15.10)	13.41 (12.75,14.10)	13.87 (13.23,14.54)	16.98 (16.19,17.80)	20.83 (19.73,21.99)	27.69 (25.96,29.54)	36.23 (33.41,39.29)	50.36 (46.91,54.06)
Hazard ratio‡ (95% CI)	2.26* (2.06,2.48)	1.35* (1.23,1.47)	1.09* (1.01,1.18)	Reference group	0.96 (0.89,1.03)	1.09* (1.02,1.17)	1.20* (1.11,1.29)	1.48* (1.36,1.61)	1.86* (1.69,2.05)	2.50* (2.29,2.74)
Composite of CVD										

and Mortality										
Cumulative cases with event	1,133	1,360	2,159	3,120	3,549	3,495	2,751	1,912	1,147	1,518
Cumulative Incidence Rate	34.2%	22.0%	17.8%	17.6%	18.4%	22.3%	27.8%	35.4%	42.5%	55.5%
Person-years	17,558	36,715	74,471	109,494	118,567	94,348	56,992	29,220	13,567	11,363
Median follow-up (Months)	80.5	81.5	81.5	81.5	81.5	81.5	81.5	80.5	75.5	51.5
Incidence rate (95% CI)†	64.53 (60.88,68.40)	37.04 (35.12,39.06)	28.99 (27.79,30.24)	28.49 (27.51,29.51)	29.93 (28.96,30.93)	37.04 (35.84,38.29)	48.27 (46.50,50.11)	65.43 (62.57,68.43)	84.55 (79.79,89.58)	133.59 (127.04,140.48)
Hazard ratio‡	2.23*	1.33*	1.05	Reference	0.99	1.16*	1.41*	1.83*	2.30*	3.61*

(95% CI)	(2.08,2.38)	(1.24,1.41)	(0.99,1.11)	group	(0.95,1.04)	(1.11,1.22)	(1.34,1.48)	(1.73,1.94)	(2.15,2.47)	(3.39,3.85)

SBP = Systolic Blood Pressure; CVD = Cardiovascular Disease; CHD = Coronary Heart Disease; CI = Confidence Interval

Notes:

* Significant difference ($P < 0.05$) by multivariable Cox proportional hazards regression

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

‡ Hazard ratios were adjusted age, gender, smoking status, body mass index, haemoglobin A1c, diastolic blood pressure, triglyceride, total cholesterol to high-density lipoprotein cholesterol ratio, low-density lipoprotein cholesterol, estimated glomerular filtration rate, duration of diabetes mellitus, the usages of angiotensin converting enzyme inhibitor/angiotensin receptor blocker, β-blocker, calcium channel blocker, diuretic, other anti-hypertensive drugs, oral-diabetic drugs, insulin and lipid-lowering agent, and Charlson's Index at baseline.