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ORIGINAL RESEARCH

Blood Pressure and Cardiovascular Disease in Older Patients With Diabetes: Retrospective Cohort Study

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BACKGROUND: Blood pressure (BP) targets in elderly patients with diabetes remain unclear. We evaluated the association between BP and cardiovascular disease in elderly patients with diabetes without cardiovascular disease or heart failure.

METHODS AND RESULTS: We performed a retrospective cohort study of 225 563 elderly (aged ≥65 years) patients with diabetes without cardiovascular disease or heart failure from 2009 to 2017 using the National Health Information Database. We divided the participants by systolic BP (SBP) and diastolic BP. Primary composite outcomes were stroke, myocardial infarction, heart failure, and all-cause death analyzed by Cox proportional hazards regression analysis adjusted for baseline covariates. During a median follow-up of 7.76 years, the incidence rate of primary composite outcomes was 26.62 per 1000 person-years. In multivariable Cox proportional hazard modeling, the risk of the primary outcome had a U-curved association with SBP/diastolic blood pressure with a nadir between 120 and 129 mm Hg/65 and 69 mm Hg, respectively. Hypertension medication was associated with lower risk of primary composite outcomes in SBP ≥140 mm Hg (*P* for interaction for SBP <0.001) and diastolic blood pressure ≥90 mm Hg (*P* for interaction for diastolic blood pressure=0.018). In participants aged ≥80 years, SBP ≥160 mm Hg was only a marginally higher risk for primary composite outcomes (hazard ratio=1.11; 95% CI, 0.98–1.24).

CONCLUSIONS: In this large sample of older Korean patients with diabetes, cardiovascular events were more common in people with resting SBP or diastolic BP ≥140 or 95 mm Hg, respectively, and also more common in people with resting SBP or diastolic BP <120 or 65 mm Hg, respectively.

Key Words: diastolic blood pressure ■ hypertension ■ myocardial infarction ■ stroke ■ systolic blood pressure

In patients with diabetes, hypertension is common (60%–85%)[1–3] and is a major risk factor for both macrovascular and microvascular complications.[4,5] There is considerable evidence of the benefits of blood pressure (BP) control in patients with diabetes with hypertension to reduce the major macrovascular and microvascular complications of diabetes, as well as reduce mortality.[6–8] A meta-analysis of 13 randomized controlled trials involving patients with diabetes or prediabetes showed that a reduction in systolic blood pressure (SBP) to 131 to 135 mm Hg reduced the risk of all-cause mortality by 13%, whereas more intensive SBP control (≤130 mm Hg) was only associated with a greater reduction in strokes.[9]

The global population aged ≥60 years has more than doubled since 1980. One-third of older people (aged >60 years) have diabetes. The association between elevated SBP and the risk of cardiovascular morbidity and mortality in the older population is also significantly positive.[10,11] Hence, BP control is also expected to offer

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CLINICAL PERSPECTIVE

What Is New?

- In this large sample of older Korean patients with diabetes, the risk of cardiovascular events had a U-curved association with systolic blood pressure/diastolic blood pressure with a nadir between 120 and 129 mm Hg/65 and 69 mm Hg, respectively.
- Hypertension medication was associated with lower risk of cardiovascular events in systolic blood pressure/diastolic blood pressure ≥140 mm Hg/ ≥90 mm Hg, respectively, and with higher risk in systolic blood pressure/diastolic blood pressure <110 mm Hg/<60 mm Hg, respectively.

What Are the Clinical Implications?

- This study finding supports the recent guideline that recommends initiating hypertension medication in elderly patients with diabetes and systolic blood pressure/diastolic blood pressure ≥140 mm Hg/≥90 mm Hg, respectively.
- Continuing antihypertensive therapy in elderly patients with diabetes and relative hypotension may increase cardiovascular events.

Nonstandard Abbreviations and Acronyms

CCI	Charlson Comorbidity Index
DBP	diastolic blood pressure
NHID	National Health Information Database
SBP	systolic blood pressure

benefits in older people and becomes increasingly important in the prevention of cardiovascular disease (CVD). However, little information is available on target BP levels in older patients with hypertension with type 2 diabetes, and there is some discrepancy in BP targets among guidelines.[12–15]

In this study, we evaluated the potential relationships between BP level, CVD events, and mortality in older patients with diabetes without CVD using a large-scale population data set from the National Health Information Database (NHID).

METHODS

Anonymized data and materials have been made publicly available through National Health Insurance Sharing Service and can be accessed at https://nhiss.nhis.or.kr/.

Study Database

Data used in our analysis were from the NHID, a public database on health care use and health screening that contains sociodemographic and mortality information for the entire population of South Korea. The NHID contains data for the years 2002 to 2017. The NHID, which is produced by the National Health Insurance Service, was launched in 2000 by integrating 375 insurance associations. The National Health Insurance Service provides, through the national health screening program, regular health checkups and cancer screenings biannually at no cost for all insured Koreans aged >40 years. The NHID provides longitudinal data for 97% of the Korean population, with linkage to the National Death Registry and the national health screening program.[16,17] This latter program was initiated in 2009 and includes a medical interview and postural examination, chest x-ray examination, blood test (including fasting plasma glucose and triglyceride levels), urine test, dental screening, and other tests. Approval for the study protocol was obtained from the institutional review board of Hanyang University Guri Hospital (GURI 2020-08-016). The need for informed consent was waived by the board.

Study Participants

This was a retrospective cohort study that included 249 903 individuals. From the NHID, 922 061 people with diabetes participated in the national health screening program in 2009. Among the 922 061 participants, 642 042 individuals aged <65 years, 12 250 patients with a history of stroke, 6843 patients with a history of myocardial infarction (MI), 24 340 patients with a history of heart failure (HF), and 11 023 individuals lacking complete data were excluded from our study. Therefore, the total number of eligible participants was 225 563. Participants were categorized into 8 groups by SBP and 9 groups by diastolic blood pressure (DBP).

Definitions of Diabetes and Study Outcomes (Cardiovascular Events and Death)

Patients with type 2 diabetes were identified from the insurance claims data as having at least 1 claim per year for the prescription of antidiabetic medication under *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnostic codes E11 to E14, or from national health screening program data as having fasting plasma glucose of ≥126 mg/dL. The primary outcome of the study was a composite of nonfatal stroke, nonfatal MI, nonfatal HF, and all-cause death. Secondary outcomes were newly diagnosed MI, stroke, HF, or all-cause death. Stroke was

defined as an *ICD-10* code I63 or I64 during hospitalization with claims for brain magnetic resonance imaging or brain computerized tomography. Nonfatal MI was defined as an *ICD-10* code I21 or I22 during hospitalization. Nonfatal HF was defined as an *ICD-10* code I50 during hospitalization. The study population was followed from baseline to the date of death, onset of a cardiovascular event, or until December 31, 2017, whichever came first.

Clinical and Laboratory Measurements

All participants completed a questionnaire on medical history, use of tobacco and alcohol, and exercise habits. Smoking habits were categorized as nonsmoker, ex-smoker, or current smoker. Alcohol consumption was classified as nondrinker, moderate drinker (<30 g per day), or heavy drinker (≥30 g per day). Regular exercise was defined as vigorous exercise 3 or more times per week or moderate exercise 5 or more times per week. Body mass index (BMI) was calculated as body weight (in kilograms) divided by height (in meters squared). BP was measured through a standard national health screening program protocol. All participants had rested for at least 5 minutes in a seated position before the first measurement. If SBP was >120 mm Hg or DBP was >80 mm Hg, remeasurement was performed after an interval of 2 minutes or more. BP was measured by the auscultation method using a stethoscope or using an oscilloscopic automatic sphygmomanometer in a quiet environment. The device was calibrated daily. A cuff with an appropriately sized bladder was used. The standard bladder for adults is 12 cm wide and 26 cm long. A bladder with a width of at least 40% of the circumference of the arm and a length of 80% to 100% of the circumference of the arm was used. Examinees were recommended to avoid smoking, alcohol, or caffeine before measurement. Blood samples were collected after overnight fasting. Plasma glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were measured. We calculated glomerular filtration rate using the 4-variable Modification of Diet in Renal Disease Study equation.[18] Baseline comorbidities were identified as dyslipidemia (*ICD-10* code E78 with lipid-lowering agents or serum total cholesterol ≥240 mg/dL), and chronic kidney disease (CKD) (estimated as a glomerular filtration rate <60 mL/min per 1.73 m^2). The Charlson Comorbidity Index (CCI) was used to estimate the comorbidity burden by reviewing the *ICD-10* codes. An individual was considered to have a comorbidity when the respective diagnostic codes were present >2 times within 1 year before the inclusion date.

Statistical Analysis

Baseline characteristics were analyzed using descriptive statistics. Categorical variables were described as frequency and percentage. Continuous variables were described as mean±SD for normally distributed data and as the geometric mean and 95% CI for data not normally distributed. We compared the baseline characteristics of 8 groups categorized by SBP and 9 groups categorized by DBP. Continuous variables were compared using 1-way ANOVA, whereas categorical variables were compared using the Mantel-Haenszel χ^2 test. The follow-up duration of each group was obtained. The incidence rates for stroke, MI, HF, and death were estimated for each group over the total follow-up period. Incidence curves were estimated using the Kaplan-Meier method, and the log-rank test was also conducted. All outcomes were analyzed by Cox proportional hazards regression analysis while controlling for baseline covariates. The proportional hazard assumption was assessed by visual inspection of the scaled Schoenfeld residuals plot and log-log survival plot. We deemed a 2-tailed *P* value <0.05 to be significant. Analyses were performed with SAS 9.4 (SAS Institute, Cary, NC) and R version 3.4.1 (The R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org).

RESULTS

Baseline Characteristics of Participants

The characteristics of the 8 SBP groups are described in Table 1. The group with higher SBP were older; more likely to be women, heavy drinkers, and hypertension medication users; had a higher BMI and fasting plasma glucose level; and had a higher prevalence of dyslipidemia and CKD. The group with higher SBP was less likely to comprise current smokers, regular exercisers, and insulin users. Similar patterns of baseline characteristics were noted in the 9 DBP groups (Table S1). Over half of the patients with SBP <120 mm Hg (55.6%) or DBP <65 mm Hg (59.6%) were prescribed hypertension medication.

Blood Pressure and Primary Composite Outcomes

There were 77 447 (34.3%) primary composite outcomes in the 7.76-year mean follow-up period (Table 2). The incidence rate of primary composite outcomes was 47.90 per 1000 person-years. In patients with SBP 120 to 129 mm Hg, the incidence rate of primary composite outcomes was 45.2 per 1000 person-years and lower than in the other SBP groups (Table 2 and Figure S1). In multivariable Cox proportional hazard models of the SBP reference group (SBP 120–129 mm Hg), the

Table 1. Baseline Demographic and Clinical Characteristics in SBP Groups

Characteristic	SBP, mm Hg								
	<100	100–110	110–120	120–130	130–140	140–150	150–160	>160	*P* value
No. of subjects	2228	9716	36 295	51 706	78 308	32 931	21 363	17 356	
Sex									<0.0001
Men	1109 (49.78)	4723 (48.61)	17 689 (48.74)	24 958 (48.27)	37 909 (48.41)	15 861 (48.16)	10 338 (48.39)	7975 (45.95)	
Women	1119 (50.22)	4993 (51.39)	18 606 (51.26)	26 748 (51.73)	40 399 (51.59)	17 070 (51.84)	11 025 (51.61)	9381 (54.05)	
Smoker									<0.0001
Non	1467 (65.84)	6574 (67.66)	25 105 (69.17)	36 446 (70.49)	55 937 (71.43)	23 549 (71.51)	15 505 (72.58)	12 911 (74.39)	
Ex	364 (16.34)	1548 (15.93)	5802 (15.99)	8499 (16.44)	12 650 (16.15)	5482 (16.65)	3468 (16.23)	2497 (14.39)	
Current	397 (17.82)	1594 (16.41)	5388 (14.85)	6761 (13.08)	9721 (12.41)	3900 (11.84)	2390 (11.19)	1948 (11.22)	
Alcohol consumption									<0.0001
Non	1786 (80.16)	7693 (79.18)	27 900 (76.87)	39 116 (75.65)	58 172 (74.29)	24 037 (72.99)	15 364 (71.92)	12 614 (72.68)	
Mild	364 (16.34)	1773 (18.25)	7142 (19.68)	10 664 (20.62)	16 786 (21.44)	7331 (22.26)	4859 (22.74)	3774 (21.74)	
Heavy	78 (3.5)	250 (2.57)	1253 (3.45)	1926 (3.72)	3350 (4.28)	1563 (4.75)	1140 (5.34)	968 (5.58)	
Regular exercise	815 (36.58)	3795 (39.06)	14 472 (39.87)	20 582 (39.81)	30 858 (39.41)	13 088 (39.74)	7965 (37.28)	6027 (34.73)	<0.0001
Dyslipidemia	879 (39.45)	4078 (41.97)	14 818 (40.83)	21 886 (42.33)	32 938 (42.06)	14 134 (42.92)	9119 (42.69)	7462 (42.99)	<0.0001
Chronic kidney disease	616 (27.65)	2328 (23.96)	8267 (22.78)	11 582 (22.4)	17 610 (22.49)	7557 (22.95)	4828 (22.6)	4243 (24.45)	<0.0001
Insulin	314 (18.62)	1315 (17.44)	4256 (15.4)	5620 (14.33)	8033 (13.7)	3345 (13.85)	2102 (13.87)	1779 (14.82)	<0.0001
No. of oral diabetes medications									<0.0001
0	47 (2.79)	183 (2.43)	577 (2.09)	744 (1.9)	1167 (1.99)	544 (2.25)	305 (2.01)	309 (2.57)	
1	498 (29.54)	2119 (28.1)	7958 (28.79)	11 739 (29.94)	17 903 (30.52)	7498 (31.05)	4675 (30.86)	3652 (30.43)	
2	644 (38.2)	3091 (40.99)	11 453 (41.44)	16 454 (41.96)	24 916 (42.48)	10 315 (42.72)	6603 (43.58)	5200 (43.33)	
3	403 (23.9)	1737 (23.04)	6195 (22.41)	8446 (21.54)	12 230 (20.85)	4800 (19.88)	2989 (19.73)	2412 (20.1)	
4	80 (4.74)	353 (4.68)	1295 (4.69)	1647 (4.2)	2196 (3.74)	889 (3.68)	531 (3.5)	391 (3.26)	
5	14 (0.83)	54 (0.72)	154 (0.56)	175 (0.45)	235 (0.4)	95 (0.39)	45 (0.3)	37 (0.31)	
6	0 (0)	3 (0.04)	6 (0.02)	9 (0.02)	9 (0.02)	4 (0.02)	2 (0.01)	1 (0.01)	
Hypertension medication	1130 (50.72)	5286 (54.41)	21 517 (59.28)	34 148 (66.04)	56 295 (71.89)	25 673 (77.96)	17 293 (80.95)	14 470 (83.37)	<0.0001
Mean±SD									
Age, y	71.15±5.08	70.88±4.79	71±4.81	71.02±4.78	71.14±4.77	71.19±4.83	71.27±4.83	71.59±5.01	<0.0001
BMI, kg/m^2	22.86±3.24	23.48±3.16	24.08±3.11	24.44±3.1	24.76±3.13	24.98±3.16	25.01±3.2	25±3.33	<0.0001
FBG, mg/dL	134.56±44.71	134.7±43.31	135.05±42.49	134.03±40.86	134.83±40.48	135.98±40.39	137.02±40.99	139.31±42.65	<0.0001
SBP, mm Hg	92.5±4.33	103±3.32	113.52±3.64	122.55±3.17	132.97±3.42	142.12±2.9	151.72±2.72	167.3±9.08	<0.0001
DBP, mm Hg	59.44±5.74	64.03±6.29	70.11±6.35	74.66±6.96	78.8±7.11	82.82±8.35	86.75±8.99	92.08±10.24	<0.0001

(*Continued*)

Table 1. Continued

Characteristic	SBP, mm Hg								
	<100	100–110	110–120	120–130	130–140	140–150	150–160	>160	*P* value
Median, Q1–Q3									
Age, y	70 (67–74)	70 (67–74)	70 (68–74)	70 (68–74)	70 (68–74)	70 (68–74)	70 (68–74)	70 (68–74)	<0.0001
BMI, kg/m²	22.77 (20.7–24.91)	23.42 (21.34–25.46)	24 (22.03–25.97)	24.3 (22.38–26.33)	24.61 (22.68–26.64)	24.78 (22.89–26.84)	24.86 (22.89–26.93)	24.84 (22.83–27.01)	<0.0001
FBG, mg/dL	128 (105–149)	128 (107–149)	128 (108–149)	128 (108–148)	129 (109–149)	130 (110–150)	131 (111–151)	132 (113–154)	<0.0001
SBP, mm Hg	91 (90–96)	101.5 (100–106)	112 (110–118)	120 (120–125)	131 (130–136)	140 (140–144)	150 (150–153)	164 (160–170)	<0.0001
DBP, mm Hg	60 (56–61)	62 (60–70)	70 (67–74)	76 (70–80)	80 (74–82)	81 (79–90)	90 (80–90)	90 (86–100)	<0.0001

BMI indicates body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; and SBP, systolic blood pressure.

risk of the primary outcome increased significantly with not only higher SBP but also lower SBP after adjusting for age, sex, smoking, alcohol consumption, regular exercise, BMI, dyslipidemia, CKD, insulin treatment, number of oral diabetes medications, fasting plasma glucose level, CCI, hypertension medication, and DBP (Figure 1A). In patients with DBP 65 to 69 mm Hg, the incidence rate of primary composite outcomes was 43.2 per 1000 person-years and lower than in the other DBP groups (Table 2 and Figure S1). The risk of the primary outcome increased significantly in not only higher but also lower DBP groups than the DBP reference group (DBP 65–69 mm Hg) in multivariable Cox proportional hazard modeling with age, sex, smoking, alcohol consumption, regular exercise, BMI, dyslipidemia, CKD, insulin treatment, number of oral diabetes medications, fasting plasma glucose level, CCI, hypertension medication, and SBP (Figure 1B).

Blood Pressure and Myocardial Infarction, Stroke, Heart Failure, and All-Cause Death

There were 11 683 (5.18%) incidents of MI in the 7.61-year mean follow-up period (Table S2). The incidence rate of MI was 6.80 per 1000 person-years. In patients with SBP 120 to 129 mm Hg, the incidence rate of MI was 6.39 per 1000 person-years and lower than in the other SBP groups (Table S2 and Figure S2A). The incidence rate of MI in patients with DBP 75 to 79 mm Hg was 6.01 per 1000 person-years and lower than in the other DBP groups (Table S2 and Figure S2A). In multivariable Cox proportional hazard modeling, the risk of MI was higher in patients with type 2 diabetes and SBP ≥140 mm Hg (Figure 2A) or DBP ≥90 mm Hg (Figure 2B) compared with the reference group (SBP 120–129 mm Hg, DBP 65–69 mm Hg) after adjusting for age, sex, smoking, alcohol consumption, regular exercise, BMI, dyslipidemia, CKD, insulin treatment, number of oral diabetes medications, fasting plasma glucose level, CCI, hypertension medication, and SBP or DBP.

There were 22 572 (10.00%) incidents of stroke in the 7.45-year mean follow-up period (Table S2). The incidence rate of stroke was 13.44 per 1000 person-years. In patients with SBP 120 to 129 mm Hg, the incidence rate of stroke was 12.06 per 1000 person-years and lower than in the other SBP groups (Table S2 and Figure S2B). The incidence rate of stroke in patients with DBP 65 to 69 mm Hg was 11.31 per 1000 person-years and lower than in the other DBP groups (Table S2 and Figure S2B). In multivariable Cox proportional hazard modeling, the risk of stroke was increased with higher BP and lower BP (SBP <100 mm Hg, and DBP <65 mm Hg) compared with the reference group (SBP 120–129 mm Hg, DBP 65–69 mm Hg) after adjusting

Table 2. Number, Incidence Rate, and HR for Primary Composite Outcomes (Myocardial Infarction, Stroke, and All-Cause Mortality) Stratified by SBP and DBP

	No. of patients	No. of events	Duration, person-years	Rate, events per 1000 person-years	HR (95% CI)	No. of patients	No. of events	Duration, person-years	Rate, events per 1000 person-years
SBP, mm Hg									
<100	1932	805	12 892	62.4	1.36 (1.25–1.47)	1.20 (1.11–1.30)	1.20 (1.10–1.30)	1.22 (1.12–1.33)	1.29 (1.12–1.40)
100–109	8612	3026	61 054	49.6	1.11 (1.07–1.16)	1.04 (0.99–1.08)	1.03 (0.98–1.08)	1.04 (1.00–1.09)	1.09 (1.04–1.14)
110–119	32 551	11 059	233 087	47.4	1.05 (1.02–1.08)	1.03 (1.00–1.06)	1.02 (0.99–1.05)	1.03 (1.00–1.06)	1.05 (1.02–1.08)
120–129	46 530	15 226	337 133	45.2	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
130–139	70 892	23 815	510 965	46.6	1.04 (1.02–1.06)	1.06 (1.03–1.08)	1.06 (1.03–1.08)	1.05 (1.02–1.07)	1.03 (1.01–1.06)
140–149	30 001	10 339	215 231	48.0	1.08 (1.04–1.11)	1.11 (1.08–1.14)	1.11 (1.07–1.14)	1.09 (1.06–1.12)	1.06 (1.03–1.09)
150–159	19 351	6921	137 772	50.2	1.13 (1.09–1.16)	1.16 (1.12–1.20)	1.16 (1.12–1.20)	1.14 (1.10–1.17)	1.09 (1.05–1.13)
≥160	15 694	6256	108 739	57.5	1.31 (1.27–1.36)	1.35 (1.30–1.39)	1.33 (1.29–1.38)	1.30 (1.27–1.35)	1.22 (1.17–1.27)
DBP, mm Hg									
<60	3486	1332	24 308	54.8	1.21 (1.14–1.30)	1.12 (1.05–1.20)	1.11 (1.04–1.19)	1.12 (1.04–1.19)	1.14 (1.07–1.22)
60–64	15 631	5606	110 546	50.7	1.14 (1.09–1.19)	1.10 (1.05–1.15)	1.09 (1.04–1.14)	1.09 (1.05–1.14)	1.11 (1.06–1.16)
65–69	14 266	4481	103 684	43.2	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
70–74	48 346	16 459	346 971	47.4	1.10 (1.06–1.14)	1.10 (1.06–1.14)	1.10 (1.06–1.14)	1.10 (1.06–1.14)	1.10 (1.06–1.14)
75–79	24 501	7824	177 759	44.0	1.05 (1.01–1.09)	1.08 (1.03–1.12)	1.08 (1.04–1.13)	1.08 (1.03–1.12)	1.07 (1.02–1.11)
80–84	64 746	22 307	464 584	48.0	1.13 (1.09–1.17)	1.15 (1.11–1.19)	1.15 (1.11–1.19)	1.14 (1.10–1.19)	1.13 (1.09–1.17)
85–89	18 792	6313	135 544	46.6	1.13 (1.08–1.18)	1.17 (1.12–1.23)	1.18 (1.13–1.23)	1.16 (1.11–1.22)	1.14 (1.09–1.19)
90–94	23 623	8490	168 341	50.4	1.21 (1.16–1.26)	1.25 (1.20–1.31)	1.25 (1.20–1.31)	1.23 (1.18–1.29)	1.19 (1.14–1.25)
≥95	12 172	4635	85 137	54.4	1.36 (1.29–1.42)	1.41 (1.34–1.47)	1.40 (1.34–1.47)	1.37 (1.31–1.44)	1.31 (1.24–1.38)

Model 1: age, and sex. Model 2: age, sex, smoking, alcohol consumption, regular exercise, body mass index, dyslipidemia, chronic kidney disease, and Charlson Comorbidity Index. Model 3: age, sex, smoking, alcohol consumption, regular exercise, body mass index, dyslipidemia, chronic kidney disease, Charlson Comorbidity Index, insulin treatment, number of oral diabetes medications, and fasting plasma glucose. Model 4: age, sex, smoking, alcohol consumption, regular exercise, body mass index, dyslipidemia, chronic kidney disease, Charlson Comorbidity Index, insulin treatment, number of oral diabetes medications, fasting plasma glucose, and hypertension medication. Model 5: age, sex, smoking, alcohol consumption, regular exercise, body mass index, dyslipidemia, chronic kidney disease, Charlson Comorbidity Index, insulin treatment, number of oral diabetes medications, fasting plasma glucose, hypertension medication, and systolic or diastolic blood pressure. DBP indicates diastolic blood pressure; HR, hazard ratio; Ref., reference; and SBP, systolic blood pressure.

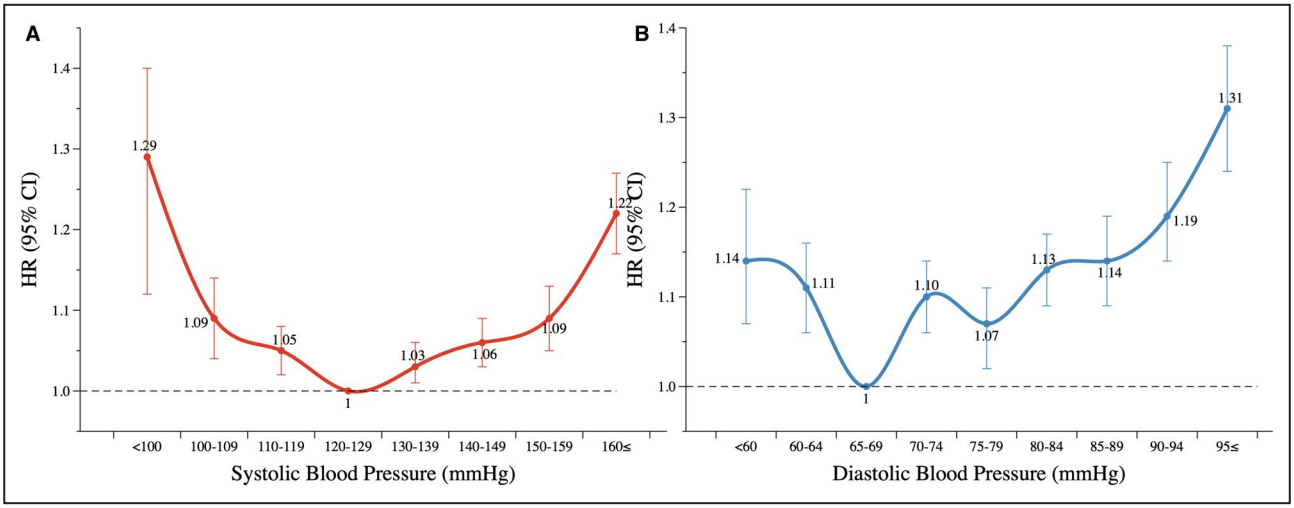

Figure 1. Hazard ratio (HR) and 95% CI for primary composite outcomes by (A) systolic blood pressure and (B) diastolic blood pressure.

Adjusted for age, sex, smoking, alcohol consumption, regular exercise, body mass index, dyslipidemia, chronic kidney disease, insulin treatment, number of oral diabetes medications, fasting plasma glucose level, Charlson Comorbidity Index, hypertension medication, and systolic or diastolic blood pressure.

for age, sex, smoking, alcohol consumption, regular exercise, BMI, dyslipidemia, CKD, insulin treatment, number of oral diabetes medications, fasting glucose level, CCI, hypertension medication, and SBP or DBP (Figure 2C and 2D).

There were 24 190 (10.72%) incidents of HF in the 7.55-year mean follow-up period (Table S2). The incidence rate for HF was 14.19 per 1000 person-years. In patients with SBP 120 to 129 mm Hg, the incidence rate of HF was 13.40 per 1000 person-years and lower than in the other SBP groups (Table S2 and Figure S2C). The incidence rate of HF in patients with DBP 75 to 79 mm Hg was 12.66 per 1000 person-years and lower than in the other DBP groups (Table S2 and Figure S2C). In multivariable Cox proportional hazard modeling, the risk of HF was higher in patients with type 2 diabetes and SBP ≥150 mm Hg or SBP <100 mm Hg (Figure 2E) and DBP ≥95 mm Hg or DBP <60 mm Hg (Figure 2F) compared with the reference group (SBP 120–129 mm Hg, DBP 65–69 mm Hg) after adjusting for age, sex, smoking, alcohol consumption, regular exercise, BMI, dyslipidemia, CKD, insulin treatment, number of oral diabetes medications, fasting plasma glucose level, CCI, hypertension medication, and SBP or DBP.

There were 46 626 (20.67%) incidents of all-cause death in the 7.76-year mean follow-up period (Table S2 and Figure S2G). The incidence rate for all-cause death was 26.6 per 1000 person-years. In patients with SBP 120–129 mm Hg, the incidence rate of all-cause death was 25.22 per 1000 person-years and lower than in the other SBP groups (Table S2 and Figure S2G). The incidence rate of stroke in patients with DBP 65–69 mm Hg was 23.68 per 1000 person-years and lower than in the other DBP groups (Table S2 and Figure S2B). In multivariable Cox proportional hazard modeling, the risk of all-cause death was increased in older patients with type 2 diabetes and SBP ≥140 mm Hg or <120 mm Hg (Figure 2G), and DBP ≥70 mm Hg or <65 mm Hg (Figure 2H) compared with the reference group (SBP 120–129 mm Hg, DBP 65–69 mm Hg) after adjusting for age, sex, smoking, alcohol consumption, regular exercise, BMI, dyslipidemia, CKD, insulin treatment, number of oral diabetes medications, fasting plasma glucose level, CCI, hypertension medication and SBP or DBP.

Sensitivity and Subgroup Analysis

Sensitivity analysis after excluding the first year of observation had consistent findings: the risk of primary composite outcomes was lowest in patients with SBP 120 to 129 mm Hg and with DBP 65 to 69 mm Hg, and the risk of primary composite outcomes increased significantly with not only higher but also lower SBP and DBP than the reference group, with SBP 120 to 129 mm Hg or DBP 65 to 69 mm Hg (Figure 3A and 3B).

Subgroup analysis of those aged ≥80 years and those aged <80 years revealed a significant interaction for the risk of the primary outcome according to SBP (*P* for interaction=0.014; Figure 3C), but not according to DBP (*P* for interaction=0.225; Figure 3D). The risk for primary composite outcomes was only marginally higher in participants aged ≥80 years and SBP ≥160 mm Hg (hazard ratio [HR], 1.11; 95% CI, 0.98–1.24;

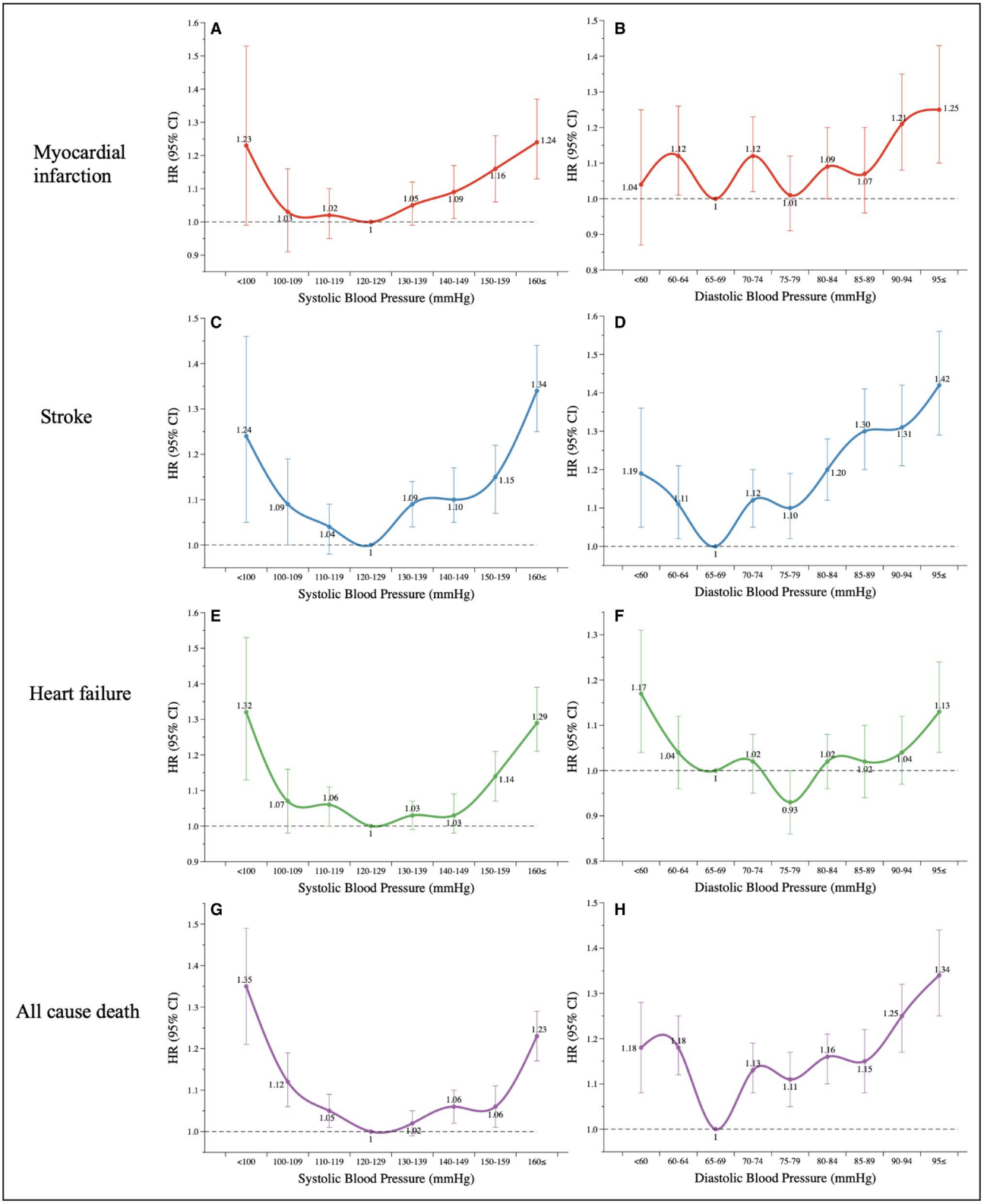

Figure 2. Hazard ratio (HR) and 95% CI for myocardial infarction by (A) systolic blood pressure and (B) diastolic blood pressure, stroke by (C) systolic blood pressure and (D) diastolic blood pressure, heart failure by (E) systolic blood pressure and (F) diastolic blood pressure, and all-cause death by (G) systolic blood pressure and (H) diastolic blood pressure.
Adjusted for age, sex, smoking, alcohol consumption, regular exercise, body mass index, dyslipidemia, chronic kidney disease, insulin treatment, number of oral diabetes medications, fasting plasma glucose level, Charlson Comorbidity Index, hypertension medication, and systolic or diastolic blood pressure.

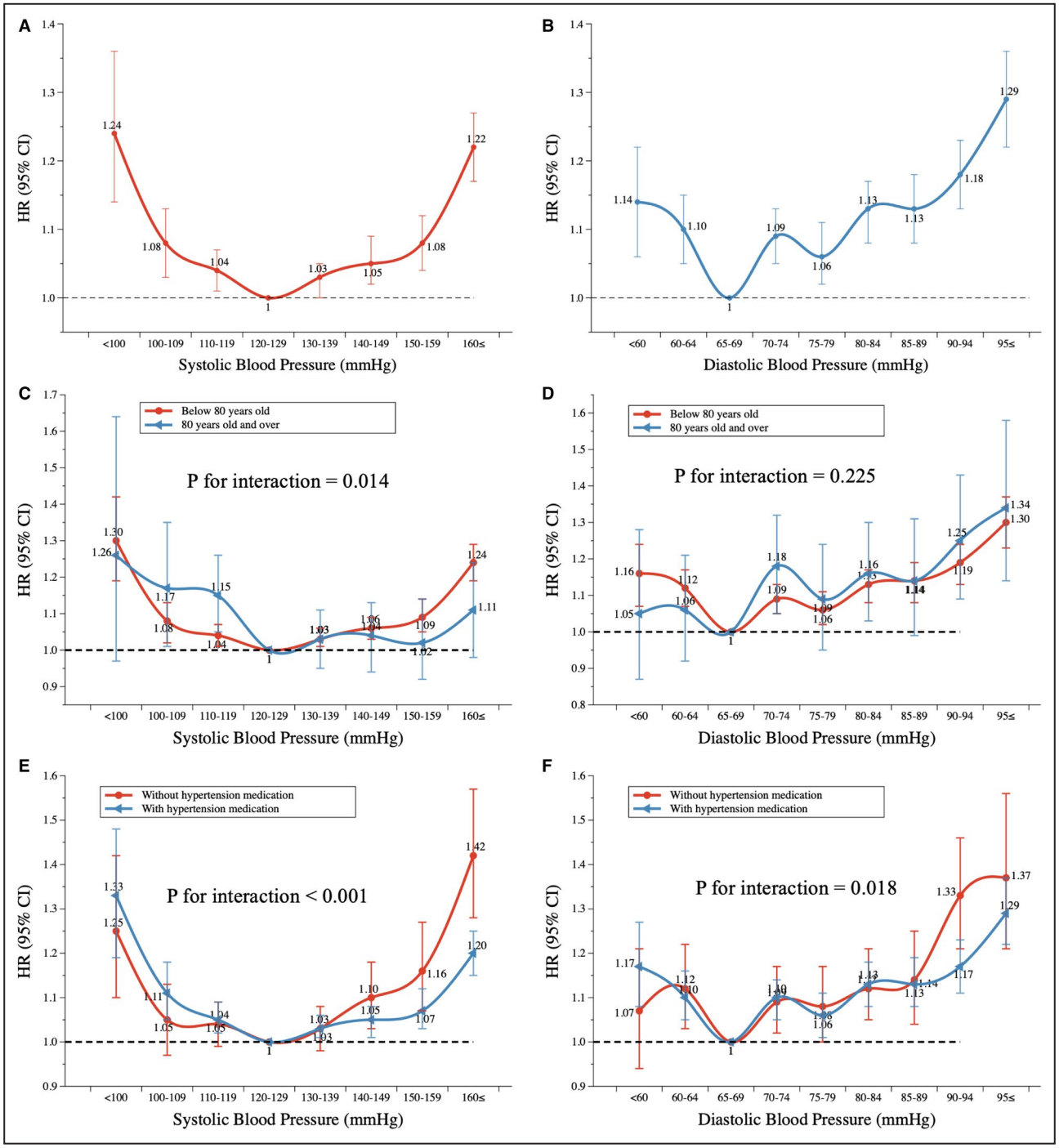

Figure 3. Hazard ratio (HR) and 95% CI for primary composite outcomes by (A) systolic blood pressure and (B) diastolic blood pressure after excluding the first year of observation, by (C) systolic blood pressure and (D) diastolic blood pressure in subgroup with aged ≥80 years or with aged <80 years, and by (E) systolic blood pressure and (F) diastolic blood pressure in subgroup with or without hypertension medication.

Adjusted for age, sex, smoking, alcohol consumption, regular exercise, body mass index, dyslipidemia, chronic kidney disease, insulin treatment, number of oral diabetes medications, fasting plasma glucose level, Charlson Comorbidity Index, hypertension medication, and systolic or diastolic blood pressure.

Figure 3C), but was significantly higher in participants aged <80 years than the reference group, with SBP 120 to 129 mm Hg (Figure 3C). Subgroup analyses were performed with hypertension medication and without hypertension medication for the risk of primary composite outcomes (Figure 3E and 3F). There was a significant interaction between the subgroups with or without hypertension medication for the risk of the

primary outcome according to the SBP group (*P* for interaction <0.001; Figure 3E) and the DBP group (*P* for interaction=0.018; Figure 3F). Hypertension medication was associated with a lower risk for primary composite outcomes in SBP ≥140 mm Hg and DBP ≥90 mm Hg and higher risk for primary composite outcomes in SBP <110 mm Hg or DBP <60 mm Hg (Figure 3E and 3F). The spline curve for primary composite outcomes by SBP and DBP and with or without hypertension medication had consistent findings. The risk of secondary outcomes after excluding the first year of observation also had consistent findings (Figure 4).

DISCUSSION

In this large retrospective study, we examined the association between SBP and DBP and the risk of MI, stroke, HF and death in older patients with diabetes and without CVD. SBP 120 to 129 mm Hg and DBP 65 to 69 mm Hg presented the lowest risk of primary composite outcomes in all participants. Hypertension medication was associated with lower risk of primary composite outcomes in SBP ≥140 mm Hg and DBP ≥90 mm Hg and higher risk for primary composite outcomes in SBP <110 mm Hg and DBP <60 mm Hg. In participants aged ≥80 years, SBP ≥160 mm Hg was only marginally higher risk for primary composite outcomes.

Hypertension is common in older patients with type 2 diabetes. Although tight BP control is particularly beneficial in younger patients with diabetes, there is little evidence for BP goals in older patients with hypertension with type 2 diabetes. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) BP trial has shown that intensive lowering of SBP (<120 mm Hg) in patients with hypertension with diabetes did not improve overall CVD events or deaths, except for a significant reduction in the risk for stroke compared with the conventional lowering of SBP (<140 mm Hg).[7] In the same study, blood pressure control after the first year of follow-up was 119.3/64.4 mm Hg in the intensive group and 133.5/70.5 mm Hg in the standard group. Other studies reported that further SBP lowering (up to 130–135 mm Hg) was associated with the lowest

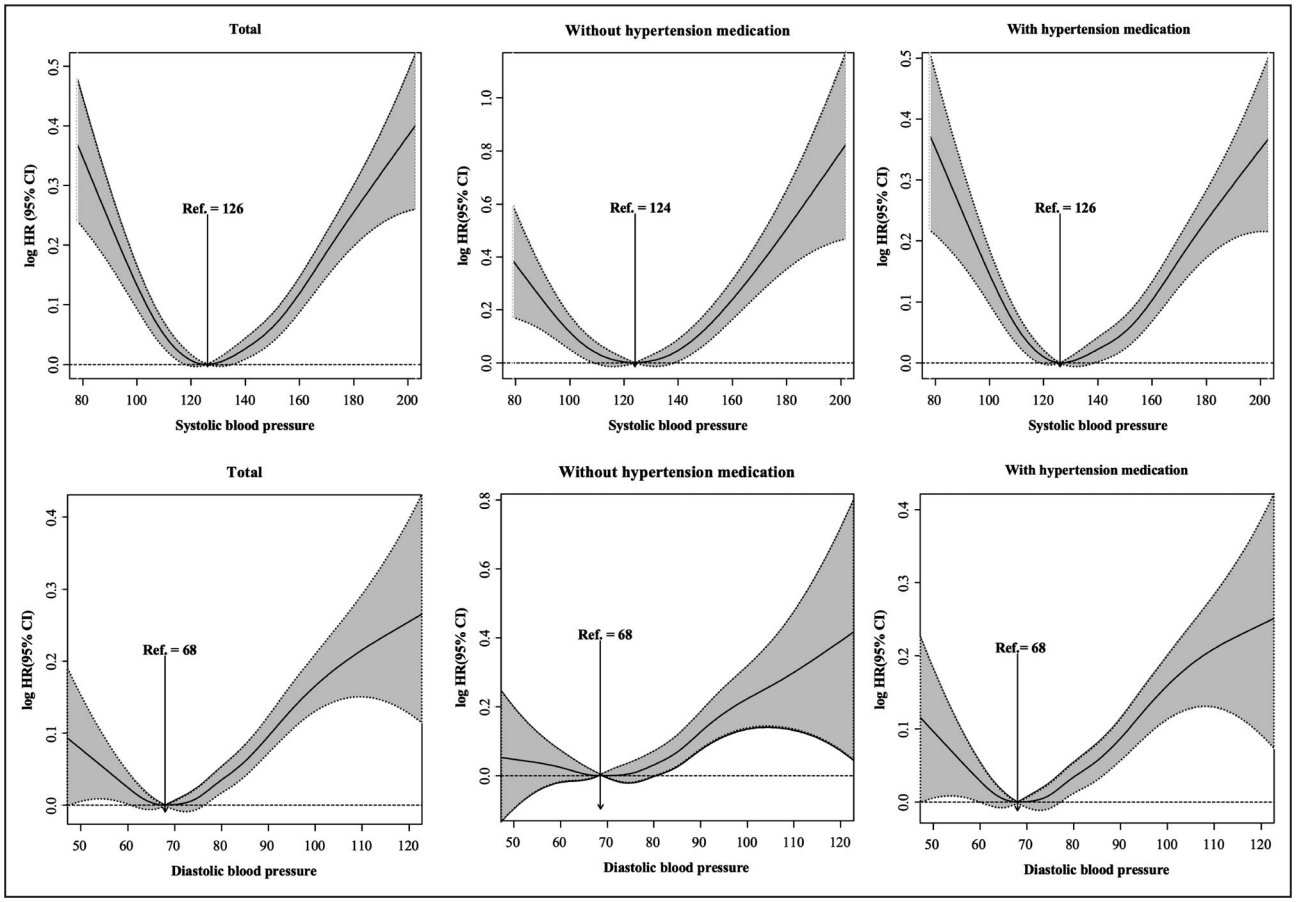

Figure 4. Spline curve for composite primary outcomes by systolic or diastolic blood pressure and by systolic or diastolic blood pressure with or without hypertension medication adjusted for age, sex, smoking, alcohol consumption, regular exercise, body mass index, dyslipidemia, chronic kidney disease, insulin treatment, number of oral diabetes medications, fasting plasma glucose, hypertension medication, Charlson Comorbidity Index, and systolic or diastolic blood pressure.
HR indicates hazard ratio; and Ref, reference.

cardiovascular event rate.[8,19,20] These findings were compatible with our study and were explained by a U-curved association between SBP/DBP and primary composite outcomes in this study. The risk of primary composite outcomes in SBP 110 to 119 mm Hg (HR, 1.05; 95% CI, 1.02–1.08) and DBP 60 to 64 mm Hg (HR, 1.11; 95% CI, 1.06–1.16) was similar to that in SBP 130 to 139 mm Hg (HR, 1.03; 95% CI, 1.01–1.06) and DBP 70 to 74 mm Hg (HR, 1.10; 95% CI, 1.06–1.14) compared with the SBP and DBP reference groups. In addition, the risk of stroke in participants with SBP 130 to 139 mm Hg was significantly higher than the reference group (SBP 120–129 mm Hg), but the risk of MI, HF, and all-cause death was not.

We also observed that SBP <120 mm Hg/DBP <65 mm Hg was associated with poor prognosis in patients with diabetes aged ≥65 years. A few studies in older patients with diabetes showed similar results. Post hoc analysis of the cohort of participants with diabetes in the INVEST (International Verapamil SR-Trandolapril Study) (mean age >65 years) reported that SBP <110 mm Hg was associated with significantly increased risk (HR, 2.18; 95% CI, 1.17–4.09) of all-cause mortality compared with SBP 125 to 130 mm Hg. A previous observational study of 1294 patients with type 2 diabetes aged ≥69.1 years showed a U-shaped association between SBP and mortality, but not in those aged <69.1 years.[21] Although hypertension is an established risk factor for HF, one study reported that low SBP (SBP <120 mm Hg) was associated with increased risks of HF among patients with diabetes without a history of HF.[22] The HOT (Hypertension Optimal Treatment) study reported that lowering DBP to a target level of ≤80 mm Hg in patients with type 2 diabetes resulted in a 51% reduction in major CVD events compared with the conventional target (≤90 mm Hg).[23] Other studies with isolated systolic hypertension, which is common in older people, showed a U-curved association between DBP and CVD events, with a nadir between 60 and 70 mm Hg.[24,25] A recent cohort study of 1.3 million adults in a general outpatient population revealed a U-curved relationship between the diastolic blood pressure and the composite outcome.[26] The risk of composite outcomes was increased below 60 mm Hg, and the author suggested that this relationship was explained by age and other covariates. Our study results were also compatible with the above study. The association between DBP and the risk of the composite outcomes was U-curved, with a nadir between 65 and 69 mm Hg. The risk of the composite outcomes was increased at <65 mm Hg. The association between lower blood pressure and poor outcomes could be explained by comorbidities common in older patients with lower blood pressure. Therefore, we adjusted for CCI in multivariable Cox proportional hazard modeling and performed sensitivity analyses excluding participants who were diagnosed with stroke, MI, HF, or all-cause death during the first year of follow-up. However, the association of lower blood pressure with increased risk of stroke, MI, HF, and all-cause death in study participants did not change.

Two decades ago, the Framingham data suggested an age-dependent threshold for hypertension.[27] This study showed a different association between SBP and primary composite outcomes by age group (*P* for interaction=0.014). In patients with diabetes who were aged ≥80 years, the risk for primary composite outcomes was marginally higher in SBP ≥160 mm Hg than SBP 120 to 129 mm Hg (HR, 1.11; 95% CI, 0.98–1.24; Figure 3C). Based on our study results, the suggested SBP threshold is ≈130 mm Hg in patients with diabetes aged 65 to 79 years, and ≈160 mm Hg in patients with diabetes aged ≥80 years. Most guidelines do not indicate a BP goal in older patients with both diabetes and hypertension, because most hypertension trials do not include an older population, do not present age-specific results, or have only a small number of older patients with diabetes in the study population. The American Diabetes Association recommends a treatment goal of <140/90 mm Hg in patients with diabetes (<130/90 mm Hg in patients with diabetes at higher cardiovascular risk), and cautiously suggests the same treatment goal in older patients with diabetes.[15,28] Interestingly, in subgroup analysis, hypertension medication was associated with lower risk of primary composite outcomes in SBP ≥140 mm Hg and DBP ≥90 mm Hg (Figure 3E and 3F). This finding supports the current American Diabetes Association cutoff value for initiating antihypertension treatment in elderly patients with diabetes.[29] However, another cutoff is needed for patients with diabetes aged ≥80 years (Figure 3C).

Another concerning finding of this study is that the prevalence of prescribed hypertensive medications was quite high in patients with SBP <120 mm Hg (55.6%) and DBP <65 mm Hg (59.6%). Hypertension medication was associated with poor prognosis in patients with SBP <110 mm Hg or DBP <60 mm Hg (Figure 3E and 3F). One of 8 patients (12.9%) in our study who were on hypertensive medications might have been overtreated for hypertension. This finding suggests that continuing antihypertensive therapy in people with relative hypotension may increase, rather than decrease, cardiovascular events.

The strengths of our study are that we used a large-scale nationwide database representing the entire Korean population. Second, we conducted fully adjusted analyses with all available confounding cardiovascular risk factors. However, this study also has some limitations. First, the retrospective observational study design has inherent limitations. Although the analyses were adjusted for most available demographic and clinical variables, some unidentified parameters could affect

the results. Second, there was some possibility of selection bias, because we selected participants whose BP was measured in the national health screening program, which requests that participants voluntarily visit clinics. Therefore, there was some possibility that study participants might have higher mobility than individuals who did not participate in the national health screening program and, particularly in volunteers aged >75 years, may have less overall morbidity because of fewer serious chronic health conditions compared with the general elderly Korean population. However, our study excluded patients with stroke (including those with cerebral palsy) before analysis and might cover most elderly patients with diabetes in an outpatient setting. Third, we defined MI and stroke based on claims data; this may not be a completely accurate method for determining the number of cases. To overcome this problem, we defined outcomes using an operational definition by combining diagnostic and prescription records. Fourth, the BP measurement protocol of the national health screening program, which focused on screening hypertension, does not follow published guidelines and may have introduced measurement bias, which is likely to have estimated BP with reasonable accuracy in low or normal BP participants, but truncated the actual BP of individuals with high values. However, a recent study evaluated the performance of hypertension screening in medical institutions conducting the national health screening program in the Republic of Korea. According to this study, medical institutions used mainly oscilloscopic devices for BP measurement, and most had measurement manuals and training protocols. The majority of the institutions measured BP multiple times with a resting period and used the average values as an individual's BP level.[30] Fifth, this study is not a prospective study; therefore, causality cannot be determined. However, to minimize the possible effects of reverse causality, participants with preexisting MI or stroke were excluded. Lastly, we did not analyze the cause of death, because the details were unavailable in the national database.

In conclusion, this retrospective cohort study of older patients with diabetes without CVD suggests that patients with SBP 120 to 129 mm Hg and DBP 65 to 69 mm Hg had the lowest risk of primary composite outcomes for MI, stroke, HF, and all-cause death. This study also suggested that hypertension medication may decrease CVD events in patients with SBP ≥140 mm Hg and DBP >90 mm Hg and increase CVD events in patients with SBP <110 mm Hg and DBP <60 mm Hg.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S2
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Baseline demographic and clinical characteristics according to diastolic blood pressure groups

Diastolic Blood Pressure (mmHg)	<60	60-64	65-69	70-74	75-79	80-84	85-89	90-94	95≤	P-value
Number of subjects	3486	15631	14266	48346	24501	64746	18792	23623	12172	
Sex (%)										0.0006
Male	1749 (50.17)	7781 (49.78)	7046 (49.39)	23754 (49.13)	12439 (50.77)	31991 (49.41)	9469 (50.39)	11666 (49.38)	6135 (50.4)	
Female	1737 (49.83)	7850 (50.22)	7220 (50.61)	24592 (50.87)	12062 (49.23)	32755 (50.59)	9323 (49.61)	11957 (50.62)	6037 (49.6)	
Smoking (%)										<.0001
Non	2285 (65.55)	10476 (67.02)	9734 (68.23)	33706 (69.72)	16960 (69.22)	46058 (71.14)	13388 (71.24)	17097 (72.37)	8680 (71.31)	
Ex	605 (17.36)	2697 (17.25)	2593 (18.18)	7917 (16.38)	4322 (17.64)	10265 (15.85)	3144 (16.73)	3720 (15.75)	2001 (16.44)	
Current	596 (17.1)	2458 (15.73)	1939 (13.59)	6723 (13.91)	3219 (13.14)	8423 (13.01)	2260 (12.03)	2806 (11.88)	1491 (12.25)	
Drink (%)										<.0001
Non	2769 (79.43)	12043 (77.05)	10786 (75.61)	36502 (75.5)	17834 (72.79)	47593 (73.51)	13485 (71.76)	16876 (71.44)	8450 (69.42)	
Mild	625 (17.93)	3129 (20.02)	3026 (21.21)	9934 (20.55)	5584 (22.79)	14170 (21.89)	4408 (23.46)	5443 (23.04)	2960 (24.32)	
Heavy	92 (2.64)	459 (2.94)	454 (3.18)	1910 (3.95)	1083 (4.42)	2983 (4.61)	899(4.78)	1304 (5.52)	762 (6.26)	
Regular exercise (%)	1353 (38.81)	6313 (40.39)	5996 (42.03)	19280 (39.88)	10212 (41.68)	25967 (40.11)	7507 (39.95)	8943 (37.86)	4377 (35.96)	<.0001
Dyslipidemia (%)	1523 (43.69)	6511 (41.65)	6396 (44.83)	20017 (41.4)	10297 (42.03)	26233 (40.52)	7615 (40.52)	9654 (40.87)	4989 (40.99)	<.0001
Chronic kidney disease (%)	895 (25.67)	3741 (23.93)	3249 (22.77)	10484 (21.69)	5091 (20.78)	13836 (21.37)	3890 (20.7)	5187 (21.96)	2641 (21.7)	<.0001
Insulin (%)	556 (19.58)	2165 (17.38)	1722 (14.84)	5322 (14.38)	2372 (12.85)	6122 (13)	1691 (12.52)	2096 (12.86)	986 (12.58)	<.0001
Number of oral diabetes medication (%)										<.0001
0	94 (3.31)	324 (2.6)	283 (2.44)	791 (2.14)	357 (1.93)	817 (1.74)	237 (1.75)	303 (1.86)	149 (1.9)	
1	784 (27.61)	3439 (27.61)	3394 (29.26)	10682 (28.87)	5616 (30.43)	14333 (30.44)	4320 (31.97)	5076 (31.14)	2459 (31.37)	
2	1114(39.23)	5238 (42.06)	4882 (42.08)	15666 (42.34)	7880 (42.69)	20009 (42.5)	5721 (42.34)	7029 (43.13)	3474 (44.32)	
3	681 (23.98)	2841 (22.81)	2510 (21.64)	8132 (21.98)	3802 (20.6)	9944 (21.12)	2696 (19.95)	3258 (19.99)	1482 (18.91)	
4	147(5.18)	537 (4.31)	465 (4.01)	1553 (4.2)	730 (3.95)	1774 (3.77)	490 (3.63)	574 (3.52)	253 (3.23)	
5	19 (0.67)	71 (0.57)	64 (0.55)	163 (0.44)	70 (0.38)	202 (0.43)	45 (0.33)	58 (0.36)	19 (0.24)	
6	1 (0.04)	4 (0.03)	3 (0.03)	10 (0.03)	3 (0.02)	6 (0.01)	2 (0.01)	0 (0)	3 (0.04)	
Hypertension medication (%)	2103 (60.33)	9377 (59.99)	9253 (64.86)	31299 (64.74)	16463 (67.19)	45116 (69.68)	14032 (74.67)	18168 (76.91)	9674 (79.48)	<.0001
Mean ±SD										
Age (years)	71.52±4.93	71.27±4.82	70.92±4.59	71.03±4.75	70.71±4.59	70.98±4.74	70.7±4.62	71.06±4.81	70.89±4.76	<.0001
BMI (kg/m^2)	23.45±3.05	23.74±3.05	24.25±2.96	24.3±3.09	24.56±3.08	24.65±3.13	24.92±3.17	24.95±3.21	25.04±3.3	<.0001
Glucose (mg/dL)	133±44.06	133.72±42.07	132.55±39.94	134.79±41.06	135.11±39.62	136.16±41.28	135.76±40.1	137.77±41.47	140.09±41.62	<.0001
SBP (mmHg)	109.67±12.95	114.44±12.85	123.89±11.33	123.91±12.58	130.75±12.08	132.4±11.72	139.89±11.3	146.3±12.81	158.39±14.72	<.0001
DBP (mmHg)	55.7±2.83	61.21±1.53	67.07±1.42	70.76±1.32	77.01±1.55	80.44±1.06	86.82±1.65	90.32±0.91	100.97±5.21	<.0001
PP* (mmHg)	71.52±4.93	71.27±4.82	70.92±4.59	71.03±4.75	70.71±4.59	70.98±4.74	70.7±4.62	71.06±4.81	70.89±4.76	<.0001
Median (Q1-Q3)										
Age (years)	70 (68-74)	70 (68-74)	70 (68-74)	70 (68-74)	70 (67-74)	70 (68-74)	70 (67-74)	70 (68-74)	70 (67-74)	<.0001
BMI (kg/m^2)	23.34 (21.37-25.32)	23.63 (21.75-25.65)	24.14 (22.31-26.03)	24.22 (22.23-26.22)	24.44 (22.53-26.4)	24.52 (22.59-26.56)	24.77 (22.81-26.84)	24.84 (22.84-26.89)	24.89 (22.89-27.05)	<.0001
Glucose (mg/dL)	126 (105-148)	127 (107-148)	127 (107-146)	128 (109-149)	129 (110-149)	130 (110-150)	130 (110-150)	131 (112-152)	133 (115-154)	<.0001
SBP (mmHg)	109 (101-117)	114 (105-122)	124 (116-131)	121 (111-130)	130 (120-138)	130 (122-140)	138 (135-144)	145 (140-150)	160 (150-170)	<.0001
DBP (mmHg)	56 (54-58)	60 (60-62)	67 (66-68)	70 (70-71)	77 (75-78)	80 (80-80)	87 (85-89)	90 (90-90)	100 (99-100)	<.0001
PP* (mmHg)	70 (68-74)	70 (68-74)	70 (68-74)	70 (68-74)	70 (67-74)	70 (68-74)	70 (67-74)	70 (68-74)	70 (67-74)	<.0001

Table S2. Number, Incidence Rate, and Hazard Ratio of myocardiac infarction, stroke, heart failure and all-cause mortality stratified by SBP, and DBP.

		Number of patients	Number of events	Duration (person-years)	Rate (events per 1000 person-years)	Hazard ratio (95% CI)				
						Model1	Model2	Model3	Model4	Model4
Myocardial infarction										
SBP	<100	1932	114	13744	8.29	1.30(1.05,1.61)	1.16(0.94,1.44)	1.15(0.93,1.42)	1.19(0.96,1.47)	1.23(0.99,1.53)
	100-109	8612	439	64410	6.82	1.06(0.95,1.19)	0.99(0.88,1.11)	0.98(0.87,1.10)	1.00(0.89,1.13)	1.03(0.91,1.16)
	110-119	32551	1616	246518	6.56	1.03(0.96,1.11)	1.01(0.94,1.08)	1.00(0.93,1.08)	1.02(0.94,1.09)	1.02(0.95,1.10)
	120-129	46530	2274	356025	6.39	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
	130-139	70892	3654	542022	6.74	1.05(0.99,1.12)	1.07(1.01,1.14)	1.07(1.01,1.14)	1.06(1.00,1.12)	1.05(0.99,1.12)
	140-149	30001	1580	229144	6.90	1.10(1.02,1.18)	1.13(1.05,1.22)	1.13(1.05,1.22)	1.10(1.03,1.19)	1.09(1.01,1.17)
	150-159	19351	1083	147516	7.34	1.19(1.09,1.29)	1.23(1.13,1.33)	1.22(1.13,1.33)	1.18(1.09,1.29)	1.16(1.06,1.26)
	160≤	15694	923	117870	7.83	1.32(1.21,1.44)	1.35(1.24,1.48)	1.34(1.22,1.46)	1.29(1.18,1.41)	1.24(1.13,1.37)
DBP	<60	3486	182	25828	7.05	1.10(0.92,1.31)	1.01(0.85,1.21)	1.00(0.84,1.19)	1.01(0.84,1.20)	1.04(0.87,1.25)
	60-64	15631	849	116766	7.27	1.14(1.02,1.28)	1.10(0.99,1.23)	1.09(0.98,1.22)	1.10(0.99,1.23)	1.12(1.01,1.26)
	65-69	14266	684	109311	6.26	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
	70-74	48346	2520	367247	6.86	1.12(1.02,1.23)	1.12(1.02,1.23)	1.12(1.02,1.23)	1.12(1.02,1.23)	1.12(1.02,1.23)
	75-79	24501	1128	187808	6.01	0.99(0.90,1.10)	1.03(0.92,1.14)	1.03(0.93,1.15)	1.02(0.92,1.14)	1.01(0.91,1.12)
	80-84	64746	3346	493870	6.78	1.10(1.00,1.20)	1.12(1.03,1.23)	1.13(1.03,1.23)	1.11(1.02,1.22)	1.09(1.00,1.20)
	85-89	18792	964	144457	6.67	1.08(0.96,1.20)	1.13(1.01,1.26)	1.13(1.02,1.27)	1.11(0.99,1.24)	1.07(0.95,1.20)
	90-94	23623	1322	179977	7.35	1.25(1.13,1.39)	1.30(1.18,1.44)	1.31(1.18,1.45)	1.27(1.15,1.41)	1.21(1.08,1.35)
	95≤	12172	688	91984	7.48	1.36(1.20,1.53)	1.41(1.25,1.59)	1.41(1.25,1.58)	1.36(1.21,1.53)	1.25(1.10,1.43)
Stroke										
SBP	<100	1932	193	13553	14.24	1.20(1.02,1.41)	1.11(0.94,1.30)	1.10(0.94,1.29)	1.12(0.96,1.32)	1.24(1.05,1.46)
	100-109	8612	790	63330	12.47	1.06(0.97,1.15)	1.01(0.93,1.10)	1.00(0.92,1.09)	1.02(0.93,1.11)	1.09(1.00,1.19)
	110-119	32551	2990	241907	12.36	1.02(0.97,1.08)	1.01(0.95,1.06)	1.00(0.95,1.05)	1.01(0.96,1.06)	1.04(0.98,1.09)
	120-129	46530	4216	349555	12.06	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
	130-139	70892	7051	530396	13.29	1.12(1.07,1.17)	1.13(1.08,1.18)	1.13(1.08,1.18)	1.12(1.07,1.17)	1.09(1.04,1.14)
	140-149	30001	3110	223539	13.91	1.16(1.10,1.23)	1.18(1.12,1.25)	1.18(1.12,1.24)	1.16(1.10,1.22)	1.10(1.05,1.17)
	150-159	19351	2160	143454	15.06	1.25(1.17,1.32)	1.26(1.19,1.34)	1.26(1.19,1.34)	1.23(1.16,1.31)	1.15(1.07,1.22)
	160≤	15694	2062	113683	18.14	1.54(1.45,1.64)	1.55(1.46,1.65)	1.53(1.44,1.63)	1.49(1.40,1.59)	1.34(1.25,1.44)
DBP	<60	3486	349	25306	13.79	1.21(1.07,1.38)	1.15(1.01,1.31)	1.13(1.00,1.29)	1.14(1.00,1.30)	1.19(1.05,1.36)
	60-64	15631	1449	115044	12.60	1.11 (1.02,1.21)	1.09(1.00,1.18)	1.08(0.99,1.17)	1.08(0.99,1.18)	1.11(1.02,1.21)
	65-69	14266	1216	107510	11.31	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
	70-74	48346	4588	360065	12.74	1.13(1.06,1.21)	1.13(1.05,1.21)	1.13(1.05,1.21)	1.12(1.05,1.20)	1.12(1.05,1.20)
	75-79	24501	2222	184181	12.06	1.11(1.03,1.20)	1.13(1.05,1.22)	1.13(1.05,1.22)	1.13(1.04,1.22)	1.10(1.02,1.19)
	80-84	64746	6556	482899	13.58	1.23(1.15,1.32)	1.24(1.16,1.33)	1.24(1.16,1.33)	1.23(1.15,1.32)	1.20(1.12,1.28)
	85-89	18792	2007	140569	14.28	1.35(1.24,1.46)	1.38(1.27,1.49)	1.38(1.28,1.50)	1.36(1.26,1.47)	1.30(1.20,1.41)
	90-94	23623	2645	175058	15.11	1.41(1.31,1.52)	1.43(1.33,1.54)	1.43(1.32,1.54)	1.40(1.30,1.51)	1.31(1.21,1.42)
	95≤	12172	1540	88786	17.35	1.60(1.47,1.75)	1.62(1.49,1.77)	1.61(1.48,1.76)	1.58(1.44,1.72)	1.42(1.29,1.56)
Heart failure										
SBP	<100	1932	247	13609	18.15	1.36(1.17,1.57)	1.27(1.10,1.47)	1.26(1.09,1.46)	1.31(1.13,1.51)	1.32(1.13,1.53)
	100-109	8612	905	63863	14.17	1.08(1.00,1.17)	1.04(0.96,1.13)	1.03(0.95,1.12)	1.06(0.98,1.15)	1.07(0.98,1.16)
	110-119	32551	3397	244715	13.88	1.06(1.00,1.11)	1.04(0.99,1.10)	1.04(0.99,1.09)	1.05(1.00,1.11)	1.06(1.00,1.11)
	120-129	46530	4736	353355	13.40	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
	130-139	70892	7447	538542	13.83	1.04(1.00,1.08)	1.04(1.00,1.09)	1.04(1.00,1.09)	1.03(0.99,1.07)	1.03(0.99,1.07)
	140-149	30001	3175	227442	13.96	1.05(1,10.11)	1.06(1.01,1.12)	1.06(1.01,1.12)	1.03(0.98,1.09)	1.03(0.98,1.09)
	150-159	19351	2239	146225	15.31	1.18(1.11,1.25)	1.18(1.11,1.26)	1.18 (1.12,1.26)	1.15(1.08,1.21)	1.14(1.07,1.21)
	160≤	15694	2044	116421	17.56	1.37(1.30,1.46)	1.37(1.29,1.46)	1.36(1.28,1.44)	1.31(1.23,1.39)	1.29(1.21,1.39)
DBP	<60	3486	429	25518	16.81	1.20(1.07,1.35)	1.14(1.02,1.28)	1.12(1.00,1.26)	1.13(1.01,1.27)	1.17(1.04,1.31)
	60-64	15631	1732	115926	14.94	1.05(0.97,1.13)	1.03(0.95,1.11)	1.01(0.94,1.09)	1.02(0.95,1.10)	1.04(0.96,1.12)
	65-69	14266	1487	108298	13.73	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
	70-74	48346	5115	364642	14.03	1.02(0.96,1.09)	1.02(0.95,1.08)	1.02(0.95,1.08)	1.01(0.95,1.08)	1.02(0.95,1.08)
	75-79	24501	2361	186519	12.66	0.93(0.86,1.00)	0.94(0.88,1.01)	0.95(0.88,1.02)	0.94(0.88,1.01)	0.93(0.86,1.00)
	80-84	64746	6974	490196	14.23	1.04(0.98,1.11)	1.04(0.98,1.11)	1.05(0.99,1.12)	1.04(0.97,1.10)	1.02(0.96,1.08)
	85-89	18792	1993	143416	13.90	1.06(0.98,1.14)	1.07(1.00,1.16)	1.08(1.00,1.16)	1.06(0.98,1.14)	1.02(0.94,1.10)
	90-94	23623	2622	178590	14.68	1.11(1.04,1.19)	1.12(1.04,1.20)	1.13(1.05,1.21)	1.09(1.02,1.17)	1.04(0.97,1.12)

	95≤	12172	1477	91065	16.22	1.26(1.16,1.37)	1.26(1.16,1.37)	1.27(1.17,1.38)	1.22(1.13,1.33)	1.13(1.04,1.24)
All Cause death										
SBP	<100	1932	559	14093	39.67	1.55(1.40,1.71)	1.27(1.15,1.40)	1.26(1.14,1.39)	1.27(1.15,1.41)	1.35(1.21,1.49)
	100-109	8612	1956	65607	29.81	1.21(1.14,1.28)	1.08(1.02,1.14)	1.07(1.01,1.13)	1.08(1.02,1.14)	1.12(1.06,1.19)
	110-119	32551	6851	251266	27.27	1.08(1.04,1.12)	1.04(1.00,1.07)	1.03(0.99,1.06)	1.03(1.00,1.07)	1.05(1.01,1.09)
	120-129	46530	9144	362578	25.22	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
	130-139	70892	14076	552914	25.46	1.02(0.99,1.05)	1.04(1.01,1.07)	1.04(1.01,1.07)	1.04(1.00,1.07)	1.02(0.99,1.05)
	140-149	30001	6160	233665	26.36	1.05(1.01,1.09)	1.10(1.06,1.15)	1.10(1.06,1.14)	1.09(1.05,1.13)	1.06(1.02,1.10)
	150-159	19351	4046	150587	26.87	1.07(1.03,1.12)	1.12(1.08,1.17)	1.12(1.07,1.17)	1.10(1.06,1.15)	1.06(1.01,1.11)
	160≤	15694	3834	120488	31.82	1.30(1.24,1.36)	1.35(1.29,1.41)	1.33(1.27,1.39)	1.31(1.25,1.37)	1.23(1.17,1.29)
DBP	<60	3486	869	26326	33.01	1.30(1.19,1.42)	1.17(1.07,1.27)	1.15 (1.06,1.26)	1.16(1.06,1.26)	1.18(1.08,1.28)
	60-64	15631	3622	119203	30.39	1.24(1.17,1.31)	1.18(1.11,1.25)	1.17(1.10,1.24)	1.17(1.11,1.24)	1.18(1.12,1.25)
	65-69	14266	2635	111261	23.68	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
	70-74	48346	10018	374433	26.76	1.14(1.08,1.19)	1.13(1.08,1.19)	1.13(1.08,1.19)	1.13(1.08,1.19)	1.13(1.08,1.19)
	75-79	24501	4671	191202	24.43	1.07(1.02,1.13)	1.12(1.06,1.18)	1.12(1.06,1.18)	1.12(1.06,1.18)	1.11(1.05,1.17)
	80-84	64746	13252	503830	26.30	1.14(1.09,1.19)	1.17(1.12,1.23)	1.18(1.12,1.23)	1.17(1.12,1.23)	1.16(1.10,1.21)
	85-89	18792	3662	147244	24.87	1.11(1.05,1.17)	1.17(1.11,1.24)	1.18(1.12,1.25)	1.17(1.11,1.24)	1.15(1.08,1.22)
	90-94	23623	5125	183735	27.89	1.22(1.16,1.29)	1.29(1.22,1.36)	1.29(1.22,1.36)	1.28(1.21,1.35)	1.25(1.17,1.32)
	95≤	12172	2772	93964	29.50	1.34(1.26,1.43)	1.42(1.34,1.51)	1.42(1.33,1.51)	1.40(1.31,1.49)	1.34(1.25,1.44)

Model 1; Age, sex

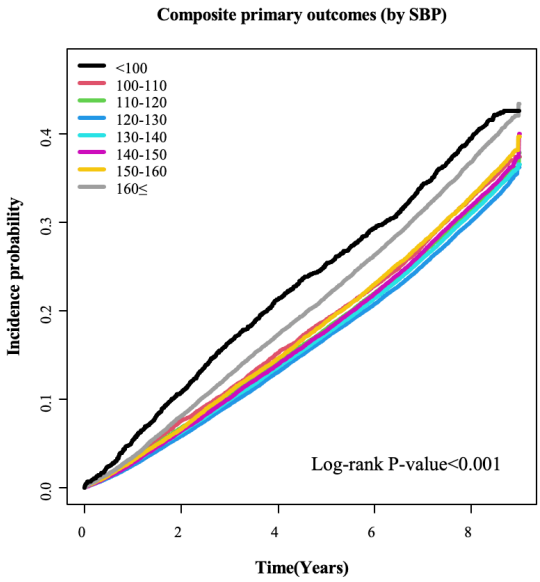
Model 2: Age, sex, smoking, alcohol consumption, regular exercise, body mass index, dyslipidemia, chronic kidney disease, Charlson Comorbidity Index

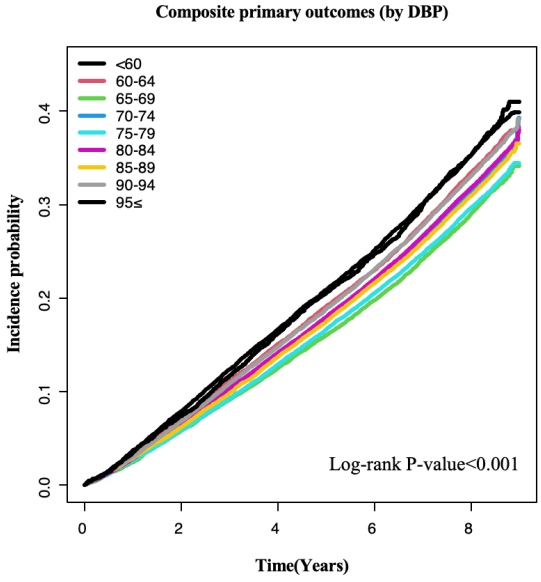
Model 3: Age, sex, smoking, alcohol consumption, regular exercise, body mass index, dyslipidemia, chronic kidney disease, insulin treatment, number of oral diabetes medication, fasting plasma glucose. Charlson Comorbidity Index

Model 4: Age, sex, smoking, alcohol consumption, regular exercise, body mass index, dyslipidemia, chronic kidney disease, insulin treatment, number of oral diabetes medication, fasting plasma glucose, hypertension medication, Charlson Comorbidity Index

Model 5: Age, sex, smoking, alcohol consumption, regular exercise, body mass index, dyslipidemia, chronic kidney disease, insulin treatment, number of oral diabetes medication, fasting plasma glucose, hypertension medication, Charlson Comorbidity Index, systolic or diastolic blood pressure

Figure S1. Kaplan–Meier estimates of survival and Incidence probability by eight groups of systolic blood pressure and diastolic blood pressure for composite primary outcomes.



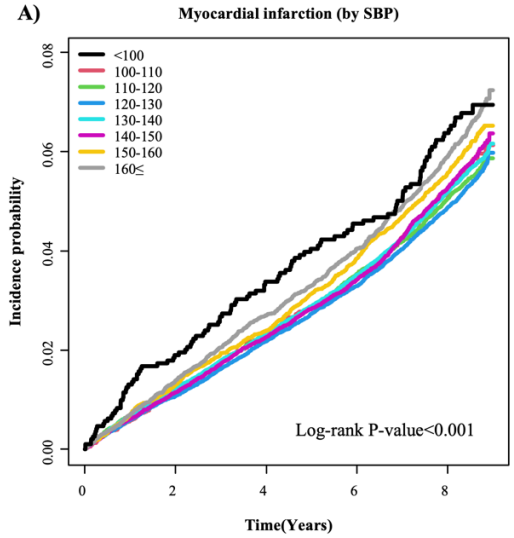


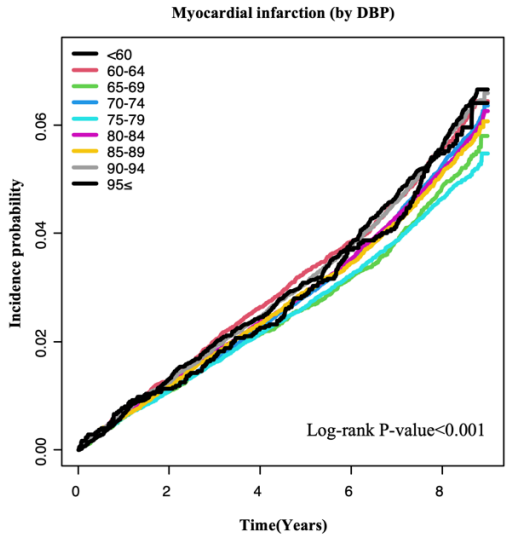
SBP	Baseline	1 year	2 year	3 year	4 year	5 year	6 year	7 year	8year	9year
<100	1932	1829	1724	1614	1521	1446	1366	1272	1170	0
100-109	8612	8321	7962	7661	7301	6977	6648	6251	5794	1
110-119	32551	31548	30343	29159	27939	26699	25384	23906	22275	5
120-129	46530	45361	43820	42170	40457	38645	36883	34843	32522	9
130-139	70892	68896	66458	63872	61246	58572	55742	52508	48932	12
140-149	30001	29158	28074	26968	25818	24686	23432	22007	20447	6
150-159	19351	18751	18069	17252	16523	15718	14896	13991	12976	5
160≤	15694	15152	14423	13692	12982	12302	11570	10779	9919	10

DBP	Baseline	1 year	2 year	3 year	4 year	5 year	6 year	7 year	8year	9year
<60	3486	3358	3229	3080	2922	2771	2624	2445	2257	0
60-64	15631	15117	14499	13899	13279	12650	12044	11267	10411	1
65-69	14266	13917	13441	12965	12484	11980	11441	10817	10123	0
70-74	48346	46925	45295	43462	41638	39758	37795	35569	33139	5
75-79	24501	23862	23069	22239	21351	20434	19481	18444	17238	2
80-84	64746	62924	60476	58059	55600	53124	50496	47517	44185	23
85-89	18792	18256	17634	16957	16223	15516	14738	13921	12982	3
90-94	23623	22906	22016	21059	20139	19177	18179	17063	15818	9
95≤	12172	11751	11214	10668	10151	9635	9123	8514	7882	5

Figure S2. Kaplan–Meier estimates of survival and Incidence probability by eight groups of systolic blood pressure and diastolic blood pressure for myocardial infarction (A), stroke (B), heart failure (C) and all-cause death (D)

A)

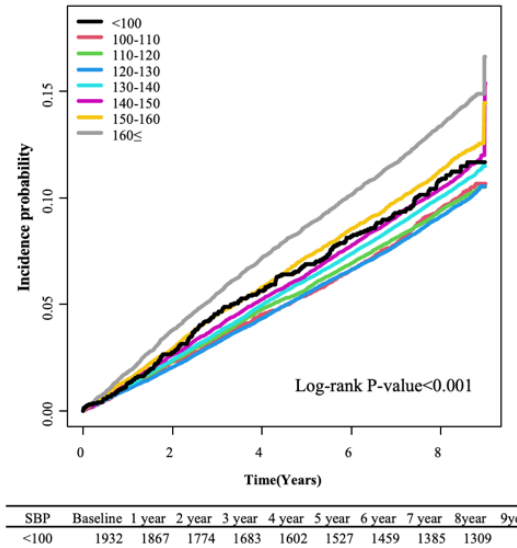


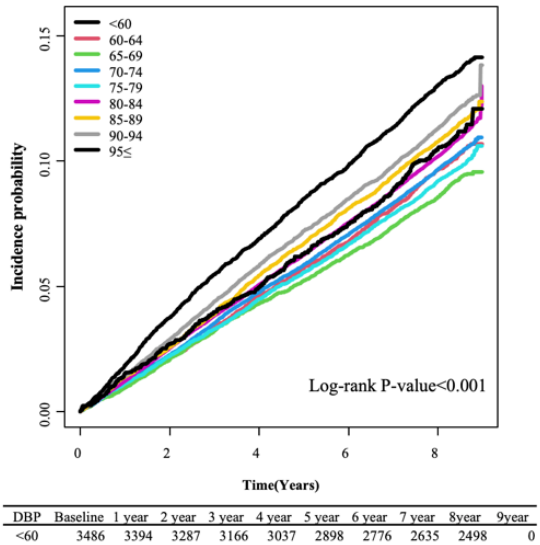


SBP	Baseline	1 year	2 year	3 year	4 year	5 year	6 year	7 year	8year	9year
<100	1932	1867	1787	1713	1626	1555	1489	1420	1344	0
100-109	8612	8444	8192	7970	7689	7432	7149	6856	6534	1
110-119	32551	32010	31195	30341	29479	28485	27448	26373	25256	5
120-129	46530	45935	44924	43805	42565	41224	39838	38363	36799	9
130-139	70892	69915	68359	66575	64761	62776	60596	58291	55779	13
140-149	30001	29626	28966	28251	27436	26565	25602	24549	23401	10
150-159	19351	19083	18667	18162	17664	17067	16397	15738	15031	5
160≤	15694	15477	15056	14593	14085	13578	12973	12347	11710	11

DBP	Baseline	1 year	2 year	3 year	4 year	5 year	6 year	7 year	8year	9year
<60	3486	3419	3332	3226	3109	2977	2853	2722	2584	0
60-64	15631	15346	14893	14456	13995	13496	12990	12435	11796	1
65-69	14266	14073	13780	13462	13123	12752	12324	11880	11407	0
70-74	48346	47590	46523	45264	43954	42493	40940	39333	37635	6
75-79	24501	24190	23677	23116	22489	21792	21053	20317	19504	2
80-84	64746	63862	62318	60677	58918	57058	55025	52868	50603	26
85-89	18792	18565	18171	17726	17246	16739	16155	15552	14880	3
90-94	23623	23299	22764	22131	21502	20805	19994	19133	18202	10
95≤	12172	12013	11688	11352	10969	10570	10158	9697	9243	6

B)

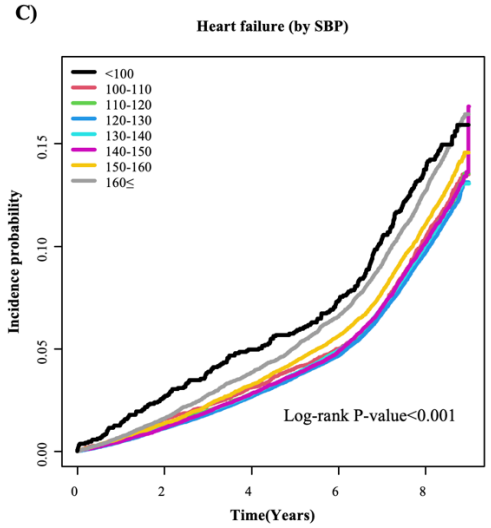


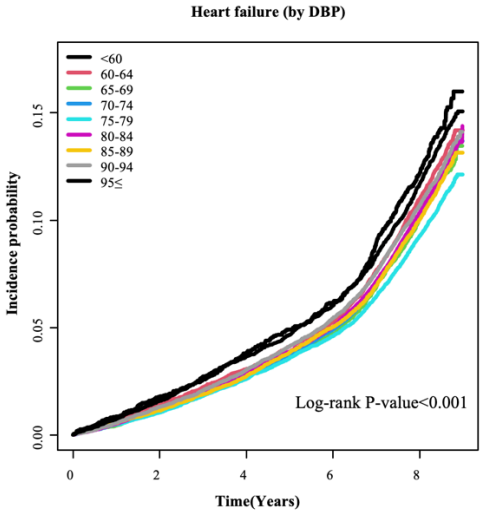


SBP	Baseline	1 year	2 year	3 year	4 year	5 year	6 year	7 year	8year	9year
<100	1932	1867	1774	1683	1602	1527	1459	1385	1309	0
100-109	8612	8401	8110	7852	7549	7280	6983	6673	6339	1
110-119	32551	31849	30871	29898	28882	27825	26715	25575	24431	5
120-129	46530	45742	44509	43181	41782	40271	38761	37229	35565	9
130-139	70892	69550	67622	65478	63292	61059	58688	56194	53600	14
140-149	30001	29414	28553	27676	26716	25761	24690	23581	22446	7
150-159	19351	18934	18389	17732	17128	16449	15744	15066	14337	5
160≤	15694	15309	14720	14131	13525	12950	12318	11681	11014	10

DBP	Baseline	1 year	2 year	3 year	4 year	5 year	6 year	7 year	8year	9year
<60	3486	3394	3287	3166	3037	2898	2776	2635	2498	0
60-64	15631	15274	14792	14298	13773	13244	12718	12112	11457	1
65-69	14266	14027	13651	13273	12885	12475	12028	11566	11103	0
70-74	48346	47360	46036	44533	43027	41433	39775	38089	36350	5
75-79	24501	24073	23434	22778	22048	21278	20468	19656	18781	2
80-84	64746	63518	61579	59584	57536	55471	53231	50968	48587	25
85-89	18792	18423	17932	17390	16765	16165	15493	14844	14174	3
90-94	23623	23126	22414	21610	20851	20054	19200	18323	17388	9
95≤	12172	11871	11423	10999	10554	10104	9669	9191	8703	6

C)

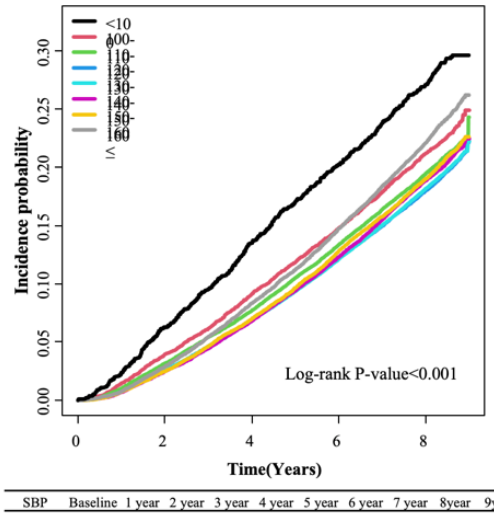


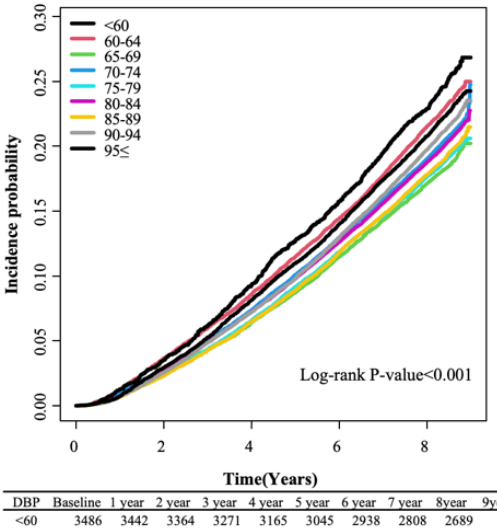


SBP	Baseline	1 year	2 year	3 year	4 year	5 year	6 year	7 year	8year	9year
<100	1932	1866	1779	1702	1624	1555	1473	1379	1289	0
100-109	8612	8435	8173	7951	7654	7375	7095	6738	6298	1
110-119	32551	32070	31206	30319	29421	28361	27243	25877	24319	5
120-129	46530	45988	44912	43759	42458	41007	39498	37674	35501	9
130-139	70892	70031	68445	66605	64700	62539	60181	57287	53876	12
140-149	30001	29669	28979	28228	27356	26446	25387	24080	22574	8
150-159	19351	19102	18667	18132	17571	16955	16241	15422	14440	5
160≤	15694	15482	15043	14523	13983	13430	12772	12011	11160	11

DBP	Baseline	1 year	2 year	3 year	4 year	5 year	6 year	7 year	8year	9year
<60	3486	3417	3322	3209	3081	2945	2818	2645	2474	0
60-64	15631	15352	14882	14445	13977	13447	12903	12197	11349	1
65-69	14266	14099	13772	13437	13065	12658	12189	11610	10961	0
70-74	48346	47644	46526	45234	43862	42306	40648	38647	36311	6
75-79	24501	24230	23706	23108	22440	21683	20890	19955	18846	2
80-84	64746	63986	62365	60635	58788	56798	54599	51907	48711	24
85-89	18792	18579	18189	17729	17215	16659	16008	15263	14370	3
90-94	23623	23332	22774	22126	21448	20671	19782	18755	17560	10
95≤	12172	12004	11668	11296	10891	10501	10053	9489	8875	5

D)





SBP	Baseline	1 year	2 year	3 year	4 year	5 year	6 year	7 year	8year	9year
<100	1932	1888	1812	1748	1672	1605	1542	1474	1409	0
100-109	8612	8488	8274	8082	7828	7593	7340	7074	6786	1
110-119	32551	32218	31517	30780	30040	29129	28204	27217	26220	5
120-129	46530	46181	45328	44401	43326	42131	40861	39567	38165	9
130-139	70892	70358	69103	67593	66034	64258	62297	60219	57999	14
140-149	30001	29794	29260	28672	27958	27182	26310	25352	24341	10
150-159	19351	19205	18871	18448	17996	17482	16877	16300	15669	5
160≤	15694	15574	15240	14836	14386	13931	13378	12805	12222	11

DBP	Baseline	1 year	2 year	3 year	4 year	5 year	6 year	7 year	8year	9year
<60	3486	3442	3364	3271	3165	3045	2938	2808	2689	0
60-64	15631	15442	15061	14694	14291	13841	13378	12863	12270	1
65-69	14266	14151	13905	13649	13351	13021	12630	12224	11823	0
70-74	48346	47872	46971	45905	44781	43468	42078	40660	39160	6
75-79	24501	24330	23903	23436	22892	22258	21594	20927	20185	2
80-84	64746	64269	63006	61599	60073	58409	56573	54646	52621	27
85-89	18792	18669	18361	17998	17578	17123	16576	16027	15447	3
90-94	23623	23447	23018	22477	21924	21307	20571	19796	18970	10
95≤	12172	12084	11816	11531	11185	10839	10471	10057	9646	6