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FULL RESEARCH PAPER
Heart failure and cardiomyopathies

Reduction in blood pressure for elevated blood pressure/stage 1 hypertension according to the American College of Cardiology/American Heart Association guideline and cardiovascular outcomes

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Aims Few studies have examined the relationship of blood pressure (BP) change in adults with elevated BP or stage 1 hypertension according to the American College of Cardiology (ACC)/American Heart Association (AHA) guideline with cardiovascular outcomes. We sought to identify the effect of BP change among individuals with elevated BP or stage 1 hypertension on incident heart failure (HF) and other cardiovascular diseases (CVDs).

Methods and results We conducted a retrospective cohort study including 616 483 individuals (median age 46 years, 73.7% men) with elevated BP or stage 1 hypertension based on the ACC/AHA BP guideline. Participants were categorized using BP classification at one-year as normal BP ($n = 173\,558$), elevated BP/stage 1 hypertension ($n = 367\,454$), or stage 2 hypertension ($n = 75\,471$). The primary outcome was HF, and the secondary outcomes included (separately) myocardial infarction (MI), angina pectoris (AP), and stroke. Over a mean follow-up of 1097 ± 908 days, 10 544 HFs, 1317 MIs, 11 070 APs, and 5198 strokes were recorded. Compared with elevated BP/stage 1 hypertension at one-year, normal BP at one-year was associated with a lower risk of developing HF [hazard ratio (HR): 0.89, 95% CI:0.85–0.94], whereas stage 2 hypertension at one-year was associated with an elevated risk of developing HF (HR:1.43, 95% CI:1.36–1.51). This association was also present in other cardiovascular outcomes including MI, AP, and stroke. The relationship was consistent in all subgroups stratified by age, sex, baseline BP category, and overweight/obesity.

Conclusion A one-year decline in BP was associated with the lower risk of HF, MI, AP, and stroke, suggesting the importance of lowering BP in individuals with elevated BP or stage 1 hypertension according to the ACC/AHA guideline to prevent the risk of developing CVD.

Keywords Stage 1 Hypertension • Elevated Blood Pressure • Heart Failure • Epidemiology

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Introduction

The inclusive blood pressure (BP) values for elevated BP and stage 1 hypertension were defined in the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) BP guideline.[1] Several epidemiological studies reported that stage 1 hypertension increased the risk of cardiovascular disease (CVD) events in the general population.[2,3] Further, it was found that not only stage 1 hypertension but also elevated BP increases the risk of developing CVD.[4] Most CVD events occur in individuals with BP <140/90 mmHg,[5] and therefore, the management of elevated BP and stage 1 hypertension is important from a public health perspective. Accordingly, the 2017 ACC/AHA BP guideline suggests lowering BP for individuals having elevated BP and stage 1 hypertension.[1] However, whether lowering BP is beneficial for individuals with elevated BP and stage 1 hypertension has not been established in public health practice. Here, we sought to examine whether a one-year change in BP is associated with incident CVD among individuals with elevated BP or stage 1 hypertension, using a nationwide population-based dataset. Specifically, we focused on the risk of developing heart failure (HF) as a primary clinical outcome, given its continued increase in prevalence and costs to the healthcare system. We analyzed atherosclerotic CVD events, including myocardial infarction (MI), angina pectoris (AP), and stroke separately as secondary outcomes.

Methods

Study design and data source

We performed a retrospective cohort study using the JMDC Claims Database (JMDC Inc., Tokyo, Japan), which is a health check-up and insurance claims database, between January 2005 and April 2020.[4,6] The JMDC Claims Database includes the records of individuals' health check-up records, including data on BP, body mass index, medical history, current medications, and insurance claims data, including the diagnosis of CVD events according to the International Classification of Diseases, 10th Revision (ICD-10) coding. We extracted data on 2 135 455 adults who underwent the health check-up including physical examination and blood tests, more than 1 year after insurance enrolment (1-year look-back period) and had available BP data 1 year later. In this study, we sought to exclude people having a history of CVD or taking BP-lowering medications from our primary analysis and therefore set a look-back period. In this cohort, 978 380 adults had normal BP, 288 419 had elevated BP, 420 456 had stage 1 hypertension, and 448 200 had stage 2 hypertension (individuals taking BP-lowering medications were categorized in stage 2 hypertension). Among 708 875 individuals having elevated BP or stage 1 hypertension, we excluded individuals with CVD ($n = 16\,833$), those with prior history of renal disease or dialysis ($n = 63$), those who developed CVD within 1 year after the initial health check-up ($n = 6971$), those with missing data on cigarette smoking ($n = 59\,894$), and those taking BP-lowering medications at 1 year after the initial health check-up ($n = 8631$). To uncover the association of non-modified BP at 1 year after the initial health check-up with a subsequent CVD risk, we excluded people taking BP-lowering medications at 1 year after the initial health check-up, which could influence BP values. Finally, we analyzed 616 483 participants in this study (see Supplementary material online, *Figure S1*; *Figure 1*).

Ethics

The Ethical Committee of the University of Tokyo approved this study (number: 2018-10862), and we conducted this study in accordance with the Declaration of Helsinki. Because all of the data included in the JMDC Claims Database were anonymized and deidentified after combining individual's health check-up and insurance claims records, the requirement for informed consent was waived. This database is available for anyone who purchases it from the JMDC Inc (http://www.jmdc.co.jp/en).

Measurements and definitions

Health check-up measures were collected using standardized protocols, and the following data were obtained: BP, body mass index, history of CVD or dialysis, medication status, and fasting blood levels of glucose, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. Experienced healthcare professionals measured the BP at least twice after the participant had been in a resting condition using a mercury or aneroid sphygmomanometer or a validated automated device, and the average BP values were recorded according to the recommendations of the Ministry of Health, Labour and Welfare, and the Japanese Society of CVD Prevention.[4] Detailed BP measurement methods are summarized in the Supplementary Material. Consistent with the 2017 ACC/AHA BP guideline, we defined normal BP as systolic BP (SBP) of <120 mmHg and diastolic BP (DBP) of <80 mmHg, elevated BP as SBP of 120–129 mmHg and DBP of <80 mmHg, stage 1 hypertension as SBP of 130–139 mmHg or DBP of 80–89 mmHg, and stage 2 hypertension as SBP of ≥140 mmHg or DBP of ≥90 mmHg. We defined overweight/obesity as a body mass index of ≥25 kg/m^2. We defined diabetes mellitus as fasting glucose of ≥126 mg/dL or use of glucose-lowering medications. We defined dyslipidaemia as low-density lipoprotein cholesterol of ≥140 mg/dL or high-density lipoprotein cholesterol of <40 mg/dL or triglyceride of ≥150 mg/dL or use of lipid-lowering medications.[7] Information on cigarette smoking (current or non-current) was self-reported.

Outcomes

We collected data on outcomes that occurred between January 2005 and April 2020. We defined incident HF as the primary outcome and MI, AP, and stroke (separately) as secondary outcomes. ICD-10 codes used in this study are summarized in Supplementary Material online.

Statistical analysis

Continuous variables are presented as median (quartile 1 and quartile 3), and categorical variables are presented as numbers (percentages). We categorized study participants by BP category at one-year after the initial health check-up (normal BP, elevated BP/stage 1 hypertension, and stage 2 hypertension at 1 year). We calculated the statistical significance of differences between the three groups using analysis of variance for continuous variables and chi-square tests for categorical variables. We conducted Cox regression analysis to identify the association of each BP category at 1 year after the initial health check-up and subsequent incidence of HF and other CVD events. We set the elevated BP or stage 1 hypertension group as reference. Model 1 included BP categories alone (unadjusted model). Model 2 included BP categories, age, and sex, and we conducted the multivariable Cox regression analyses (forced entry model). Further, as Model 3, we added conventional CVD risk factors, including body mass index, SBP, diabetes mellitus, dyslipidaemia, and cigarette smoking at baseline to Model 2, and we performed the multivariable Cox regression analyses (forced entry model).

We performed eight sensitivity analyses to confirm the robustness of our findings. First, we analyzed the association of change in SBP or DBP (as continuous value) with incident CVD. Second, we evaluated the BP change from the initial health check-up to 1 year after the initial health check-up using a restricted cubic spline regression model. We used five cutoff points for change in BP (5, 27.5, 50, 72.5, and 95 percentiles), with the reference point set at ±0 mmHg (no change in BP). We fitted three cubic spline models using 3, 4, and 5 knots. We selected the model with five knots since it had the lowest Akaike's information criterion. Third, we adjusted the association

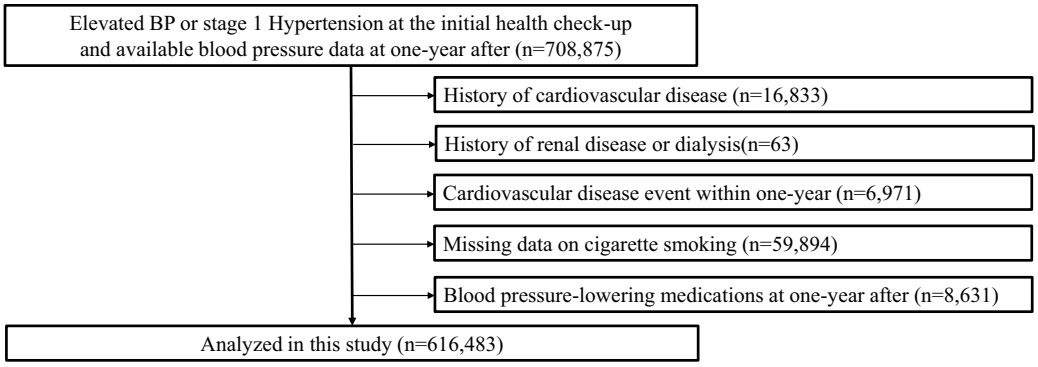


Figure 1 Flowchart. Among 708 875 individuals having elevated blood pressure or stage 1 hypertension, we excluded individuals with cardiovascular disease ($n = 16\,833$), those with prior history of renal disease or dialysis ($n = 63$), those who developed cardiovascular disease within 1 year after the initial health check-up ($n = 6971$), those with missing data on cigarette smoking ($n = 59\,894$), and those taking blood pressure-lowering medications at 1 year after the initial health check-up ($n = 8631$). Finally, we analyzed 616 483 participants.

of BP categories with incident CVD for parameters at 1 year after the initial health check-up. Fourth, because death should be considered a competing risk with CVD events, we conducted Fine and Gray's proportional subhazards model as a competing risks analysis, as previously described.[4] Fifth, we included individuals taking BP-lowering medications at 1 year after the initial health check-up and analyzed the relationship between BP categories at 1 year and incident CVD. Sixth, we examined the relationship of BP categories with incident HF stratified by age, sex, BP category at baseline (elevated BP or stage 1 hypertension), and overweight/obesity. Seventh, we categorized study participants into four groups by BP category at 1 year after the initial health check-up (normal BP, elevated BP, stage 1 hypertension, and stage 2 hypertension at one-year). Eighth, we divided study participants into two groups using BP values at baseline according to the European guideline [normal BP (SBP of 120–129 mmHg and/or DBP of 80–84 mmHg) or high normal BP (SBP of 130–139 mmHg and/or DBP of 85–89 mmHg)][8] and examined the association of change in SBP or DBP (as continuous value) with incident HF.

The null hypothesis was rejected for (two-tailed) values of $P < 0.05$. Statistical analyses were performed using STATA v17 (StataCorp LLC, College Station, TX, USA).

Results

Clinical characteristics

The clinical characteristics of the study participants are presented in *Table 1*. Overall, median age was 46 (40–53) years, and 454 586 (73.7%) were men. We categorized study participants into three groups according to BP categories at one-year after the initial health check-up: normal BP ($n = 173\,558$), elevated BP ($n = 131\,370$) or stage 1 hypertension ($n = 236\,084$), and stage 2 hypertension ($n = 75\,471$). The median age and the proportion of men increased with increasing BP category. The prevalence of overweight/obesity, diabetes mellitus, dyslipidaemia, and cigarette smokers also increased with increasing BP category.

BP category at one-year and risk of heart failure

During a mean follow-up of 1097 ± 908 days, 10 544 HF events were recorded. The cumulative incidence of HF was lowest in normal BP group at 1 year after initial health check-up, followed by the elevated BP/stage 1 hypertension group, and the stage 2 hypertension group (*Figure 2*). The incidence rates for HF events were lowest in the normal BP group [43.9 (42.2–45.8) per 10000 person-years], followed by the elevated BP/stage 1 hypertension group [55.9 (54.5–57.3) per 10000 person-years], and the stage 2 hypertension group [92.8 (88.8–96.9) per 10000 person-years]. In an unadjusted model, compared with elevated BP/stage 1 hypertension at 1 year, normal BP was associated with a lower incidence of HF [hazard ratio (HR) 0.79, 95% CI 0.75–0.82], and stage 2 hypertension was associated with a higher incidence of HF (HR 1.67, 95% CI 1.59–1.75). After multivariable adjustment, the HRs (95% CI) for HF events were 0.89 (95% CI, 0.85–0.94) for normal BP and 1.43 (95% CI, 1.36–1.51) for stage 2 hypertension (*Figure 3*).

BP category at one-year and risk of myocardial infarction, angina pectoris, and stroke

During a follow-up, 1317 MI, 11 070 AP, and 5198 stroke events were recorded. The cumulative incidence of MI, AP, and stroke was lowest in those with normal BP at 1 year, followed by the elevated BP/stage 1 hypertension category, and the stage 2 hypertension category (*Figure 2*). The incidence rates for MI, AP, and stroke events were lowest in the normal BP category, followed by elevated BP/stage 1 hypertension, and stage 2 hypertension. After multivariable adjustment, compared with the elevated BP/stage 1 hypertension category at 1 year, normal BP was associated with a lower risk for developing MI, AP, or stroke, whereas stage 2 hypertension was associated with a higher risk for developing MI, AP, or stroke (*Figure 3*).

Sensitivity analyses

Change in SBP or DBP per 1-SD decrease was associated with lower risk of developing HF and other CVD events (see Supplementary material online, *Table S1*). The restricted cubic spline model showed that the risk of developing HF increased with change in SBP linearly. The risk of developing HF was nearly constant while DBP was decreasing, but increased as DBP increased (*Figure 4*). Third, adjusting the association of BP categories with incident HF for parameters at 1 year

Table 1 Clinical characteristics

	Overall	Blood pressure category at 1 year after the initial health check-up			*P* value
		Normal blood pressure (*n* = 173 558)	Elevated blood pressure/stage1 hypertension (*n* = 367 454)	Stage 2 hypertension (*n* = 75 471)	
Blood pressure at the initial health check-up					
Systolic blood pressure, mmHg	126 (122–130)	123 (121–127)	126 (122–131)	130 (125–134)	<0.001
Diastolic blood pressure, mmHg	79 (74–83)	76 (71–81)	80 (74–83)	83 (79–86)	<0.001
Elevated blood pressure, *n* (%)	249 177 (40.4)	99 888 (57.6)	137 705 (37.5)	11 584 (15.3)	<0.001
Stage 1 hypertension, *n* (%)	367 306 (59.6)	73 670 (42.4)	229 749 (62.5)	63 887 (84.7)	<0.001
Blood pressure at 1 year after					
Systolic blood pressure, mmHg	124 (117–131)	113 (108–116)	126 (122–131)	141 (136–146)	<0.001
Diastolic blood pressure, mmHg	78 (72–84)	70 (66–74)	80 (75–83)	91 (87–94)	<0.001
Age, years	46 (40–53)	44 (39–51)	46 (40–53)	49 (43–55)	<0.001
Men, *n* (%)	454 586 (73.7)	118 963 (68.5)	277699 (75.6)	57 924 (76.8)	<0.001
Overweight/obesity, *n* (%)	184 927 (30.0)	38 861 (22.4)	116 811 (31.8)	29 255 (38.8)	<0.001
Body mass index, kg/m^2	23.2 (21.2–25.5)	22.5 (20.6–24.7)	23.4 (21.4–25.7)	24.0 (21.9–26.5)	<0.001
Diabetes mellitus, *n* (%)	19 102 (3.1)	4037 (2.3)	11 746 (3.2)	3319 (4.4)	<0.001
Dyslipidaemia, *n* (%)	284 988 (46.2)	70 948 (40.9)	174 026 (47.4)	40 014 (53.0)	<0.001
Cigarette Smoking, *n* (%)	175 716 (28.5)	47 645 (27.5)	105 182 (28.6)	22 889 (30.3)	<0.001
Laboratory data					
Glucose, mg/dL	93 (87–100)	92 (86–98)	93 (87–100)	95 (89–102)	<0.001
Low-density lipoprotein cholesterol, mg/dL	123 (103–145)	120 (101–142)	124 (104–145)	127 (107–148)	<0.001
High-density lipoprotein cholesterol, mg/dL	59 (50–71)	60 (51–72)	59 (49–70)	58 (49–70)	<0.001
Triglycerides, mg/dL	92 (64–137)	85 (60–126)	94 (66–139)	102 (71–150)	<0.001

Data are reported as medians (interquartile range) or numbers (percentage), where appropriate.

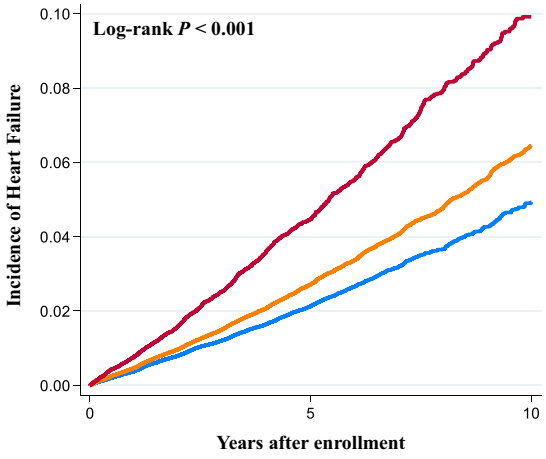
after the initial health check-up did not change the primary results (see Supplementary material online, *Table S2*). The relationship of BP categories with the risk of developing HF was unchanged in the Fine and Gray's proportional subhazards model as a competing risks analysis (see Supplementary material online, *Table S3*). Inclusion of 8631 individuals taking BP-lowering medications one-year after the initial health check-up did not change the primary results (see Supplementary material online, *Table S4*). The association between BP categories and incident HF was present irrespective of age, sex, BP category at baseline, and the presence of overweight/obesity (see Supplementary material online, *Table S5*). The risk of developing HF increased with BP category, and HR of elevated BP, stage 1 hypertension, and stage 2 hypertension for HF compared with normal BP at one-year after the initial heath check-up were 1.04 (95% CI 0.97–1.10), 1.17 (95% CI 1.11–1.23), and 1.62 (95% CI 1.52–1.72), respectively (see Supplementary material online, *Table S6*). Change in SBP or DBP per 1-SD decrease was associated with lower risk of developing HF in both participants with normal BP (see Supplementary material online, *Table S7*) and high normal BP (see Supplementary material online, *Table S8*) according to the European guideline.

Discussion

The current study used data from a nationwide population-based database, including a general population of more than 600 000 adults having elevated BP or stage 1 hypertension with no history of CVD. We found that reduction in BP in individuals with elevated BP or stage 1 hypertension was associated with the lower risk of developing HF, MI, AP, and stroke, whereas an increase in BP was associated with the higher risk of developing HF, MI, AP, and stroke. This is the first large-scale epidemiological analysis demonstrating the potential benefit of reduction in BP for elevated BP or stage 1 hypertension according to the 2017 ACC/AHA BP guideline in a general population.

Defining stage 1 hypertension and elevated BP was a bold revision in the 2017 ACC/AHA BP guideline and has great public health implications. After the publication of this guideline, several epidemiological studies including our own showed the clinical significance of stage 1 hypertension or elevated BP.[2–4] This guideline also recommended lowering BP for individuals with stage 1 hypertension or elevated BP. Although it is well known that BP-lowering treatment would benefit people having BP of ≥140/90 mmHg, clinical evidence supporting the effect of lowering BP for stage 1 hypertension or elevated BP is still accruing.[9] Based on the new guideline recommendations, the number of patients diagnosed with hypertension increased substantially.[10,11] In addition, if individuals with elevated BP are also included among those to be treated, individuals requiring BP-lowering treatment would further increase. From this point of view, whether reduction in BP can benefit people having elevated BP or stage 1 hypertension is a crucial issue in the field of preventive

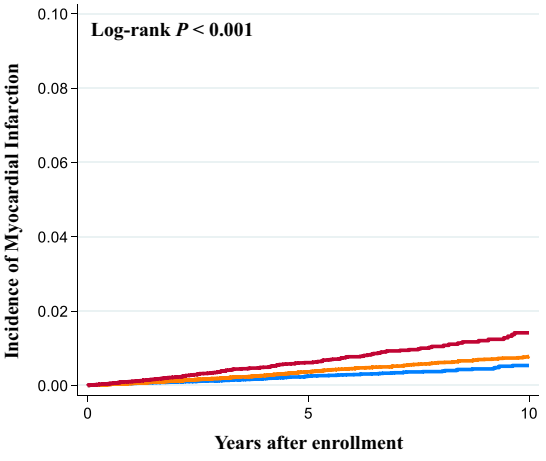
A Heart Failure



Category of BP at one-year after
Stage 2 Hypertension
Elevated Blood Pressure/Stage 1 Hypertension
Normal Blood Pressure

Numbers at risk							
Category		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
Stage 2 Hypertension	75,471	56,536	41,199	25,328	20,723	13,493	1,556
Elevated Blood Pressure /Stage 1 Hypertension	367,454	274,469	201,362	131,632	109,206	72,156	8,056
Normal BP	173,558	127,641	94,100	61,984	51,472	33,385	3,611
Y, year.							

B Myocardial Infarction



Category of BP at one-year after
Stage 2 Hypertension
Elevated Blood Pressure/Stage 1 Hypertension
Normal Blood Pressure

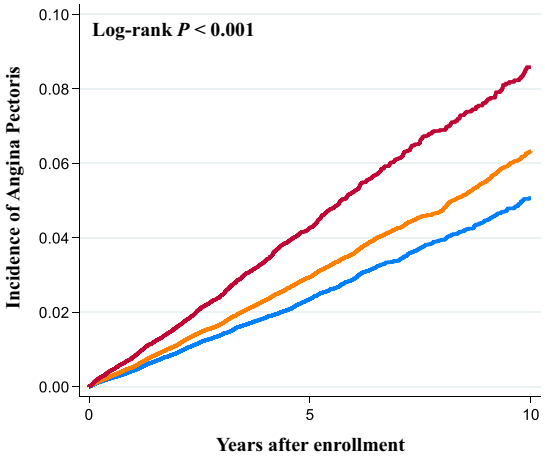
Numbers at risk							
Category		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
Stage 2 Hypertension	75,471	56,913	41,786	25,850	21,361	33,899	1,685
Elevated Blood Pressure /Stage 1 Hypertension	367,454	275,623	203,059	133,157	110,947	73,630	8,445
Normal BP	173,558	128,046	94,748	62,558	52,116	13,964	3,727
Y, year.							

Figure 2 Kaplan–Meier Curves. Kaplan–Meier curves for heart failure (*A*), myocardial infarction (*B*), angina pectoris (*C*), and stroke (*D*).

cardiology, and results of the present study using a large-scale epidemiological database support the validity of this recommendation, providing great public health value.

Three randomized trials have shown the clinical efficacy of BP-lowering treatment on the development of stage 2 hypertension among people with elevated BP or stage 1 hypertension.[12–14] In the

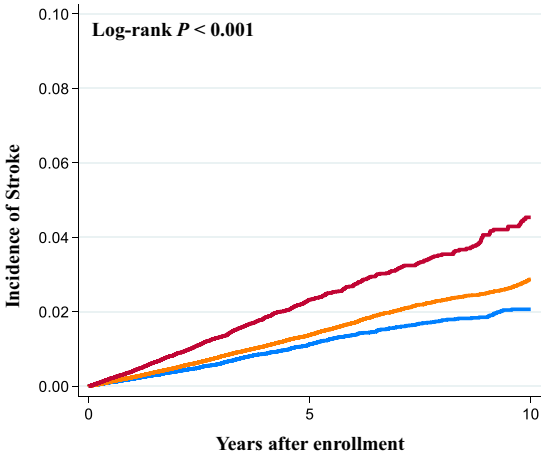
C Angina Pectoris



Category of BP at one-year after
Stage 2 Hypertension
Elevated Blood Pressure/Stage 1 Hypertension
Normal Blood Pressure

Numbers at risk							
Category		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
Stage 2 Hypertension	75,471	56,503	41,187	25,307	20,742	13,468	1,555
Elevated Blood Pressure /Stage 1 Hypertension	367,454	274,271	200,967	131,167	108,662	71,733	7,993
Normal BP	173,558	127,530	93,934	61,759	51,246	33,177	3,556
Y, year.							

D Stroke



Category of BP at one-year after
Stage 2 Hypertension
Elevated Blood Pressure/Stage 1 Hypertension
Normal Blood Pressure

Numbers at risk							
Category		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
Stage 2 Hypertension	75,471	56,730	41,502	25,604	21,072	13,733	1,643
Elevated Blood Pressure /Stage 1 Hypertension	367,454	275,078	202,238	132,405	110,124	72,971	8,305
Normal BP	173,558	127,851	94,455	62,271	51,780	33,622	3,671
Y, year.							

Figure 2 Continued

Prevention of Hypertension in Patients with PreHypertension trial, the combination of low doses thiazide diuretic and a potassium-sparing agent prevented developing stage 2 hypertension in people having stage 1 hypertension or elevated BP.[12] Use of this combination decreased left ventricular mass assessed through Sokolow-Lyon voltage and voltage-duration product compared with the placebo group, suggesting the potential impact of preventing progression to stage 2 hypertension on decreased risk for

	Number	Events	Incidence	Model 1	Model 2	Model 3
Heart Failure						
Normal Blood Pressure	173,558	2,286 (1.3)	43.9 (42.2-45.8)	0.79 (0.75-0.82)	0.86 (0.82-0.90)	0.89 (0.85-0.94)
Elevated Blood Pressure/ Stage 1 Hypertension	367,454	6,213 (1.7)	55.9 (54.5-57.3)	1 [Reference]	1 [Reference]	1 [Reference]
Stage 2 Hypertension	75,471	2,045 (2.7)	92.8 (88.8-96.9)	1.67 (1.59-1.75)	1.48 (1.41-1.56)	1.43 (1.36-1.51)
Myocardial Infarction						
Normal Blood Pressure	173,558	252 (0.1)	4.8 (4.2-5.4)	0.69 (0.60-0.79)	0.79 (0.68-0.91)	0.84 (0.73-0.97)
Elevated Blood Pressure/ Stage 1 Hypertension	367,454	785 (0.2)	7.0 (6.5-7.5)	1 [Reference]	1 [Reference]	1 [Reference]
Stage 2 Hypertension	75,471	280 (0.4)	12.5 (11.1-14.0)	1.79 (1.56-2.05)	1.56 (1.36-1.78)	1.46 (1.27-1.67)
Angina Pectoris						
Normal Blood Pressure	173,558	2,501 (1.4)	48.2 (46.3-50.1)	0.80 (0.77-0.84)	0.87 (0.83-0.91)	0.89 (0.85-0.93)
Elevated Blood Pressure/ Stage 1 Hypertension	367,454	6,656 (1.8)	60.1 (58.6-61.5)	1 [Reference]	1 [Reference]	1 [Reference]
Stage 2 Hypertension	75,471	1,913 (2.5)	86.8 (83.0-90.8)	1.45 (1.38-1.52)	1.31 (1.24-1.37)	1.28 (1.21-1.35)
Stroke						
Normal Blood Pressure	173,558	1,127 (0.6)	21.6 (20.3-22.9)	0.79 (0.73-0.84)	0.87 (0.81-0.93)	0.89 (0.83-0.96)
Elevated Blood Pressure/ Stage 1 Hypertension	367,454	3,067 (0.8)	27.4 (26.5-28.4)	1 [Reference]	1 [Reference]	1 [Reference]
Stage 2 Hypertension	75,471	1,004 (1.3)	45.1 (42.4-47.9)	1.65 (1.53-1.77)	1.43 (1.33-1.53)	1.39 (1.29-1.49)

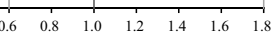


Figure 3 Association between blood pressure category at 1 year after the initial health check-up and the risk for heart failure, myocardial infarction, angina pectoris, and stroke event. Relationship of blood pressure category at one-year after the initial health check-up with the risk of heart failure, myocardial infarction, angina pectoris, and stroke is summarized. The incidence rate (95% confidence interval) per 10000 person-years is presented. Hazard ratios (95% confidence intervals) are shown. Model 1 is unadjusted. Model 2 includes adjustment for age and sex. Model 3 includes adjustment for age, sex, body mass index, systolic blood pressure, diabetes mellitus, dyslipidaemia, and cigarette smoking at baseline.

subsequent CVD among adults with stage 1 hypertension or elevated BP. Trial of Preventing Hypertension study demonstrated that angiotensin-receptor blocker therapy reduces the risk for developing stage 2 hypertension among people having stage 1 hypertension.[13] Similarly, the PHARAO study: prevention of hypertension with the angiotensin converting enzyme inhibitor ramipril in patients with high-normal blood pressure demonstrated that use of an angiotensin converting enzyme inhibitor for adults with high-normal office BP could lower the risk of developing hypertension compared to a control group.[14] However, these studies used surrogate markers as study endpoints, and to our knowledge there have been no reports of the relationship of BP-lowering with incident CVD events among people with elevated BP or stage 1 hypertension. An analysis of the Chinese Multi-provincial Cohort Study, including 5529 participants ≥35 years old with stage 1 hypertension at baseline did not show the clinical benefit of lowering BP in stage 1 hypertension.[15] Our study differs from preceding studies in that we demonstrated robust results in people with elevated BP or stage 1 hypertension with BP-lowering over a period of only 1 year, resulting in a significant reduction in subsequent HF, MI, AP, and stroke.

This study has clinical implications. Our study demonstrates the potential clinical benefit of lowering BP in individuals having elevated BP or stage 1 hypertension from the perspective of primary prevention of HF, MI, AP, and stroke. This result was present irrespective of participants' clinical background (e.g. age, sex, baseline BP category, overweight/obesity). Further, our results did not change after including participants taking BP-lowering medications at 1 year. Therefore, we may need to consider more aggressive BP-lowering treatment (non-pharmacologic and/or pharmacologic) for adults with elevated BP or stage 1 hypertension. Regarding pharmacologic treatment, the SPRINT trial clearly demonstrated that intensive BP lowering (targeting SBP <120 mmHg) resulted in a lower rate of MI and all-cause mortality, compared with standard BP lowering (targeting SBP <140 mmHg), in individuals with increased CVD risk and SBP ≥130 mmHg (mean SBP 139.7 mmHg).[16] Similarly, the STEP study examined old Chinese patients (60–80 years of age) with hypertension (mean SBP 146.1 mmHg), and reported that intensive BP treatment (targeting SBP 110 to <130 mmHg) resulted in a lower incidence of CVD events than standard treatment (targeting SBP <150 mmHg).[17] Although these two randomized trials support the benefit of intensive pharmacologic intervention for patients with hypertension (mainly stage 2 hypertension), whether pharmacologic treatment would benefit individuals with elevated BP or stage 1 hypertension remains to be clarified. Further investigations are warranted to establish the optimal BP lowering strategy for adults with elevated BP or stage 1 hypertension. Particularly, we need to clarity whether the use of BP-lowering medications would improve the clinical outcomes for people having elevated BP or stage 1 hypertension. Although a randomized trial would be needed to identify the effects and safety of BP lowering treatment for individuals with elevated BP or stage 1 hypertension, conducting such a trial would not be easy because the incidence of CVD in the elevated BP or stage 1 hypertension category is relatively low, and such a study would require a large sample size and long follow-up period. Given this background, utilizing real-world data including administrative claims data is a practical alternative.

Strengths of this study include the use of a large, nationwide, longitudinal dataset with a high retention of study participants

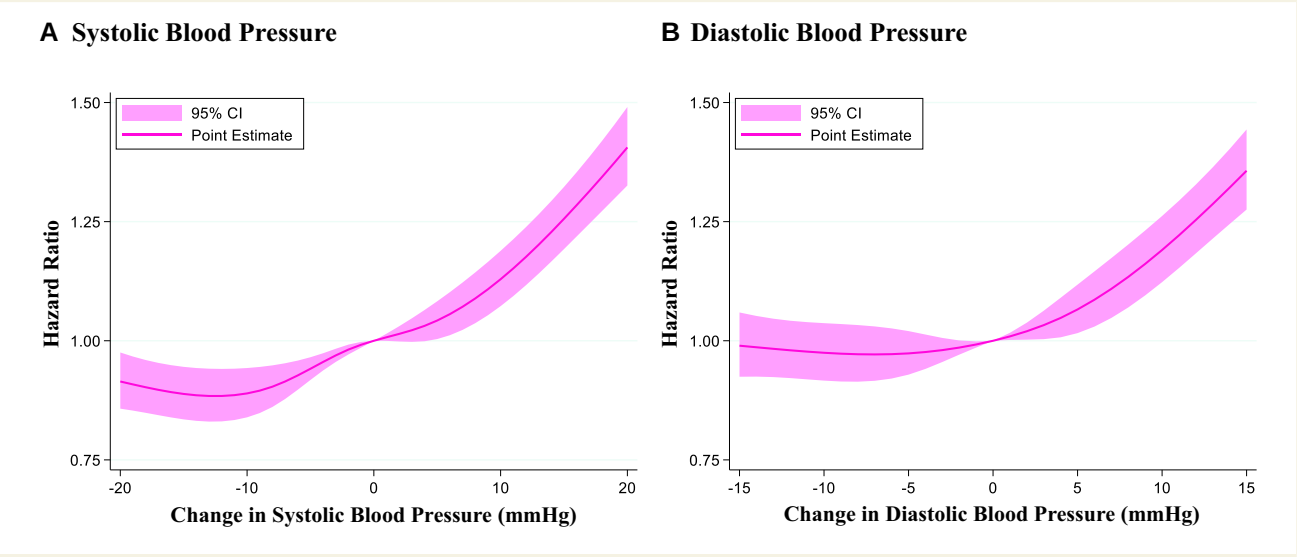


Figure 4 Restricted cubic spline. Restricted cubic spline shows the relationship of changes in systolic blood pressure (*A*) and diastolic blood pressure (*B*) with the risk of developing heart failure.

because of electronic linkage to insurance claims records. Because the JMDC Claims Database is capable of tracking an individual as long as he/she remains under the coverage of the same insurance, clinical diagnosis data (including HF, MI, AP, and stroke) can be obtained even if he/she visits multiple medical providers. We confirmed the robustness of our primary results through various sensitivity analyses.

We acknowledge several limitations to this study, and most limitations are attributed to the characteristics of the JMDC Claims Database as we previously described.[4,6] First, the BP measurements taken on a single occasion (i.e. during a health check-up) may not fully represent the BP phenotype of the study participants. Second, experienced healthcare professionals measured BP at health check-ups according to the methods recommended by the Japanese Ministry of Health, Labour and Welfare.[4] However, adherence to this BP measurement protocol may be limited on a nationwide scale. Third, diagnoses recorded in administrative databases are sub-optimally validated. Although our data on the incidence of CVD from the JMDC Claims Database are comparable to other epidemiological data in Japan,[18,19] there remains uncertainty regarding the CVD diagnoses in our dataset due to the nature of administrative claims database. Diagnoses recorded in inpatient and outpatient settings were included in our dataset. Unfortunately, we are unable to distinguish completely diagnoses made in the inpatient and outpatient settings using the JMDC Claims Database. Fourth, because this dataset primarily includes an employed population, we should acknowledge the possibility of selection bias. Further investigations are required to clarify whether results of the present study can be replicated in other populations. Fifth, data on the cause of death and the aetiology of HF were not available. Sixth, clinical characteristics of study participants were different among normal BP, elevated BP/stage 1 hypertension, and stage 2 hypertension at one-year (e.g. age, co-morbidities). Although we conducted multivariable analyses, these differences could have influenced the study results. Seventh, the BP and medication status could change during the observational period which could have influenced the clinical course of study participants.

In conclusion, our analysis of a nationwide population-based dataset demonstrates the association of a reduction in BP with a lower risk of developing HF, MI, AP, and stroke in adults having elevated BP or stage 1 hypertension. The optimal management strategy for individuals with elevated BP and stage 1 hypertension needs to be established.

Authorship

H.K., Y.Y., A.O., A.J.V., J.L., S.O., R.M.C., H.Y., and I.K. contributed to the conception and design of this study. Y.S., A.O., H.I., S.M., N.M., T.J., and H.Y. analyzed all data. H.K., Y.Y., A.O., A.J.V., J.L., S.O., R.C., C.S.P.L., R.M.C., K.F., N.T., H.M., K.N., H.Y., and I.K. interpreted the results. H.K., Y.Y., N.T., H.M., A.J.V., J.L., S.O., C.S.P.L., and R.M.C. drafted the manuscript. N.T., H.M., H.Y., and I.K. contributed to the critical revision for important intellectual content. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Data availability

The JMDC Claims Database is available for purchase from JMDC Inc. (https://www.jmdc.co.jp/en/index).

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