Association of Blood Pressure and Risk of Cardiovascular and Chronic Kidney Disease in Hong Kong Hypertensive Patients

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Abstract—The association between systolic blood pressure, cardiovascular disease, and chronic kidney disease remains unclear. This study aimed to evaluate these relationships. A population-based cohort of 267,469 adult patients with hypertension but without diabetes mellitus, cardiovascular disease, or chronic kidney disease were identified. Using baseline and repeated systolic blood pressure (average of all systolic blood pressure measurements in the past 5 years), the risks of cardiovascular disease and chronic kidney disease associated with systolic blood pressure were evaluated by Cox regression. Subgroup analyses were conducted by baseline characteristics. Over 1.4 million person-years follow-up (median 6 years), 29,500 cardiovascular disease and 30,993 chronic kidney disease events diagnosed. A J-shape association between baseline systolic blood pressure and risks of cardiovascular disease and chronic kidney disease was observed. Using repeated systolic blood pressure, a positive and log-linear association was identified. There was no evidence of a threshold down to the repeated systolic blood pressure of 120 mm Hg. Increases of 10 mm Hg of repeated systolic blood pressure was associated with a 16% (hazard ratio, 1.15; [95% CI, 1.13–1.16]), 11% (1.11; [1.08–1.13]), and 22% (1.22; [1.20–1.24]) higher risk of composite of cardiovascular disease and chronic kidney disease, individual cardiovascular disease and chronic kidney disease, respectively. Strength of the associations was similar across different subpopulations. This study showed that hypertensive patients with elevated repeated systolic blood pressure are at increased risk of cardiovascular disease or chronic kidney disease, irrespective of different characteristics. Very low single measurement of systolic blood pressure may be a potential indicator for poor health, but there seems to be no threshold for usual systolic blood pressure.

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Key Words: blood pressure • cardiovascular diseases • cohort studies • diabetes mellitus • mortality

Over the past 3 decades, the rate of elevated systolic blood pressure (SBP) has risen substantially, with corresponding increases in disability-adjusted life-years and premature mortality associated with elevated SBP.1 International guidelines recommend a target SBP as one of the primary goals for hypertension management.2–5 SBP has been linked to not only cardiovascular disease (CVD) but also chronic kidney disease (CKD).6,7 Current literature shows that patients with CKD have similar mortality risks and medical costs compared with those with CVD.8,9 Nevertheless, the effect of SBP on both CVD and CKD remains controversial. Epidemiological studies have observed different patterns of association between SBP and CVD/CKD such as linear or J-shaped relationships.10–25 More recently, the benefits of using repeated time points (multiple measurements in the past) instead of the single time point (baseline) of BP has been advocated as a better method for CVD risk prediction.26–29 It is well known that SBP can be variable over time and that errors in measurement occur easily. Previous studies have often relied on single measurements,13,14,16–20 but the use of repeated measurements could potentially minimize these biases and take into account the rate of change over time, helping to attain a more reliable usual SBP. Current guidelines also focus on repeated BP measurements to determine the risk of CVD attributable to BP and the benefits of antihypertensive treatments.30,31 Given that global prevalence of hypertension in adults is around 40%,32 it is likely that there will be some heterogeneity in the association between SBP and
CVD/CKD. A few studies have revealed that patient’s characteristics, such as the age in younger and older patients, can be an influencing factor.

The aim of this study was to investigate the association between SBP and incidence of CVD and CKD in patients with hypertension using both the baseline and repeated SBP, and to explore the variations in the associations among patients of different characteristics, including sex, age, smoking status, body mass index (BMI), LDL-C (low-density lipoprotein cholesterol), fasting glucose, kidney function, severity of comorbidities, and treatment modalities. Understanding these relationships can assist researchers and clinicians in setting evidence-based SBP targets and recommendations for potential interventions.

Methods

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

Study Design

This was a population-based retrospective cohort study that included all patients aged ≥18, who were clinically diagnosed with hypertension in public clinics with primary care setting between October 1, 2011, and March 31, 2012, but with no prior history of diabetes mellitus, CVD, or CKD before baseline. Clinical diagnosis of hypertension was identified using the International Classification of Primary Care-2 code of K86/K87, that the cutoff value of SBP ≥140 mm Hg or diastolic BP ≥90 mm Hg is considered hypertensive BP. All baseline and outcome measures were extracted from the electronic health database in the computerized Clinical Management System of the Hong Kong Hospital Authority. The Hospital Authority is the statutory body governing all 42 public-sector hospitals, 47 specialist outpatient clinics, and 73 primary care in Hong Kong. Because of the large subsidized public health system managing in Hong Kong, the Hospital Authority provides care for at least 90% of the diagnosed local patients with chronic diseases. About the antihypertensive drug treatments, the clinicians follow the Hong Kong Care-2 code of K86/K87, that the cutoff value of SBP ≥140 mm Hg or diastolic BP ≥90 mm Hg is considered hypertensive BP. All baseline and outcome measures were extracted from the electronic health database in the computerized Clinical Management System of the Hong Kong Hospital Authority. The Hospital Authority is the statutory body governing all 42 public-sector hospitals, 47 specialist outpatient clinics, and 73 primary care in Hong Kong. Because of the large subsidized public health system managing in Hong Kong, the Hospital Authority provides care for at least 90% of the diagnosed local patients with chronic diseases. About the antihypertensive drug treatments, the clinicians follow the Hong Kong Reference Framework for Hypertension Care for Adults in Primary Care Settings, which is established by the Department of Health, the Government of the Hong Kong Special Administrative Region. Generally, the physicians will tailor choice of drugs to the individual patient, after considering several factors, including health conditions, possibilities of interactions with drugs used, drug response in the patients, etc. Clinical information, including patient demographics and clinical data, such as diagnosis, prescription use, laboratory test results, accident and emergency visits, hospitalization, outpatient clinics visits, is directly recorded into the Clinical Management System by clinicians and other health care professionals. This population-wide electronic health database has been validated with high coding accuracy and adopted for conducting several high quality population-based epidemiological studies. A high coding accuracy was found in the diagnosis for myocardial infarction and stroke with positive predictive values of 85.4% (95% CI, 78.8%–90.6%) and 91.1% (83.2%–96.1%), respectively. The date of the first SBP record between October 1, 2011, and March 31, 2012, was defined as the baseline. Each patient was followed-up until the date of diagnosis or the censoring date of September 30, 2017, whichever occurred first.

The study was approved by the Institutional Review Boards in Hong Kong. Consent from individual subjects was deemed not needed as all information was extracted anonymously from the computerized administrative system of the Hospital Authority. This study complies with the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001.

Outcome Measures

The primary outcome was the incidence of CKD or subtypes of CVD, including coronary heart disease, all stroke, and heart failure. The secondary outcomes were overall CVD, CKD, each subtype of CVD, and CVD-related mortality. CKD was defined if patients with estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m². The details of each outcome were defined and identified using the relevant clinical parameters or diagnostic codes, International Classification of Primary Care-2 or the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) as described in Table S1 in the online-only Data Supplement.

Baseline and Repeated SBP

There is a standardized guideline for measuring and documenting SBP readings in patients with hypertension during each consultation in all clinics. SBP was measured multiple times at every visit, with an interval of at least 1 minute, after 5 minutes without any distractions in a seated position, using a standardized automated sphygmomanometer (UA-853, Tokyo, Japan; or EDAN M3A, Shenzhen, China). Measurements were conducted by a nurse or trained patient care assistant. If the difference between the 2 readings exceeded 5 mm Hg, an additional measurement was performed. The record of each SBP measurement was regarded as the average of these 3 readings.

Baseline SBP was defined as the SBP record at baseline. Repeated SBP was defined as the average of all SBP measurements in the past 5 years on or before baseline. This approach has been described in the previous study for the accuracy improvement of CVD risk prediction. The average number of SBP readings recorded was 16.6 for the calculation of repeated SBP.

Covariates

Baseline covariates consisted of sex, age, smoking status, BMI, diastolic BP, LDL-C, fasting glucose, eGFR, the Charlson comorbidity index, the usages of antihypertensive drug (eg, ACE [angiotensin-converting enzyme] inhibitor or ARB [angiotensin receptor blocker], β-blocker, calcium channel blocker, diuretics, and others [hydralazine, methyldopa, and prazosin]), and lipid-lowering agents. The eGFR for baseline and outcome measure was calculated based on the creatinine level from blood test according to the abbreviated Modification of Diet in Renal Disease Study formula recalibrated for Chinese (eGFR in mL/min per 1.73 m² =186×(serum creatinine in μmol/L)×0.011−1.154×(age)−0.203×(0.742 if female)×1.233), where 1.233 is the adjusted coefficient for Chinese. 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). In this study, each missing value was imputed 5 times by the chained equation method adjusted with the outcomes. For each of the 5 imputed data sets, the same analysis was performed with the 5 sets of results combined based on Rubin rules. All the subjects were categorized into one of the 7 groups according to the baseline and repeated SBP (<115, 115–124, 125–134, 135–144, 145–154, 155–164, and ≥165 mm Hg). Descriptive statistics were adopted to summarize the patient’s characteristics after multiple imputation for each subgroup of SBP.

The incidence rate was estimated by an exact 95% CI based on a Poisson distribution. The association of SBP with the incidence of CVD or CKD was examined using multivariable Cox proportional hazards regressions, adjusted by all baseline clinical parameters or diagnostic codes, International Classification of Primary Care-2 or the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) as described in Table S1 in the online-only Data Supplement.
absolute risk, it does not require the selection of a baseline group for display of SE. The details of this method were described in literature and has been widely adopted in several epidemiological studies. Moreover, the nonlinear association between SBP groups and the outcomes was assessed by the restricted cubic splines with 3 knots in Cox models. Regression dilution ratio based on Rosner regression method using SBP readings about 1 year after baseline was applied to all analysis to adjust the random errors in the measurement of SBP. The proportional hazards assumption was inspected by examining plots of the scaled Schoenfeld residuals against time for the covariates. Presence of multicollinearity was also checked by assessing the variance inflation factor. Analysis of the data disclosed that all models fulfilled the proportional hazards assumption and no multicollinearity existed. Repeated analysis using 1-, 2-, 3-, and 4-year instead of the 5-year interval for repeated SBP were performed. Four sensitivity analyses were conducted to include SD of repeated SBP accounting for the variability of SBP; exclude the patients with <1 year after baseline; apply complete data analysis rather than multiple imputation analysis, use the third quartile of SBP measurements in a distribution of SBP in an individual as repeated SBP. To explore variations in associations among patients of different characteristics, subgroup analysis based on the repeated SBP was performed on the incidence of each outcome by stratifying sex (male; female), age (<65, 65–79, and ≥80 years), smoking status (nonsmoker and smoker), BMI (<25 and ≥25 kg/m²), LDL-C (<3 and ≥3 mmol/L), fasting glucose (<6.1 and ≥6.1 mmol/L), eGFR (<60–89 and ≥90 mL/min per 1.73 m²), Charlson index (<4 and ≥4), and the usages of different antihypertensive drugs at baseline.

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

Results

After excluding 56,316 patients with a prior diagnosis of CVD or CKD, and 396 patients with no follow-up after baseline, a total of 267,469 primary care patients aged ≥18 with hypertension but without diabetes mellitus, CVD, or CKD. Table S2 demonstrates over 89% of data completion rates for most baseline covariates. The baseline characteristics for each group by baseline and repeated SBP after multiple imputation are summarized in Table 1. Overall, 41.5% were male and the mean age was 64.3 years (SD=11.7). The average of baseline and repeated mean SBP were 136.3 mmHg (SD=16.6) and 137.6 mmHg (SD=11.7), respectively.

Over 1.4 million person-years of follow-up (median 6 years), there were 51,153 incident CVD or CKD events comprising 29,500 CVD and 30,993 CKD events diagnosed, equating to 37.9 per 1000 person-years for the incidence rate of the composite of CVD and CKD (21.1 and 22.0 per 1000 person-years for the incidence rate of CVD and CKD, respectively). The number and incidence rates of CVD and CKD for each SBP group are displayed in Table 2. A J-shape trend of incidence rates was observed in the baseline SBP groups but a linear increasing trend in the repeated SBP groups. A nearly identical trend was observed for the adjusted association between baseline/repeated SBP groups and the event outcomes by Cox regression adjusting for all baseline characteristics (Figure 1). The J-shape association between baseline SBP and incidence for each outcome but the log-linear association between repeated SBP and outcomes were preserved (Figure 1). Similar patterns were demonstrated for coronary heart disease, stroke, heart failure, and CVD mortality (Figure S1). Repeated analyses using 1-, 2-, 3-, and 4-year instead of the 5-year intervals for repeated measurements of SBP by Cox regression with and without restricted cubic spline also obtained log-linear patterns (Figures S2 and S3). The results from 4 sensitivity analyses by including SD of repeated SBP, excluding patients with a follow-up period ≤1 year after baseline and without complete data, taking upper quartiles of SBP measurements as repeated SBP, demonstrated similar patterns to the main analysis.

The forest plot in Figure 2 summed up the adjusted HR for the marginal effects of SBP on each outcome in the main and subgroup analysis. As a whole, each 10 mmHg incremental increase in SBP was associated with 16% (HR, 1.15; [95% CI, 1.13–1.16]), 11% (HR, 1.11; [95% CI, 1.08–1.13]), 22% (HR, 1.22; [95% CI, 1.20–1.24]) higher risk of composite of CVD and CKD, individual CVD and CKD, respectively. A similar effect of SBP on each outcome was observed when stratified by sex, age groups, smoking status, diastolic BP, BMI, LDL-C, fasting glucose, eGFR, Charlson index, and different antihypertensive drugs at baseline.

Discussion

This population-based cohort study is the first to evaluate the association between SBP and incident CVD and CKD among patients with hypertension using baseline and repeated SBP. The key finding in the current study is the identification of J-shape association between baseline SBP and the risk of CVD and CKD but the positive and log-linear association for repeated SBP, with no evidence of threshold down to 120 mmHg. The strength of associations of repeated SBP was similar between different subpopulations. Our findings also indicated that the use of multiple measurements instead of the single measurement of SBP should be applied to obtain the more reliable etiological association, and also highlighted that low baseline SBP may be a signal for poor health condition, but there is no threshold for repeated SBP.

Previous analyses have been conflicted on the effect of SBP on various clinical event outcomes in the particular CVD. The J- or U-shape association between SBP and the risk of CVD in various populations was identified in the literature. Compared with earlier studies, this current study had much larger numbers of patients and events. This helps to provide more significant power to evaluate the outcomes for patients, particularly those with lower SBP. Meanwhile, patients in most of the previous studies were with coronary heart disease, diabetes mellitus, CKD, or other clinical conditions and relied on the single measurement of SBP at baseline. This may increase the likelihood of reverse causality for the explanation of J-phenomenon that the worse outcomes in patients with lower SBP in their studies were attributable to the effect of concomitant diseases leading to SBP fall and adverse outcomes at the same time. Two analyses on 7 randomized clinical trials from the individual
Table 1. Baseline Characteristics Among Subjects, Stratified by Baseline and Repeated SBP

| Baseline Characteristic | Baseline SBP | Repeated SBP |
|-------------------------|--------------|--------------|
|                         | <115 mm Hg (N=21126) | 115–124 mm Hg (N=43144) | 125–134 mm Hg (N=65369) | 135–144 mm Hg (N=63216) | 145–154 mm Hg (N=41176) | 155–164 mm Hg (N=20591) | ≥165 mm Hg (N=13847) |
| Male                    | 38.0%        | 37.0%        | 41.7%        | 42.6%        | 42.6%        | 42.6%        | 42.6%        |
| Age, y                  | 64.2±11.5    | 63.6±11.4    | 63.7±11.5    | 64.2±11.7    | 65.0±11.9    | 65.6±12.2    | 65.5±12.5    |
| Current smoker          | 7.5%         | 7.3%         | 7.4%         | 7.7%         | 8.2%         | 8.3%         | 10.1%        |
| Baseline SBP, mm Hg     | 108.8±4.8    | 120.0±2.8    | 129.7±2.8    | 139.2±2.8    | 149.1±2.8    | 158.6±2.7    | 176.0±11.0   |
| Baseline DBP, mm Hg     | 66.5±7.1     | 71.7±7.7     | 75.4±8.5     | 78.4±9.3     | 81.1±10.2    | 83.8±11.0    | 89.9±13.1    |
| Fasting glucose, mmol/L | 5.3±0.7      | 5.3±0.7      | 5.3±0.7      | 5.3±0.6      | 5.4±0.7      | 5.4±0.7      | 5.4±0.9      |
| BMI, kg/m²              | 24.9±4.4     | 25.2±4.6     | 25.5±4.2     | 25.6±4.3     | 25.7±4.4     | 25.6±4.1     | 25.6±4.4     |
| LDL-C, mmol/L           | 3.2±0.8      | 3.2±0.9      | 3.2±0.9      | 3.3±0.8      | 3.3±0.8      | 3.3±0.9      | 3.3±1.0      |
| eGFR, mL/min per 1.73 m²| 103.6±23.2   | 104.3±23.5   | 104.5±23.8   | 104.4±23.6   | 104.5±38.6   | 104.0±39.0   | 103.7±28.2   |
| eGFR, ≥60–89 mL/min per 1.73 m² | 28.0%   | 26.2%        | 26.2%        | 26.5%        | 27.3%        | 27.8%        | 27.8%        |
| eGFR, ≥90 mL/min per 1.73 m² | 72.0% | 73.8%        | 73.8%        | 73.5%        | 72.7%        | 72.2%        | 72.2%        |
| Charlson index          | 2.9±1.2      | 2.9±1.2      | 2.9±1.2      | 2.9±1.2      | 3.0±1.2      | 3.0±1.2      | 3.0±1.2      |
| Use of ACE inhibitor/ARB| 16.5%        | 26.2%        | 17.2%        | 17.9%        | 19.0%        | 19.7%        | 20.0%        |
| Use of β-blocker        | 41.3%        | 39.0%        | 37.7%        | 36.4%        | 35.2%        | 34.4%        | 31.8%        |
| Use of CCB              | 66.8%        | 67.6%        | 68.0%        | 68.0%        | 68.3%        | 68.3%        | 72.4%        |
| Use of diuretic         | 13.9%        | 14.4%        | 13.4%        | 12.6%        | 11.5%        | 10.5%        | 9.3%         |
| Use of other antihypertensive drugs | 9.0% | 8.5%         | 8.9%         | 9.9%         | 10.8%        | 11.0%        | 10.6%        |
| Lipid-lowering agents used | 7.2% | 7.5%         | 7.7%         | 7.7%         | 7.6%         | 6.8%         | 6.1%         |

All parameters are expressed in either percentage or mean±SD. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.
### Table 2. Number, Incidence Rate, and Hazard Ratio of CVD and CKD Stratified by Baseline and Repeated SBP

| Outcome Event | Baseline SBP | Repeated SBP |
|---------------|--------------|--------------|
|               | <115 mm Hg (N=21 126) | 115–124 mm Hg (N=43 144) | 125–134 mm Hg (N=65 369) | 135–144 mm Hg (N=63 216) | 145–154 mm Hg (N=40 176) | 155–164 mm Hg (N=20 591) | ≥165 mm Hg (N=13 847) |
|               | CVD or CKD | | | | | | |
| Cumulative cases with event | 4175 | 7642 | 11 625 | 11 708 | 8255 | 4507 | 3241 |
| Cumulative incidence rate | 19.8% | 17.7% | 17.8% | 18.5% | 20.5% | 21.9% | 23.4% |
| Person-years | 105 914 | 220 783 | 334 779 | 321 678 | 200 416 | 100 829 | 65 739 |
| Median follow-up (mo) | 70.5 | 70.5 | 70.5 | 70.5 | 70.5 | 69.5 | 69.5 |
| Incidence rate* (95% CI) | 39.4 (38.2–40.6) | 34.6 (33.8–35.4) | 34.7 (34.1–35.4) | 36.4 (35.7–37.1) | 41.2 (40.3–42.1) | 44.7 (43.4–46.0) | 49.3 (47.6–51.0) |
| Hazard ratio† (95% CI) | 1.00 (0.92–1.08) | 0.86 (0.81–0.91) | 0.87 (0.83–0.91) | 0.93 (0.89–0.97) | 1.16 (1.10–1.23) | 1.35 (1.25–1.45) | 1.91 (1.75–2.09) |
| CVD | | | | | | | |
| Cumulative cases with event | 2451 | 4441 | 6809 | 6763 | 4680 | 2526 | 1830 |
| Cumulative incidence rate | 11.6% | 10.3% | 10.4% | 10.7% | 11.6% | 12.3% | 13.2% |
| Person-years | 109 812 | 228 062 | 345 795 | 333 075 | 208 596 | 105 503 | 69 248 |
| Median follow-up (mo) | 69.5 | 69.5 | 69.5 | 69.5 | 70.5 | 70.5 | 69.5 |
| Incidence rate* (95% CI) | 22.3 (21.5–23.2) | 19.5 (18.9–20.1) | 19.7 (19.2–20.2) | 20.3 (19.8–20.8) | 22.4 (21.8–23.1) | 23.9 (23.0–24.9) | 26.4 (25.2–27.7) |
| Hazard ratio† (95% CI) | 1.00 (0.90–1.11) | 0.82 (0.76–0.88) | 0.84 (0.79–0.89) | 0.85 (0.81–0.90) | 1.02 (0.95–1.09) | 1.11 (1.01–1.22) | 1.54 (1.37–1.73) |
| CKD | | | | | | | |
| Cumulative cases with event | 2521 | 4486 | 6821 | 7027 | 5165 | 2864 | 2109 |
| Cumulative incidence rate | 11.9% | 10.4% | 10.4% | 11.1% | 12.9% | 13.9% | 15.2% |
| Person-years | 110 747 | 229 908 | 348 832 | 335 111 | 209 397 | 105 758 | 69 216 |
| Median follow-up (mo) | 70.5 | 70.5 | 70.5 | 70.5 | 70.5 | 69.5 | 69.5 |
| Incidence rate* (95% CI) | 22.8 (21.9–23.7) | 19.5 (18.9–20.1) | 19.6 (19.1–20.1) | 21.0 (20.5–21.5) | 24.7 (24.0–25.3) | 27.1 (26.1–28.1) | 30.5 (29.2–31.8) |
| Hazard ratio† (95% CI) | 1.00 (0.90–1.11) | 0.86 (0.80–0.93) | 0.90 (0.85–0.95) | 1.00 (0.95–1.06) | 1.35 (1.27–1.45) | 1.61 (1.47–1.76) | 2.49 (2.22–2.78) |

(Continued)
data analysis of antihypertensive intervention database also
concluded poor health conditions but not antihypertensive
therapy caused low BP and an increased risk for both cardi-
vascular and noncardiovascular mortality. Our analyses
identified a J-shape association between baseline SBP and
adverse outcomes but a log-linear relationship with repeated
SBP. Therefore, lower SBP may be a potential indicator for
poorer health status.

For this study, clinical data were extracted from elec-
tronic health records. Although SBP records were typically
recorded during regular doctor follow-up consultations, rely-
ng on SBP reading at baseline may not be fully representa-
tive of the actual repeated SBP and could potentially result in
reverse causality. A recent study evaluating serial SBP read-
ings before mortality found a greater reduction in SBP in the
2 years preceding death. A chief strength of this study was
the use of multiple measurements to calculate repeated SBP.
By increasing time period of BP measurements, as shown in
Figures S2 and S3, can help to minimize the potential for
bias, such as in the case of measurement error or short-term
fluctuations in SBP. By using more measurements, a more
representative usual SBP can be obtained. This is the likely
reason why a log-linear instead of a J-shape association was
observed after replacing baseline SBP with repeated SBP.
This study helps to add new evidence to support the adoption
of multiple measurements in observational cohort studies to
reduce the probability of reverse causality and to obtain less
biased results.

The current study identified similar the pattern and
strength of associations of repeated SBP between different
patients’ characteristics. Because of a huge number of hy-
pertensive patients, a few current guidelines including the
Eighth Joint National Committee Report suggested patient
center BP target for patients with hypertension. For instance,
a looser treatment SBP target (<150 mm Hg) is applied for
elderly patients. However, the findings from 2 randomized
controlled trials showed the CVD risk reduction for lower-
ning SBP to 140 mm Hg among elderly. Similar to previous
cohort studies and meta-analyses, our results revealed a log-
linear association between repeated SBP and risk of CVD and
CKD, irrespective of sex or age. Although the magni-
date of the effect of SBP on the risk of CVD and CKD was
adjusted for regression dilution bias, the results were lower
than those observed in general population studies, including
the China Kadoorie Biobank (36% and 40% greater risk of
CVD and CKD, respectively, per each 10 mm Hg higher SBP),
the Prospective Studies Collaboration (≈40% and ≈30%
greater risk of mortality from stroke and ischemic heart di-
ase, respectively, per each 10 mm Hg higher SBP), and the
Asia Pacific Cohorts Studies Collaboration (≈40% and ≈30%
greater risk of stroke and ischemic heart disease, respectively,
per each 10 mmHg higher SBP). This is likely because of
sampling from different population. This current study sam-
ples patients with diagnosed hypertension, as opposed to the
general population, hence direct comparisons may be not ap-
licable. Nevertheless, the J-phenomenon has been postulated

| Outcome Event | Baseline SBP |
|---------------|--------------|
|               | <115 mm Hg (N=21 126) | 115–124 mm Hg (N=43 144) | 125–134 mm Hg (N=65 369) | 135–144 mm Hg (N=63 216) | 145–154 mm Hg (N=40 176) | 155–164 mm Hg (N=20 591) | ≥165 mm Hg (N=13 847) |
| Cumulative Incidence Rate | 9.0% | 9.8% | 10.5% | 11.5% | 11.9% | 11.5% | 11.0% |
| Person-years | 16 294 | 157 503 | 431 874 | 485 069 | 217 875 | 61 608 | 29 869 |
| Median follow-up (mo) | 69.5 | 69.5 | 69.5 | 69.5 | 70.5 | 70.5 | 69.5 |
| Incidence rate* (95% CI) | 17.1 (15.2–19.2) | 18.6 (17.9–19.3) | 19.9 (19.5–20.3) | 21.9 (21.5–22.3) | 23.1 (22.5–23.8) | 22.6 (21.5–23.8) | 21.9 (20.3–23.6) |
| Hazard ratio† (95% CI) | 1.00 (0.82–1.22) | 1.09 (1.03–1.17) | 1.14 (1.10–1.19) | 1.27 (1.23–1.31) | 1.35 (1.28–1.41) | 1.49 (1.36–1.63) | 1.89 (1.66–2.15) |

CVD indicates cardiovascular disease; CKD, chronic kidney disease; and SBP, systolic blood pressure.
*Incidence rate (cases/1000 person-years) with 95% CI based on Poisson distribution.
†Hazard ratios were obtained by multivariable Cox proportional hazards regression adjusted with age, sex, smoking status, body mass index, diastolic blood pressure, low-density lipoprotein cholesterol, estimated glomerular filtration rate, the usages of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, β-blocker, calcium channel blocker, diuretic, other antihypertensive drugs lipid-lowering agent, and Charlson index at baseline, and adjusted with regression dilution ratio. CIs are displayed as floating absolute risks.
to be related to antihypertensive pharmacological therapy. Compared with the low proportion of patients treated with hypertension in previous studies, nearly all of our patients were prescribed with antihypertensive drugs, and thus, their SBP level is likely the result of antihypertensive pharmacological interventions.
This study has several strengths. We sampled patients without diabetes mellitus, CVD, and CKD at baseline to examine the incidence of adverse events. The sample size and number of incident events were large allowing greater power for analyses; use of repeated measurements for the calculation of repeated SBP to reduce the likelihood for error and fluctuation bias; use of various methods to minimize the probability of reverse causality, including the use of compromising multiple imputations, regression dilution ratio, restricted cubic splines, and incorporation of a comprehensive set of confounding variables.

There were also several limitations should raise more cautions during the interpretation of results. This was a retrospective cohort study and can only evaluate associations rather than identify causation. Some patient information that could be relevant were not able to be extracted from the electronic health records, such as hospital and clinics site, drug adherence and compliance, lifestyle behaviors, and diet. As our findings were equivocal, further longitudinal studies with longer follow-up periods are needed to reevaluate how low BP and incidence of CVD and CKD are related.

Perspectives
This large population-based cohort study revealed a positive and log-linear association between SBP and risks of CVD and CKD events, with no evidence of any threshold down to 120 mm Hg. A 10 mm Hg elevation in SBP was associated with a 16% higher risk of CVD and CKD. The strength of the association was similar, irrespective of sex, age, smoking status, BMI, LDL-C, fasting glucose, kidney function, the severity of comorbidities, and treatment modalities. Very low single measurement of SBP may be a signal for poor health condition, but there seems to be no threshold for repeated SBP. We recommend the use of multiple measurements instead of the single SBP measurement to obtain more reliable BP measurements when conducting epidemiological cohort studies.

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E.Y.F. Wan, E.Y.T. Yu, and C.L.K. Lam contributed to the study design and acquisition of data, researched the data, contributed to the statistical analysis, and interpretation of the results, and wrote the article. W.Y. Chin contributed to the interpretation of the results and wrote the article. D.Y.T. Fong and E.P.H. Choi contributed to the interpretation of the results. All authors reviewed and edited the article. E.Y.F. Wan is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. We wish to acknowledge the contributions of the Risk Assessment Management Program (RAMP) for program team at the Hospital Authority head office, and the Chiefs of Service and RAMP program coordinators in each cluster, and the Statistics and Workforce Planning Department at the Hong Kong Hospital Authority.

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Disclosures
None.
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### Novelty and Significance

**What Is New?**

- This large population-based cohort study revealed a positive and log-linear association between systolic blood pressure and risks of cardiovascular diseases and chronic kidney disease events, with no evidence of any threshold down to 120 mm Hg. A 10 mm Hg elevation in systolic blood pressure was associated with a 16% higher risk of cardiovascular diseases and chronic kidney disease. The strength of the association was similar, irrespective of sex, age, smoking status, body mass index, LDL-C (low-density lipoprotein cholesterol), fasting glucose, kidney function, the severity of comorbidities, and treatment modalities.

**What Is Relevant?**

- Our findings contribute to improve the on the effect of systolic blood pressure on cardiovascular diseases and chronic kidney disease for Chinese hypertensive patients.

**Summary**

Very low single measurement of systolic blood pressure may be a signal for poor health condition, but there seems to be no threshold for repeated systolic blood pressure. We recommend the use of multiple measurements instead of the single systolic blood pressure measurement to obtain more reliable blood pressure measurements when conducting epidemiological cohort studies.