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

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Diabetes Care 2017;40:270–279 | DOI: 10.2337/dc16-1617

OBJECTIVE

This study aimed to evaluate the impact of visit-to-visit variability (VVV) of systolic blood pressure (SBP) on cardiovascular disease (CVD) and mortality among primary care Chinese patients with type 2 diabetes mellitus (T2DM).

RESEARCH DESIGN AND METHODS

A retrospective cohort study was conducted in 124,105 Chinese adult primary care patients with T2DM and without prior diagnosed CVD from August 2008 to December 2009. The VVV of SBP was evaluated using SDs of SBP over 24 months. The risks of CVD and all-cause mortality associated with variability in SBP were evaluated using Cox proportional hazards regression. Subgroup analysis was conducted by the stratification of age, sex, duration of diabetes, the presence of chronic kidney disease, baseline SBP and trend, and the number and class of antihypertensive drugs.

RESULTS

A positive linear relationship between the VVV of SBP and the first incidence of CVD and all-cause mortality was identified over a median follow-up time of 39.5 months. Patients with a low SD of SBP of <5 mmHg had the lowest risks of CVD and all-cause mortality, and patients with an SD of SBP of ≥10 mmHg had significantly higher risks. For every 1 SD increase in the SD of SBP, the risks of CVD, all-cause mortality, and the composite of both events increased by 2.9% (95% CI 2.4–3.4%), 4.0% (95% CI 3.5–4.6%), and 3.4% (95% CI 3.0–3.8%), respectively. A direct linear relationship was also observed in all selected subgroups.

CONCLUSIONS

SBP variability, irrespective of the mean SBP level, is a potential predictor for the development of CVD and all-cause mortality in patients with diabetes. In addition to monitoring BP targets for their patients with diabetes, clinicians should also remain vigilant about the visit-to-visit fluctuation of BP.

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Received 27 July 2016 and accepted 9 November 2016.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-1617/-/DC1.

Diabetes is a global public health issue, affecting 415 million people around the world. It contributes to 10% of deaths worldwide, of which 70% are caused by the main complication of diabetes, namely, cardiovascular disease (CVD) (1,2). A rapidly aging population and the increasing prevalence of obesity are reasons why the projected number of patients with diabetes is expected to reach 600 million worldwide by 2035 (2). Among the approaches advocated in diabetes management guidelines to prevent CVD and premature death is the recommendation to maintain optimal blood pressure (BP) (3,4). In addition to absolute BP readings, increasing attention is being paid to the harmful effect of BP variability in the members of the population with diabetes (5).

Many studies have shown that a large fluctuation in BP within a short period of time substantially increased the risk of morbidity and mortality (6,7), and a recent systematic review and meta-analysis (5) concluded that the visit-to-visit variability (VVV) of systolic BP (SBP) was also associated with CVD and mortality. However, very few studies have explored the long-term effect of the VVV of SBP on clinical outcomes specifically in populations with diabetes. Among the 37 studies included in the systematic review, the target populations were mainly patients with hypertension, members of the general public, or patients with end-stage renal disease, with only four studies focusing on patients specifically with type 2 diabetes mellitus (T2DM) (5). Given that patients with diabetes are two to four times more likely to have CVD than patients without diabetes (8,9), it is conceivable that the VVV of SBP may have a significantly different effect on populations with diabetes versus those without diabetes. A limited number of studies (10–12) reported that the VVV of SBP was associated with the incidence of CVD and all-cause mortality among members of the population with diabetes. However, these studies were limited by having a relatively small number of patients in whom CVD developed, or by having been conducted in a very structured but artificial setting such as a randomized clinical trial or in a trial whose study populations were from hospital-based settings. Given the heterogeneity of the population with diabetes, the results from these studies may not be generalizable to patients with diabetes managed in the real-world primary care outpatient setting. Moreover, these studies did not adjust for the natural changes, or trend, in BP over time, which has been associated with an increased risk of CVD and mortality (13).

With this gap in the current knowledge, setting-specific population-based studies are needed to confirm the effect of the VVV of SBP on CVD/mortality risk among those in the population with diabetes who are in primary care. This study aimed to respond to this need by evaluating the relationship between the VVV of SBP and CVD/mortality risk in the Chinese T2DM population that is in primary care.

RESEARCH DESIGN AND METHODS

Study Design

This territory-wide retrospective cohort study was conducted between 1 August 2008 and 31 December 2009. Subjects included Chinese T2DM patients ≥18 years of age who were without a clinical diagnosis of CVD and were managed in any one of the 74 public General Out-Patient Clinics of the Hong Kong Hospital Authority (HA). The HA is the largest governmental organization coordinating all public-sector hospitals and primary care clinics in Hong Kong and manages >50% of diabetes patients in primary care. The data obtained were from a territory-wide study (14) evaluating the effectiveness of a risk assessment and management program for patients with diabetes. Patients with a clinical diagnosis of T2DM were identified from the computerized clinical management system of the HA using the International Classification of Primary Care-2 (ICPC-2) code of T90. The date of first recording of SBP was defined as the baseline. Figure 1 shows the timeline for the assessment of the VVV of SBP and outcome ascertainment in this study. The SBP readings obtained at baseline and every 3 months until the visit 24 months after baseline (total 9 occasions) were retrieved from the electronic patient record and used for the calculation of the VVV of SBP because patients with diabetes who are managed in the General Out-Patient Clinics are typically required to book a follow-up consultation with the doctor every 3 months. To increase the precision of estimates, patients with fewer than five SBP measurements during the follow-up period were excluded from this study. The mean SBP value of an individual patient was defined as the average of all the SBP measurements taken. Each patient was tracked until the date of a cardiovascular outcome event, the date of death, or the date of the last follow-up visit until the conclusion of the study on 31 December 2013, whichever occurred first. Ethics approval has been given by all institutional review boards across the whole territory.

Outcome Measures

The outcomes of interest consisted of the following three events: *1*) CVD event, including coronary heart disease (ischemic heart disease, myocardial infarction, coronary death, and sudden death coded as K74 to K76 in the ICPC-2, or coded as 410.×, 411.× to 414.×, and 798.× in the ICD-9-CM), stroke (fatal and nonfatal was coded as K89 to K91 [ICPC-2] or 430.× to 438.× [ICD-9-CM]), or heart failure (coded as K77 [ICPC-2] or 428.× [ICD-9-CM]); *2*) all-cause mortality (identified using the population data from the Hong Kong Death Registry); and *3*) a composite of CVD and all-cause mortality.

Clinical BP Measurements

The procedure of obtaining and documenting the BP readings in patients with diabetes followed standardized guidelines, which were applicable to all

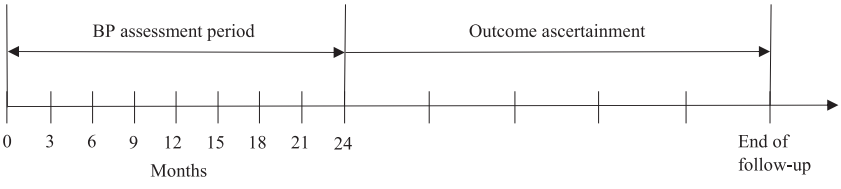

Figure 1—Study design for the investigation of the association of VVV in BP and CVD and all-cause mortality. The measurements of BP at eight visits (3, 6, 9, 12, 15, 18, 21, and 24 months after baseline) were used to calculate the mean and VVV. The median follow-up period was 39.5 months after the BP assessment period.

General Out-Patient Clinics (15). Clinicians measured BP after allowing the patient to rest for at least 5 min without any distractions, in a seated position, using a standardized automatic sphygmomanometer (TM-2655P or UA-853; A&D Company, Limited, Tokyo, Japan; or M3A; EDAN, Shenzhen, People's Republic of China). Multiple BP readings were taken at each visit, with an interval of at least 1 min between measurements. If the difference between the two readings exceeded 5 mmHg, an additional measurement would be performed. The BP measurement recorded in the patient chart was defined as the average of these readings.

BP Variability Measurements

The primary measure of SBP VVV was the SD of SBP levels, which was the most common measurement of variability. Additional measures of variability were also included as supplementary measures to increase the robustness of the analysis. These were as follows: *1*) coefficient of variation, *2*) variability independent of mean, *3*) residual SD, *4*) average real variability, and *5*) successive variation. The definitions of these indices of variability are shown in Supplementary Table 1 and have been commonly used to evaluate the relationship between variability in clinical parameters and clinical outcome events (16–18).

Baseline covariates included patients' sociodemographics, clinical parameters, disease characteristics, and treatment modalities. Sociodemographic information consisted of age, sex, smoking status, and alcohol consumption. Clinical parameters included BMI, waist-to-hip ratio, SBP, diastolic BP (DBP), lipid profile (LDL cholesterol and total cholesterol-to-HDL cholesterol ratio), triglyceride level, and urine albumin-to-creatinine ratio (ACR). Disease characteristics comprised self-reported duration of diabetes, family history of diabetes, and the presence of the comorbidities hypertension and chronic kidney disease (CKD). Patients with hypertension were identified by an ICPC-2 code of K86 or K87, whereas patients with CKD were defined as those with an estimated glomerular filtration rate of $<$60 mL/min/1.73 m^2. Treatment modalities included the baseline usage of antihypertensive drugs (e.g., ACE inhibitor [ACEI] or angiotensin receptor blocker [ARB], β-blocker, calcium channel blocker [CCB], diuretic and others [e.g., α-blockers, central-acting antihypertensive agents, vasodilators]), oral antidiabetic drugs, insulin-lowering agents, and lipid-lowering agents. All laboratory assays were performed in laboratories accredited by the College of American Pathologists, the Hong Kong Accreditation Service, or the National Association of Testing Authorities, Australia.

Data Analysis

A multiple imputation method was used to handle the missing data, except for BP (19). This method aims at increasing the power of the analysis and producing more statistically reliable and applicable models within clinical practice (20). Patients with incomplete data were also taken into account to minimize unnecessary biases (19). In this study, all missing data were imputed five times using the chained equation method. The same analysis was conducted for each of the five imputed data sets, and these results were combined based on combination rules of Rubin (21).

SBP variability was defined as the SD of the SBP. All patients were categorized into 1 of 10 of the following groups based their SBP variability: *1*) SD $<$5 mmHg, *2*) SD $\geq$5 and $<$7.5 mmHg, *3*) SD $\geq$7.5 and $<$10 mmHg, *4*) SD $\geq$10 and $<$12.5 mmHg, *5*) SD $\geq$12.5 and $<$15 mmHg, *6*) SD $\geq$15 and $<$17.5 mmHg, *7*) SD $\geq$17.5 and $<$20 mmHg, *8*) SD $\geq$20 and $<$22.5 mmHg, *9*) SD $\geq$22.5 and $<$25 mmHg, and *10*) SD $\geq$25 mmHg. Descriptive statistics were used to display the baseline covariates of each group after multiple imputation. Univariate linear and logistic regressions were used to test differences in the characteristics between groups. The incidence rate of CVD, all-cause mortality, and the composite of CVD and all-cause mortality were calculated based on an exact 95% CI with a Poisson distribution. Multivariable Cox proportional hazards regressions were conducted to evaluate the incidence of outcome events for each group. Three different models were established to investigate the association between the VVV of SBP and each of the outcome events. The first model was adjusted by all baseline covariates to investigate whether the variability in SBP was clinically significant, given that our earlier study and other literature had shown a curvilinear relationship between mean SBP level and CVD and all-cause mortality (22). The second model was established by modifying the first one with further adjustment to the mean and square of mean SBP values. The third model was modified based on the second model with the additional adjustment to the difference in SBP between baseline and the last record. This was done in order to address the observation that BP tends to decline with age, and this model adjusts for the effect of the trend over time (13). The plot of the scaled Schoenfeld residuals against time for the covariates was performed to check the proportional hazards assumption. A variance inflation factor was used to check for the presence of multicollinearity. Data analysis showed that all models fulfilled proportional hazards assumption and that no multicollinearity existed. The restricted cubic splines with three knots in Cox models were conducted to evaluate the nonlinear relationship between the VVV of SBP and the outcomes (23). In order to minimize the potential bias due to multiple imputation, the high degree of severity of the disease at baseline, and the number of SBP measurements, four sensitivity analyses were conducted. First, the analysis was repeated without using multiple imputation. Second, patients with a follow-up period $<$1 year after their 24-month visit were excluded. Third, patients with at least two SBP measurements were included. Fourth, patients who were missing one of eight SBP measurements after baseline were excluded. Subgroup analyses stratified by age ($<$65 and $\geq$65 years), sex, duration of diabetes ($<$1 year and $\geq$1 years), the presence of CKD, controlled BP (mean SBP $<$130 mmHg and DBP $<$80 mmHg), and uncontrolled BP (mean SBP $\geq$130 mmHg or DBP $\geq$80 mmHg, respectively), the change of BP ($\leq$10, within 10, $\geq$10 mmHg), and the type and number of types of antihypertensive drugs (without antihypertensive drug, one to two types, and three or more types) at baseline were performed using the SD of SBP and other indicators of the VVV of SBP as a continuous variable in order to confirm the effect of the VVV of SBP on the outcomes.

All significance tests were two tailed, and those with a *P* value $<$0.05 were

Table 1—Characteristics of patients overall and by SBP variability (SD) after multiple imputation

		Patients grouped by SBP variability (SD)										
	All patients total (*N* = 124,105)	SD of SBP Group 1 (<5 mmHg) (*N* = 2,954)	SD of SBP Group 2 (≥5 and <7.5 mmHg) (*N* = 15,766)	SD of SBP Group 3 (≥7.5 and <10 mmHg) (*N* = 29,052)	SD of SBP Group 4 (≥10 and <12.5 mmHg) (*N* = 29,646)	SD of SBP Group 5 (≥12.5 and <15 mmHg) (*N* = 20,794)	SD of SBP Group 6 (≥15 and <17.5 mmHg) (*N* = 12,020)	SD of SBP Group 7 (≥17.5 and <20 mmHg) (*N* = 6,751)	SD of SBP Group 8 (≥20 and <22.5 mmHg) (*N* = 3,493)	SD of SBP Group 9 (≥22.5 and <25 mmHg) (*N* = 1,807)	SD of SBP Group 10 (≥25 mmHg) (*N* = 1,822)	*P* value
Sociodemographics at baseline												
Sex												<0.001*
Female	55.6%	50.5%	51.9%	53.8%	55.4%	57.1%	58.4%	58.7%	61.3%	62.2%	63.0%	
Male	44.4%	49.5%	48.1%	46.2%	44.6%	42.9%	41.6%	41.3%	38.7%	37.8%	37.0%	
Age, years	63.19 ± 11.26	57.52 ± 10.94	59.40 ± 10.87	61.28 ± 11.00	63.01 ± 10.90	64.65 ± 10.92	66.29 ± 10.83	67.34 ± 10.88	68.28 ± 10.88	69.00 ± 10.69	70.50 ± 10.88	<0.001*
Smoking status												<0.001*
Never smoked	81.0%	81.5%	80.9%	80.7%	81.1%	81.0%	81.1%	81.2%	81.4%	81.6%	82.1%	
Ever smoked	19.0%	18.5%	19.1%	19.3%	18.9%	19.0%	18.9%	18.8%	18.6%	18.4%	17.9%	
Drinking habit												0.926
Nondrinker	97.0%	97.3%	97.2%	97.0%	97.0%	97.1%	97.0%	96.9%	97.2%	96.8%	97.3%	
Current drinker	3.0%	2.7%	2.8%	3.0%	3.0%	2.9%	3.0%	3.1%	2.8%	3.2%	2.7%	
Clinical parameters at baseline												
BMI, kg/m^2	25.45 ± 3.88	25.19 ± 3.80	25.43 ± 3.87	25.48 ± 3.87	25.51 ± 3.87	25.47 ± 3.91	25.45 ± 3.97	25.41 ± 3.92	25.33 ± 4.00	25.25 ± 3.98	25.23 ± 4.54	<0.001*
Waist-to-hip ratio	0.93 ± 0.20	0.92 ± 0.20	0.93 ± 0.18	0.93 ± 0.21	0.93 ± 0.17	0.94 ± 0.22	0.94 ± 0.18	0.94 ± 0.12	0.95 ± 0.33	0.94 ± 0.17	0.94 ± 0.07	<0.001*
HbA_{1c}, %	7.38 ± 1.38	7.39 ± 1.44	7.40 ± 1.39	7.40 ± 1.39	7.38 ± 1.36	7.36 ± 1.36	7.34 ± 1.37	7.35 ± 1.41	7.31 ± 1.40	7.36 ± 1.41	7.32 ± 1.54	<0.001*
HbA_{1c}, mmol/mol	57.11 ± 15.12	57.21 ± 15.71	57.38 ± 15.25	57.37 ± 15.17	57.20 ± 14.83	56.91 ± 14.89	56.72 ± 14.94	56.86 ± 15.43	56.36 ± 15.29	56.97 ± 15.42	56.48 ± 16.89	<0.001*
SBP, mmHg	135.05 ± 17.45	127.03 ± 14.12	129.97 ± 14.12	132.46 ± 14.28	134.27 ± 15.31	136.50 ± 17.18	138.59 ± 19.27	141.88 ± 21.89	144.27 ± 24.01	146.78 ± 25.87	151.37 ± 31.32	<0.001*
DBP, mmHg	75.16 ± 10.26	74.63 ± 8.93	75.15 ± 9.17	75.26 ± 9.49	74.93 ± 9.87	74.89 ± 10.48	75.02 ± 11.04	75.72 ± 11.89	76.23 ± 12.69	76.39 ± 13.12	76.96 ± 14.96	<0.001*
LDL-C, mmol/L	3.10 ± 0.85	3.04 ± 0.83	3.10 ± 0.82	3.10 ± 0.84	3.09 ± 0.84	3.10 ± 0.84	3.11 ± 0.87	3.09 ± 0.88	3.12 ± 0.89	3.10 ± 0.87	3.10 ± 0.91	0.020*
TC/HDL-C ratio	4.33 ± 1.29	4.25 ± 1.29	4.31 ± 1.23	4.32 ± 1.28	4.32 ± 1.29	4.34 ± 1.28	4.35 ± 1.31	4.39 ± 1.43	4.39 ± 1.26	4.35 ± 1.26	4.41 ± 1.31	<0.001*
Triglyceride, mmol/L	1.67 ± 1.13	1.63 ± 1.18	1.64 ± 1.11	1.66 ± 1.15	1.67 ± 1.13	1.68 ± 1.13	1.68 ± 1.09	1.72 ± 1.21	1.71 ± 1.08	1.68 ± 1.00	1.74 ± 1.12	<0.001*
Urine ACR	7.89 ± 38.46	4.74 ± 25.17	4.67 ± 22.31	5.88 ± 27.96	7.01 ± 41.13	8.57 ± 36.42	10.87 ± 45.58	12.68 ± 47.59	14.64 ± 60.94	15.70 ± 49.65	21.18 ± 74.21	<0.001*
Disease characteristics at baseline												
Duration of diabetes, years	6.24 ± 6.48	5.34 ± 5.49	5.74 ± 6.56	5.91 ± 6.22	6.23 ± 6.62	6.51 ± 6.51	6.67 ± 6.90	6.84 ± 7.00	6.84 ± 7.27	7.10 ± 7.50	7.27 ± 7.33	<0.001*
Family history of diabetes	42.5%	49.6%	47.9%	45.4%	42.9%	40.9%	36.8%	36.6%	35.0%	34.1%	29.4%	<0.001*
Treated hypertension	69.0%	45.6%	54.8%	61.9%	68.6%	74.9%	79.6%	85.0%	87.9%	90.1%	91.8%	<0.001*
CKD	13.0%	6.0%	7.3%	9.4%	11.7%	15.0%	17.8%	21.7%	23.8%	24.2%	31.5%	<0.001*
Treatment modalities at baseline												
Antihypertensive drugs used												
ACEI or ARB	29.8%	18.7%	21.9%	25.9%	29.2%	33.2%	35.7%	37.8%	40.6%	41.7%	45.8%	<0.001*
β-Blocker	26.9%	17.0%	20.8%	22.6%	26.0%	28.7%	32.1%	36.9%	39.2%	42.4%	48.5%	<0.001*
CCB	35.6%	21.2%	25.7%	29.9%	34.9%	39.8%	43.7%	47.8%	49.5%	51.1%	54.6%	<0.001*
Diuretic	11.7%	8.9%	11.0%	11.6%	11.9%	11.8%	12.1%	12.2%	12.7%	11.8%	12.3%	<0.001*
Other antihypentensive drugs	9.7%	4.6%	6.2%	7.4%	9.0%	10.7%	13.0%	15.1%	15.9%	18.6%	19.5%	<0.001*
Oral antidiabetic drugs used	79.3%	80.1%	79.0%	79.3%	79.3%	79.2%	79.4%	80.3%	78.8%	81.5%	78.6%	0.168
Insulin used	0.6%	0.3%	0.6%	0.5%	0.6%	0.8%	0.6%	0.7%	0.7%	0.6%	1.3%	<0.001*
Lipid-lowering agents used	5.4%	5.2%	5.1%	5.3%	5.4%	5.8%	5.5%	5.7%	5.7%	5.2%	5.3%	0.25
SBP and variability of SBP during follow-up												
Number of SBP measurements	8.41 ± 0.93	8.04 ± 1.19	8.35 ± 0.98	8.44 ± 0.91	8.46 ± 0.88	8.46 ± 0.89	8.41 ± 0.93	8.38 ± 0.94	8.34 ± 1.01	8.27 ± 1.02	8.18 ± 1.12	<0.001*
Mean SBP	135.28 ± 12.02	127.19 ± 13.60	130.39 ± 12.66	133.20 ± 11.54	135.07 ± 10.92	136.96 ± 10.82	138.61 ± 11.18	140.38 ± 11.42	142.16 ± 11.81	143.69 ± 12.18	146.07 ± 12.74	<0.001*
Change SBP	−1.95 ± 19.20	−0.04 ± 5.98	−0.23 ± 9.35	−0.25 ± 12.89	−0.95 ± 16.48	−2.25 ± 20.37	−3.72 ± 24.30	−6.35 ± 28.35	−7.46 ± 32.38	−9.81 ± 35.52	−13.25 ± 43.80	<0.001*

Continued on p. 274

Table 1—Continued

		Patients grouped by SBP variability (SD)										
	All patients	SD of SBP Group 1 (<5 mmHg)	SD of SBP Group 2 (≥5 and <7.5 mmHg)	SD of SBP Group 3 (≥7.5 and <10 mmHg)	SD of SBP Group 4 (≥10 and <12.5 mmHg)	SD of SBP Group 5 (≥12.5 and <15 mmHg)	SD of SBP Group 6 (≥15 and <17.5 mmHg)	SD of SBP Group 7 (≥17.5 and <20 mmHg)	SD of SBP Group 8 (≥20 and <22.5 mmHg)	SD of SBP Group 9 (≥22.5 and <25 mmHg)	SD of SBP Group 10 (≥25 mmHg)	
	total (*N* = 124,105)	(*N* = 2,954)	(*N* = 15,766)	(*N* = 29,052)	(*N* = 29,646)	(*N* = 20,794)	(*N* = 12,020)	(*N* = 6,751)	(*N* = 3,493)	(*N* = 1,807)	(*N* = 1,822)	*P* value
Measurements of variability of SBP												
SD	11.88 ± 4.62	4.17 ± 0.69	6.47 ± 0.69	8.80 ± 0.72	11.21 ± 0.71	13.65 ± 0.72	16.13 ± 0.72	18.61 ± 0.72	21.11 ± 0.71	23.63 ± 0.73	28.56 ± 3.50	<0.001*
CV	11.86 ± 4.36	4.59 ± 0.98	6.88 ± 1.10	9.08 ± 1.24	11.34 ± 1.37	13.56 ± 1.53	15.78 ± 1.75	17.92 ± 1.99	20.02 ± 2.23	22.10 ± 2.45	26.11 ± 3.85	<0.001*
VIM	8.76 ± 3.23	3.31 ± 0.65	5.01 ± 0.70	6.65 ± 0.77	8.35 ± 0.85	10.03 ± 0.94	11.71 ± 1.05	13.34 ± 1.19	14.95 ± 1.33	16.56 ± 1.46	19.66 ± 2.64	<0.001*
RSD	12.92 ± 5.43	4.79 ± 1.24	7.38 ± 1.65	9.90 ± 2.13	12.42 ± 2.65	14.86 ± 3.26	17.18 ± 3.87	19.41 ± 4.57	21.66 ± 5.20	23.83 ± 5.87	28.40 ± 8.12	<0.001*
ARV	18.03 ± 7.31	16.19 ± 9.88	15.17 ± 8.03	15.27 ± 6.28	16.54 ± 5.41	18.59 ± 5.19	21.21 ± 5.43	23.98 ± 5.48	26.97 ± 5.85	29.91 ± 6.36	35.65 ± 8.06	<0.001*
SV	15.66 ± 6.47	5.76 ± 1.36	8.86 ± 1.77	11.91 ± 2.26	14.97 ± 2.81	17.97 ± 3.45	20.91 ± 4.12	23.76 ± 4.92	26.65 ± 5.56	29.61 ± 6.22	35.51 ± 9.07	<0.001*

All parameters are expressed as the mean ± SD or percentages, as appropriate. ARV, average real variability; CV, coefficient of variation; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; Other antihypentensive drugs, acarbose, glucagon-like peptide 1 agonist, meglitinides; RSD, residual SD; SV, successive variation; TC, total cholesterol; VIM, variation independent of mean. *Significant difference ($P < 0.05$) by univariate linear or logistic regression.

considered to be statistically significant. All data analyses were conducted using STATA version 13.0.

RESULTS

A total of 148,713 Chinese primary care patients with T2DM who were ≥18 years old and had at least one previous SBP value recorded between 1 August 2008 and 31 December 2009 were identified. After excluding 11,098 patients with a clinical diagnosis of CVD, 250 patients without follow-up, 10,242 patients with fewer than five SBP measurements, and 3,018 patients with CVD or mortality in the first 24 months after baseline, the remaining 124,105 patients with T2DM were included in the data analysis. The data completion rate for each baseline covariate was >90%.

Table 1 summarizes the baseline characteristics of patients in each SBP variability group after multiple imputation. Overall, the mean age was 63.2 years (SD 11.3), females comprised 55.6% of the group, and patients' mean duration of T2DM was 6.2 years (SD 6.5). The average number of SBP readings recorded in the medical chart was 8.4 (SD 0.9), the mean SBP was 135.3 mmHg (SD 12.0), and the SD of SBP was 11.9 mmHg (SD 4.6). There were significant differences in all baseline characteristics except for drinking habit, and the usage of oral hypoglycemic drugs and lipid-lowering agents between groups. Groups of patients with higher SBP variability were older, female, had a relatively longer duration of diabetes but were without a family history of diabetes, had hypertension and CKD, were taking antihypertensive drugs, and had a higher urine ACR.

Table 2 demonstrates the number and incidence rates for CVD events and all-cause mortality by SBP variability. After a median follow-up period of 38.5–39.5 months, the incidence rates for CVD events, all-cause mortality, and the composite of both events from the lowest variability (SD <5 mmHg) to the highest variability (SD ≥25 mmHg) were from 9.5 to 48.9, from 7.1 to 44.6, and from 15.0 to 81.3 per 1,000 person-years, respectively. Table 2 also shows the results of multivariable Cox proportional hazard regressions. After adjusting for all baseline characteristics, the mean SBP, and the difference in SBP between baseline and the last record, the

Table 2—Incidence rate and adjusted hazard ratios for CVDs and all-cause mortality among subjects

	SD of SBP Group 1 (<5 mmHg) (*N* = 2,954)	SD of SBP Group 2 (≥5 and <7.5 mmHg) (*N* = 15,766)	SD of SBP Group 3 (≥7.5 and <10 mmHg) (*N* = 29,052)	SD of SBP Group 4 (≥10 and <12.5 mmHg) (*N* = 29,646)	SD of SBP Group 5 (≥12.5 and <15 mmHg) (*N* = 20,794)	SD of SBP Group 6 (≥15 and <17.5 mmHg) (*N* = 12,020)	SD of SBP Group 7 (≥17.5 <20 mmHg) (*N* = 6,751)	SD of SBP Group 8 (≥20 and <22.5 mmHg) (*N* = 3,493)	SD of SBP Group 9 (≥22.5 and <25 mmHg) (*N* = 1,807)	SD of SBP Group 10 (≥ 25 mmHg) (*N* = 1,822)
CVD										
Cumulative cases with event	87	561	1,289	1,594	1,366	911	595	349	189	248
Cumulative incidence rate	2.9%	3.6%	4.4%	5.4%	6.6%	7.6%	8.8%	10.0%	10.5%	13.6%
Person-years	109,737	585,915	1,073,173	1,089,110	752,823	432,458	239,495	121,382	62,861	60,847
Median follow-up, months	39.5	39.5	39.5	39.5	39.5	39.5	39.5	39.5	39.5	38.5
Incidence rate (95% CI)†	9.5 (7.7–11.7)	11.5 (10.6–12.5)	14.4 (13.6–15.2)	17.6 (16.7–18.4)	21.8 (20.6–23.0)	25.3 (23.7–27.0)	29.8 (27.5–32.3)	34.5 (31.1–38.3)	36.1 (31.3–41.6)	48.9 (43.2–55.4)
Adjusted HR (95% CI)										
Model 1	Reference	1.06 (0.84–1.33)	1.17 (0.94–1.45)	1.26* (1.01–1.56)	1.40* (1.13–1.74)	1.45* (1.16–1.81)	1.57* (1.25–1.97)	1.74* (1.38–2.21)	1.75* (1.36–2.26)	2.11* (1.65–2.70)
Model 2	Reference	1.06 (0.84–1.32)	1.16 (0.93–1.44)	1.25* (1.00–1.55)	1.38* (1.11–1.72)	1.42* (1.14–1.78)	1.53* (1.22–1.92)	1.68* (1.33–2.13)	1.68* (1.30–2.17)	1.99* (1.55–2.55)
Model 3	Reference	1.06 (0.84–1.32)	1.16 (0.94–1.44)	1.25* (1.00–1.55)	1.38* (1.11–1.72)	1.43* (1.14–1.78)	1.53* (1.22–1.92)	1.68* (1.33–2.14)	1.68* (1.30–2.18)	2.00* (1.56–2.56)
All-cause mortality										
Cumulative cases with event, *n*	66	342	846	1,097	1,043	710	486	318	173	239
Cumulative incidence rate	2.2%	2.2%	2.9%	3.7%	5.0%	5.9%	7.2%	9.1%	9.6%	13.1%
Person-years	110,873	594,096	1,091,760	1,110,887	772,159	444,392	247,959	126,202	65,527	64,324
Medium follow-up, months	39.5	39.5	39.5	39.5	39.5	39.5	39.5	39.5	39.5	39.5
Incidence rate (95% CI)†	7.1 (5.6–9.1)	6.9 (6.2–7.7)	9.3 (8.7–9.9)	11.8 (11.2–12.6)	16.2 (15.3–17.2)	19.2 (17.8–20.6)	23.5 (21.5–25.7)	30.2 (27.1–33.8)	31.7 (27.3–36.8)	44.6 (39.3–50.6)
Adjusted HR (95% CI)										
Model 1	Reference	0.84 (0.64–1.09)	0.96 (0.75–1.24)	1.05 (0.82–1.35)	1.24 (0.97–1.60)	1.28 (0.99–1.65)	1.42* (1.10–1.84)	1.72* (1.31–2.24)	1.70* (1.28–2.27)	2.06* (1.56–2.71)
Model 2	Reference	0.85 (0.65–1.11)	1.00 (0.77–1.28)	1.10 (0.85–1.41)	1.31* (1.02–1.68)	1.34* (1.04–1.73)	1.49* (1.15–1.94)	1.80* (1.38–2.36)	1.78* (1.34–2.38)	2.14* (1.62–2.83)
Model 3	Reference	0.85 (0.65–1.11)	1.00 (0.78–1.28)	1.10 (0.85–1.41)	1.30* (1.01–1.67)	1.34* (1.04–1.73)	1.48* (1.14–1.92)	1.79* (1.37–2.34)	1.77* (1.33–2.36)	2.11* (1.60–2.79)
CVD or all-cause mortality										
Cumulative cases with event, *n*	137	827	1,942	2,409	2,145	1,440	932	573	310	412
Cumulative incidence rate	4.6%	5.2%	6.7%	8.1%	10.3%	12.0%	13.8%	16.4%	17.2%	22.6%
Person-years	109,737	585,915	1,073,173	1,089,110	752,823	432,458	239,495	121,382	62,861	60,847
Medium follow-up, months	39.5	39.5	39.5	39.5	39.5	39.5	39.5	39.5	39.5	38.5
Incidence rate (95% CI)†	15.0 (12.7–17.7)	16.9 (15.8–18.1)	21.7 (20.8–22.7)	26.5 (25.5–27.6)	34.2 (32.8–35.7)	40.0 (37.9–42.1)	46.7 (43.8–49.8)	56.6 (52.2–61.5)	59.2 (52.9–66.1)	81.3 (73.8–89.5)
Adjusted HR (95% CI)										
Model 1	Reference	0.99 (0.83–1.19)	1.12 (0.94–1.33)	1.20* (1.01–1.42)	1.38* (1.16–1.64)	1.43* (1.20–1.71)	1.54* (1.28–1.84)	1.79* (1.48–2.16)	1.79* (1.46–2.19)	2.17* (1.78–2.63)
Model 2	Reference	1.00 (0.84–1.20)	1.13 (0.95–1.35)	1.22* (1.02–1.45)	1.40* (1.18–1.67)	1.45* (1.22–1.73)	1.55* (1.29–1.86)	1.79* (1.49–2.17)	1.78* (1.45–2.18)	2.14* (1.76–2.60)
Model 3	Reference	1.00 (0.84–1.20)	1.13 (0.95–1.35)	1.22* (1.02–1.45)	1.40* (1.18–1.66)	1.45* (1.22–1.73)	1.55* (1.29–1.85)	1.79* (1.48–2.16)	1.78* (1.45–2.18)	2.13* (1.75–2.59)

HR, hazard ratio; Model 1, HRs were adjusted for age, sex, smoking status, drinking habit, BMI, waist-to-hip ratio, glycated hemoglobin A_{1c}, DBP, LDL cholesterol, total cholesterol-to-HDL cholesterol ratio, triglyceride, urine ACR, self-reported duration of diabetes, family history of diabetes, treated hypertension, the presence of CKD, the usage of antihypertensive drugs (ACEI or ARB, β-blocker, CCB, diuretic and other [acarbose, glucagon-like peptide 1 agonist, meglitinides]), oral antidiabetic drugs, insulin and lipid-lowering agents at baseline; Model 2, HRs were adjusted for variables in Model 1 and additional adjustment for mean SBP; Model 3, HRs were adjusted for variables in Model 2, and there was additional adjustment for the difference in SBP between baseline and the last record. *Significant difference ($P < 0.05$) by multivariable Cox proportional hazards regression; †Incidence rate (cases/1,000 person-years) with 95% CI based on Poisson distribution.

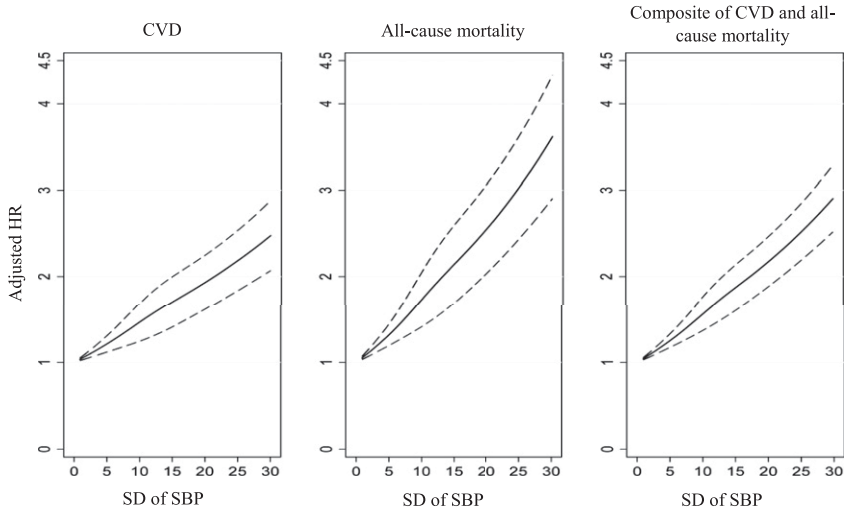

Figure 2—Adjusted hazard ratios (HRs) of SD of SBP associated with the incidence of CVD, all-cause mortality, and the composite of CVD and mortality by the restricted cubic splines in multivariable Cox proportional hazards regression. HRs were adjusted for age, sex, smoking status, drinking habit, BMI, waist-to-hip ratio, glycated hemoglobin A_{1c}, DBP, LDL cholesterol, total cholesterol-to-HDL cholesterol ratio, triglyceride, urine ACR, self-reported duration of diabetes, family history of diabetes, diagnosed hypertension, the presence of CKD, the usage of antihypertensive drugs (ACEI or ARB, β-blocker, CCB, diuretic and other [acarbose, glucagon-like peptide 1 agonist, meglitinides]), oral antidiabetic drugs, insulin and lipid-lowering agents at baseline, and mean SBP and the difference in SBP between baseline and last record. Solid lines and dashed lines indicate the adjusted HRs and its 95% CIs, respectively.

results showed a direct linear association between SBP variability (defined as SD) and the CVD/all-cause mortality risk. Patients with low SBP variability (SD $<$5 mmHg) had the lowest risk of CVD and mortality, whereas patients with high SBP variability (SD $\geq$10 mmHg) had significantly higher risks. Figure 2 demonstrated that no nonlinear association between the variability of SBP and clinical outcomes existed by restricted cubic spline in Cox models. These suggested that there was a direct linear association between the VVV of SBP and the risks of CVD and all-cause mortality, and that the VVV of SBP was an independent predictor of CVD and all-cause mortality, irrespective of the SBP levels. In the sensitivity analysis, with a complete case cohort or after excluding patients with a follow-up period of $<$1 year after their 24-month visit or with an incomplete number of SBP measurements, similar results were obtained, supporting the main analysis. Figure 3 and Supplementary Table 2 show that the SD of SBP and all other measures of the VVV of SBP were associated with a significant elevation in the risk of CVD and all-cause mortality among all selected subgroups. For every 1 SD increase in the SD of SBP, the risks of CVD, all-cause mortality, and composite of both events increased by 2.9% (95% CI 2.4–3.4%), 4.0% (95% CI 3.5–4.6%), and 3.4% (95% CI 3.0–3.8%), respectively.

CONCLUSIONS

This population-based cohort study was the first to evaluate the association between the VVV of SBP and CVD/all-cause mortality risk among Chinese primary care patients with T2DM. Our findings demonstrated a direct linear relationship between all measurements of the VVV of SBP and CVD/all-cause mortality risk, indicating that greater SBP variability increased the risks for adverse outcomes. Our results also identified that the optimal SD of SBP target should be $<$10 mmHg in order to reduce the incidence of CVD and all-cause mortality. The impact of the VVV of SBP on the risk of the development of CVD events and all-cause mortality was essentially unchanged by age group, sex, duration of diabetes, the presence of CKD, type and number of antihypertension drugs used after adjustments of mean SBP, and the difference in SBP between baseline and the last follow-up record. This suggests that SBP variability may provide additional valuable information as a potential predictor for the incidence of CVD events and mortality in the population with diabetes, irrespective of the absolute mean SBP readings, and is consistent with the findings of earlier studies in other populations with diabetes (10–12).

Of interest, the magnitude of the effect of the variability of SBP on the risk of CVD and all-cause mortality among patients in primary care in our study was lower, compared with previous studies. A post hoc analysis of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial (10) showed that every 1 SD increase in the SD of SBP was associated with an 18% (95% CI 7–30%) and 29% (95% CI 17–43%) increase in the risks of CVD and all-cause mortality, respectively. The two studies conducted in a hospital setting in Japan and Taiwan (11,12) showed that the risks of CVD and all-cause mortality increased by 40% (95% CI 10–79%) and 4.8% (95% CI 0.5–9.2%), respectively, for every 1 SD increase in the SD of SBP. This supported our hypothesis that the health care setting, in which patients under primary care are less likely to have severe disease, influences the impact of the variability of SBP on the adverse events. It may be that patients with chronic diseases that are relatively less complicated or less severe, and are therefore managed in primary care, may be less susceptible to the impact of SBP variability on adverse outcomes.

The pattern of association between the variability of SBP and outcomes may also differ between Chinese and non-Chinese populations. A study in the U.K. (24) revealed that patients with diabetes who were of Chinese ethnicity have a lower CVD risk than those of Caucasian, Indian, and African-Caribbean descent. However, the observed direct linear relationship may be subject to the definition of the variability of BP, as evidenced by the extensive debate on the calculation method for determining the variability of BP (5,10,25,26). This current study was based on 6 different measures of variability, all of which produced consistent results across all VVV estimates, concluding that the optimal SBP variability is SD $<$10 mmHg. Therefore, the variability of BP can be considered as a potential indicator of good-quality care in a population with diabetes. More investigations are warranted to develop a

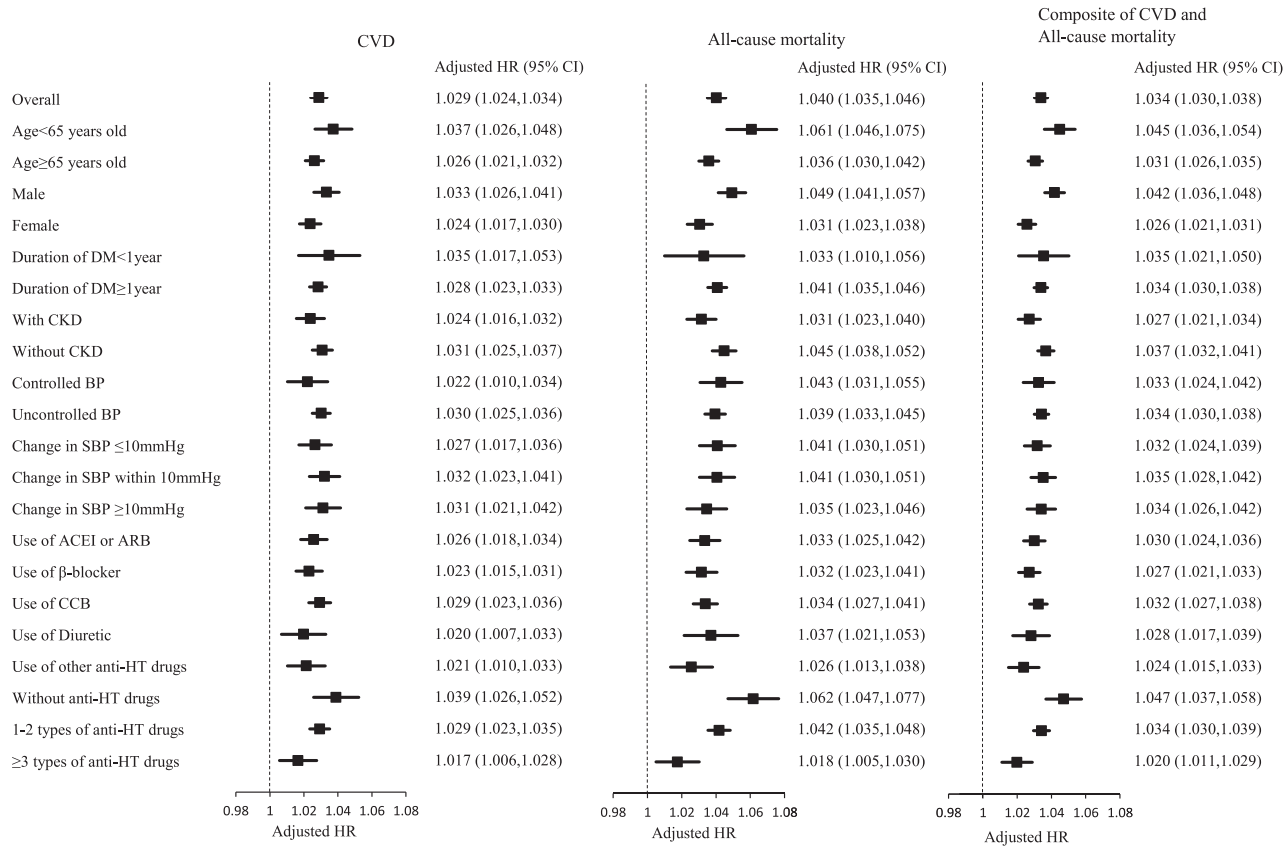

Figure 3—Adjusted hazard ratios (HRs) of SD of SBP associated with the incidence of CVDS, all-cause mortality, and the composite of CVD and mortality in selected subgroups by multivariable Cox proportional hazards regression. HRs were adjusted for age, sex, smoking status, drinking habit, BMI, waist-to-hip ratio, glycated hemoglobin A_{1c}, DBP, LDL cholesterol, total cholesterol-to-HDL cholesterol ratio, triglyceride, urine ACR, self-reported duration of diabetes, family history of diabetes, diagnosed hypertension, the presence of CKD, the usage of antihypertensive (anti-HT) drugs (ACEI or ARB, β-blocker, CCB, diuretic and other [acarbose, glucagon-like peptide 1 agonist, meglitinides]), oral antidiabetic drugs, insulin and lipid-lowering agents at baseline, and mean SBP and the difference in SBP between baseline and last record. Adjusted HR indicated the risk estimates per 1 SD increase in SD of SBP.

standardized definition of the variability of BP and to determine a reasonable therapeutic target, before variability can serve as a clinically useful predictor of outcomes and a practical management tool.

There are several possible explanations for the positive associations between BP variability and the incidence of CVD and all-cause mortality. From a pathophysiological perspective, increased BP variability is associated with endothelial dysfunction and inflammation (27,28), which accelerates atherosclerosis, resulting in increased risk of CVD and mortality. Arterial stiffness, coronary artery calcification, and left ventricular diastolic dysfunction have also been reported (29–31) as possible mechanisms underlying the relationship between BP variability and negative clinical outcomes. On the contrary, other research suggests that the impact of the variability of BP may be attributed to low patient adherence to antihypertension medications, suboptimal BP control, the class of antihypertensive drug, and change in antihypertensive medications (32–34). However, the results of our subgroup analysis were consistent with those of several studies (35,36) showing that risk estimates for different BP control levels and the usage of different types of antihypertensive drugs were similar. Although information about antihypertensive medication adherence and a change in antihypertensive drugs after baseline were unavailable in this current study, the subgroup analysis demonstrated that risk estimates for different numbers of antihypertensive drugs remained significant, and recent research (10,35) also reported that these factors cannot explain the links between the variability of SBP and the incidence of CVD and all-cause mortality. Further studies are required to better understand the mechanistic relationship.

Some risk factors associated with the high variability of BP were identified in our study. These observations were similar to those in a previous study (10), which also found that groups of patients with high SBP variability were older; female; had higher SBP, DBP, and urine ACR levels; had hypertension and CKD; and used antihypertensive drugs, compared with those in groups with low SBP variability. Some studies (10,27) also showed that hyperglycemia and increased waist circumference were associated with higher variability of SBP. Apart from the clinical factors, psychological and behavioral factors such as emotional state, mental stress, exercise, salt intake, and amount of rest also play an important role in BP variability (37). These observations may help in the early identification of patients with high BP variability, who are at higher risk of the development of CVD and early death. More attention should be given to patients with

diabetes who have these risk factors to minimize the negative impact of high SBP variability. Additional research is needed to confirm the type and extent of the risk factors associated with high BP variability.

Strengths and Limitations of This Study

This study has several strengths. First, our subjects consisted of a large population of Chinese primary care patients with T2DM, which is highly representative of the Hong Kong Chinese population with diabetes managed in the primary care setting. Second, all the clinical characteristics and laboratory data were retrieved from the HA computerized administrative database, which was more reliable and accurate. Last, multiple imputations were adopted to replace the missing data in order to obtain less biased results.

There were several limitations to this study. First, our retrospective cohort study design can only conclude association but not causation. To confirm the association and to determine causation, further study using a randomized clinical trial or a prospective cohort study design is required. Second, the incidence of CVD relied on the clinical diagnosis of comorbidity predefined by ICPC-2 and ICD-9-CM codes and recorded in the HA computerized administrative database, which may be subject to misclassification bias. There were no prior studies conducted to audit the accuracy and completeness of ICPC-2 and ICD-9-CM diagnosis coding in this database. However, previous studies (38,39) showed an almost perfect level of data completeness regarding drug prescription (99.98%) in this database, and clinicians are required to provide adequate coding for each episode of care in routine clinical practice in the HA. Third, potential confounding factors related to lifestyle, like exercise and diet, were unavailable in the current study. However, physical and clinical parameters such as BMI, hemoglobin A_{1c} level, and lipid profile were available that can reflect lifestyle habits and the severity of the disease. Last, further longitudinal studies with a longer follow-up period are important to confirm the relationship between SBP variability and CVD/mortality risk.

To conclude, in this population-based cohort study, SBP variability was associated with a higher risk of CVD and all-cause mortality among Chinese primary care patients with T2DM. The positive linear associations were significant in all subgroups with different age groups, sex, duration of diabetes, the presence of CKD, BP levels and trend, and class and number of antihypertensive drugs. The variability of BP may be useful as a potential predictor for the development of CVD and all-cause mortality in the population with diabetes. The positive association between the VVV of SBP and the cardiovascular events and mortality supported the importance of having steady BP control (i.e., less fluctuation) as well as having stable BP control (i.e., achieving the optimal target BP). In addition to monitoring BP targets for their patients with diabetes, clinicians should also remain vigilant about the visit-to-visit fluctuation of BP.

Future work is recommended to investigate the effect of the variability of DBP, standardize the definition of the variability of BP, compare the effect of three clinical indicators (mean SBP, changes in SBP, and SD of SBP), and determine a therapeutic target for SBP variability in order to provide management of BP in patients with diabetes.

Acknowledgments. The authors thank the Department of Primary and Community Services and the Department of Statistics and the Workforce Planning Department at the head office of the Hong Kong HA for their contributions. Also, the authors thank Anca Chan and Karina Chan of the Department of Family Medicine and Primary Care of the University of Hong Kong for providing administrative support.

Funding. The current study has been supported by the Hong Kong HA (Reference no. 8011014157) and by the Health and Health Services Research Fund, Food and Health Bureau, HKSAR Commissioned Research on Enhanced Primary Care Study (Reference no. EPC-HKU-2).

The funders had no role in conducting and submitting this work.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. 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., D.Y.T.F., and J.Y.C. contributed to the interpretation of the results and wrote the manuscript. C.L.K.L. contributed to the study design and acquisition of the data. All authors reviewed and edited the manuscript. E.Y.F.W. 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.

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