The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2022; 29: 1487-1498. http://doi.org/10.5551/jat.63262

Incorporation of Retinal Arteriolosclerosis into Risk Stratification of Blood Pressure Category According to the 2017 ACC/AHA Blood Pressure Guideline

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Aim: We investigated whether retinal arteriolosclerosis (RA) could be used for cardiovascular disease (CVD) risk stratification of individuals categorized according to the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) Blood Pressure (BP) guideline.

Methods: We studied 291,522 participants without a history of CVD and not taking any BP-lowering medications from the JMDC Claims Database. RA was defined as Keith–Wagener–Barker system grade ≥ 1. Each participant was classified into one of the six groups: (1) normal or elevated BP without RA, (2) normal or elevated BP with RA, (3) stage 1 hypertension without RA, (4) stage 1 hypertension with RA, (5) stage 2 hypertension without RA, and (6) stage 2 hypertension with RA.

Results: Median (interquartile range) age was 46 (40–53) years, and 141,397 (48.5%) of the participants were men. During a mean follow-up of 1,223 ± 830 days, 527 myocardial infarction (MI), 5,718 angina pectoris, 2,890 stroke, and 5,375 heart failure (HF) events occurred. Multivariable Cox regression analyses revealed that the risk of CVD increased with BP category, and this association was pronounced by the presence of RA. Compared with normal or elevated BP without RA, the hazard ratios (HRs) for MI (HR 1.17, 95% CI 0.93–1.47) were higher in stage 1 hypertension without RA. The HRs for MI further increased in stage 1 hypertension with RA (1.86 [1.17–2.95]). This association was present in stroke and HF.

Conclusion: Incorporation of the assessment for RA may facilitate the CVD risk stratification of people classified based on the 2017 ACC/AHA BP guideline, particularly for those categorized in stage 1 hypertension.

See editorial vol. 29: 1430-1431

Key words: Retinal arteriolosclerosis, Hypertension, Cardiovascular disease, Risk

Non-standard Abbreviations and Acronyms: ACC = American College of Cardiology, AHA = American Heart Association, AP = Angina Pectoris, BP = Blood Pressure, CI = Confidence Interval, CVD = Cardiovascular Disease, HF = Heart Failure, HR = Hazard Ratio, MI = Myocardial Infarction, RA = Retinal arteriolosclerosis

Introduction

High blood pressure (BP) and hypertension are associated with a greater risk of cardiovascular disease (CVD)[1-3]. Current epidemiological data show that most of CVD events occur in individuals with BP < 140/90 mmHg[4]. The Systolic Blood Pressure Intervention Trial demonstrated that intensive BP control that targeted systolic BP (SBP) <120 mmHg significantly reduced the risk of subsequent CVD events compared with standard BP control that targeted SBP <140 mmHg[5]. Taking these data into consideration, the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) BP guidelines lowered the BP threshold for hypertension from SBP and diastolic BP (DBP) of 140/90 mmHg to SBP/DBP of 130/80 mmHg[6]. The 2017 ACC/AHA BP guideline newly defines stage 1 hypertension as 130–139/80–89 mmHg and suggests a 10-year predicted atherosclerotic CVD risk to assess the individual's CVD risk and to determine the management strategy[6, 7]. However, this risk assessment is known to overestimate the CVD risk[8]. Further, the risk of heart failure (HF), which is currently increasing its clinical importance, cannot be assessed by these equations. Atherosclerosis is a key factor of the pathology for various CVDs, and therefore, detecting changes associated with atherosclerosis, such as increase in carotid intima media thickness or coronary artery calcium, is known to help identify population at a high risk of future CVD, including HF[9-12]. Retinal arteriolosclerosis (RA), assessed using the Keith–Wagener–Barker system, is also an established marker of atherosclerosis and is reported to be associated with incident CVD events[13-15]. Furthermore, the assessment of RA is widely used for the screening of atherosclerosis in the general population because of its simplicity and low invasiveness. Therefore, RA could be used as a marker of atherosclerosis, which could stratify the CVD risk of the general population classified using the 2017 ACC/AHA BP guideline. In this study, we aimed to clarify whether RA could help identify people at a high risk of future CVD among the general population classified based on the 2017 ACC/AHA BP guideline using a nationwide epidemiological database.

Methods

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

Study Population

This study is an observational analysis using the JMDC Claims Database (JMDC Inc., Tokyo, Japan), a nationwide health claims database, conducted between January 2005 and April 2020 [16-22]. The JMDC Claims Database includes the employed population and their family members (e.g., their spouse or children). Detailed information on this database is described elsewhere[23]. The JMDC Claims Database includes health insurance claims records of more than 60 insurers. It also contains the workplace employees' annual health check-up data, including demographics, medical history, medications, and hospital claims recorded using the International Classification of Diseases, 10th Revision (ICD-10) coding. We extracted the records of 373,700 individuals with available retinography and BP data at health check-up. We excluded the records of individuals aged <20 years (n=519), taking BP-lowering medications (n=40,209), with missing data on BP-lowering medications (n=5,625), with history of CVD or hemodialysis (n=9,692), and with missing data on body mass index (n=157), waist circumference (n=8,076), lipid profile and fasting plasma glucose (n=17,833), medications for dyslipidemia or diabetes (n=16), and cigarette smoking (n=51), leaving a final analytic sample of 291,522 participants **(Fig. 1)**.

Ethics

We conducted this study according to the ethical guidelines of our institution (approval by the Ethics Committee of the University of Tokyo: 2018-10862) and in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because all data from the JMDC Claims Database were de-identified.

BP Classification According to the 2017 ACC/AHA Guidelines

In the Japanese health check-up system, BP was measured according to the recommended protocol of the Japanese Ministry of Health, Labour and Welfare

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Received: September 15, 2021 Accepted for publication: November 3, 2021

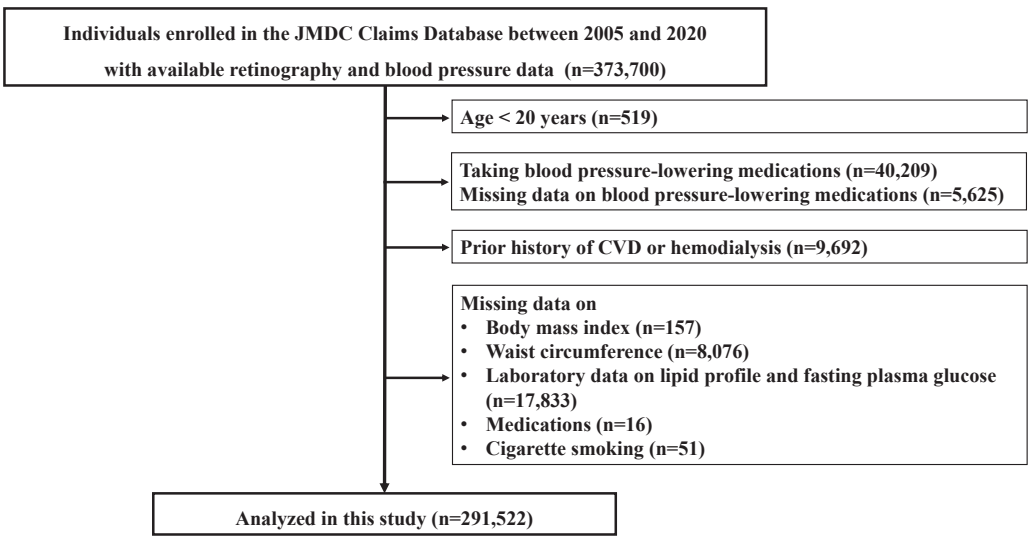


Fig. 1. Flowchart

We extracted the records of 373,700 individuals with available retinography and BP data. We excluded the records of individuals aged <20 years (n=519), taking BP-lowering medications (n=40,209), with missing data on BP-lowering medications (n=5,625), with history of CVD or hemodialysis (n=9,692), and with missing data on body mass index (n=157), waist circumference (n=8,076), lipid profile and fasting plasma glucose (n=17,833), medications for dyslipidemia or diabetes (n=16), and cigarette smoking (n=51), leaving a final analytic sample of 291,522 participants.

by healthcare professionals using a standard sphygmomanometer or an automated device on the right arm after participants had rested for 5 min in a seated position. The measurements were performed twice at an interval of ≥ 1 min, and the average of two measurements on a single occasion was used for analyses. The participants were categorized as having normal BP, elevated BP, stage 1 hypertension, or stage 2 hypertension. The normal BP group included participants with untreated SBP <120 mm Hg and untreated DBP <80 mm Hg. The elevated BP group included participants with untreated SBP of 120–129 mm Hg and untreated DBP <80 mm Hg. The stage 1 hypertension group included participants with untreated SBP of 130–139 mmHg or untreated DBP of 80–89 mmHg. The stage 2 hypertension group included participants with untreated SBP ≥ 140 mm Hg or untreated DBP ≥ 90 mm Hg[6].

Retinal Arteriolosclerosis

Nonmydriatic retinal photography of the right or left eye was conducted by experienced medical laboratory technicians. Retinal microvascular abnormalities were evaluated using the Keith–Wagener–Barker system, as previously described[24, 25]: normal; Keith–Wagener–Barker system grade 1, defined as mild or moderate generalized narrowing or sclerosis of the retinal arteries; Keith–Wagener–Barker system grade 2, defined as moderate to marked sclerosis of the retinal arteries, moderate focal narrowing of the retinal arteries, or arteriosclerotic retinopathy or thrombosis of the retinal veins; Keith–Wagener–Barker system grade 3, defined as angiospastic retinopathy that is characterized by edema, cotton-wool spots, and hemorrhages in the retina, in addition to marked sclerosis of the retinal arteries; and Keith–Wagener–Barker system grade 4, defined as measurable edema of the disks in addition to grade 3 findings. RA was defined as Keith–Wagener–Barker system grade ≥ 1.

Stratification Based on BP Classification and RA

Participants were classified into six groups: (1) normal BP or elevated BP without RA, (2) normal BP or elevated BP with RA, (3) stage 1 hypertension without RA, (4) stage 1 hypertension with RA, (5) stage 2 hypertension without RA, and (6) stage 2 hypertension with RA.

Other Measurements

Data, including body mass index, waist circumference, history of diabetes mellitus, dyslipidemia, and CVD, and fasting laboratory values were collected using standardized protocols across study centers. Information on cigarette smoking (current or non-current) was self-reported. Obesity was defined as body mass index (BMI) ≥ 25 kg/m^2 [26]. High waist circumference was defined as waist

circumference ≥ 85 cm for men and ≥ 90 cm for women[27]. Diabetes mellitus was defined as fasting blood glucose ≥ 126 mg/dL or use of glucose-lowering medications. Dyslipidemia was defined as low-density lipoprotein cholesterol ≥ 140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, triglycerides ≥ 150 mg/dL, or use of lipid-lowering medications.

Outcomes

Outcomes were collected between January 2005 and April 2020. The primary outcomes included myocardial infarction (MI) (ICD-10: I210, I211, I212, I213, I214, I219), AP (ICD-10: I200, I201, I208, I209), stroke (ICD-10: I630, I631, I632, I633, I634, I635, I636, I638, I639, I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I610, I611, I613, I614, I615, I616, I619, I629, G459), and HF (ICD-10: I500, I501, I509, I110). Each CVD event was analyzed separately. For example, if a participant had a stroke and then had an MI a month later, both the stroke and MI events were counted as separate outcomes. For an individual who left his/her insurance, we defined the last follow-up date as the date of leaving the insurance.

Statistical Analysis

Data are presented as median (interquartile range) for continuous variables or number (percentage) for categorical variables. *P* values were calculated using the analysis of variance for continuous variables and chi-squared tests for categorical variables. We conducted Cox regression analyses to assess the association of six groups stratified by BP classification and RA with subsequent risk for CVD outcomes. Hazard ratios (HRs) were calculated in an unadjusted model and after adjustment for potential confounders, including age, sex, obesity, high waist circumference, diabetes mellitus, dyslipidemia, and cigarette smoking. We conducted multiple imputation for missing data, as previously described[17, 28]. On the assumption of data missing at random, we imputed missing data using the chained equation method with 20 iterations, as described by Aloisio[29]. HRs and standard errors were obtained using Rubin's rules[30]. We conducted subgroup analyses stratified by age or sex. A *P*-value of <0.05 was considered statistically significant. Statistical analyses were performed using the SPSS software version 25 (IBM corp., Armonk, NY, USA) and STATA version 16 (StataCorp LLC, College Station, TX, USA).

Results

Clinical characteristics of the study participants are presented in **Table 1**. Overall, the median (interquartile range) age was 46 (40–53) years, and 141,397 (48.5%) of the participants were men. The participants were getting older with increasing BP classification, and those with RA. The prevalence of obesity, high waist circumference, diabetes mellitus, and dyslipidemia was higher in participants with advanced BP classification and RA.

The mean follow-up period of the overall study population was 1,223 ± 830 days. The mean ± SD follow-up period of each group was as follows: 1,223 ± 828 days for normal/elevated BP without RA, 1,252 ± 788 days for normal/elevated BP with RA, 1,231 ± 833 for stage 1 hypertension without RA, 1,237 ± 824 days for stage 1 hypertension with RA, 1,196 ± 852 days for stage 2 hypertension without RA, and 1,200 ± 824 days for stage 2 hypertension with RA. During the follow-up period, 527 MI, 5,718 AP, 2,890 stroke, and 5,375 HF events were recorded. Although there was no statistically significant difference in the incidence of MI between participants having normal or elevated BP without RA and those having stage 1 hypertension without RA, the incidence of MI was higher in participants having stage 1 hypertension with RA (HR 1.86, 95% confidence interval [CI] 1.17–2.95) compared with those having normal or elevated BP without RA. The risk of MI further increased in participants having stage 2 hypertension without RA (HR 2.04, 95% CI 1.61–2.59) and with RA (HR 2.54, 95% CI 1.77–3.65) **(Fig. 2A)**. The risk of AP was higher in both participants having stage 1 hypertension without and with RA compared with those having normal or elevated BP without RA. It was also higher in participants having stage 2 hypertension without RA (HR 1.44, 95% CI 1.33–1.56) and further increased in those having stage 2 hypertension with RA (HR 1.78, 95% CI 1.56–2.03) **(Fig. 2B)**. The risk of stroke was higher in participants having normal or elevated BP with RA (HR 1.34, 95% CI 1.12–1.61) than those having normal or elevated BP without RA. It was also higher in participants having stage 1 hypertension (HR 1.20, 95% CI 1.09–1.33) or stage 2 hypertension (HR 1.83, 95% CI 1.65–2.04) without RA. This association was pronounced in participants having stage 1 hypertension (HR 1.74, 95% CI 1.41–2.13) or stage 2 hypertension (HR 2.48, 95% CI 2.11–2.91) with RA **(Fig. 2C)**. The risk of HF was higher in participants having stage 1 hypertension (HR 1.28, 95% CI 1.19–1.37) or stage 2 hypertension (HR 1.91, 95% CI 1.76–2.06) without RA compared with those having normal or elevated BP without RA. This association was further stronger in participants having stage 1 hypertension

Table 1. Clinical Characteristics

	Blood Pressure Category according to the 2017 ACC/AHA Guideline						
	Normal Blood Pressure/Elevated Blood Pressure		Stage 1 Hypertension		Stage 2 Hypertension		
	Retinal arteriolosclerosis		Retinal arteriolosclerosis		Retinal arteriolosclerosis		
	(-)	(+)	(-)	(+)	(-)	(+)	P-value
Number	195,678	7,830	51,884	4,473	25,693	5,964	-----
Age, years	44 (40-51)	53 (47-60)	48 (42-55)	55 (48-61)	50 (44-57)	53 (48-60)	<0.001
Male sex, n (%)	82,875 (42.4)	3,950 (50.4)	32,144 (62.0)	2,961 (66.2)	15,661 (61.0)	3,806 (63.8)	<0.001
Body Mass Index, kg/m^2	21.4 (19.6-23.6)	22.1 (20.1-24.2)	23.3 (21.2-25.8)	23.5 (21.5-25.8)	24.2 (21.8-27.1)	24.4 (22.0-27.0)	<0.001
Obesity, n (%)	28,855 (14.7)	1,441 (18.4)	16,819 (32.4)	1,478 (33.0)	10,870 (42.3)	2,579 (43.2)	<0.001
Waist Circumference, cm	78 (72-84)	80 (74-86)	83 (77-90)	84 (79-90)	85 (79-93)	86 (80-93)	<0.001
High Waist Circumference, n (%)	33,581 (17.2)	1,869 (23.9)	19,208 (37.0)	1,800 (40.2)	11,825 (46.0)	2,892 (48.5)	<0.001
Systolic Blood Pressure, mmHg	109 (101-117)	112 (104-120)	128 (122-133)	130 (124-134)	144 (138-151)	148 (141-158)	<0.001
Diastolic Blood Pressure, mmHg	67 (61-72)	69 (63-74)	82 (80-85)	83 (80-86)	92 (89-97)	94 (90-101)	<0.001
Diabetes Mellitus, n (%)	3,791 (1.9)	457 (5.8)	2,429 (4.7)	363 (8.1)	1,859 (7.2)	644 (10.8)	<0.001
Dyslipidemia, n (%)	64,102 (32.8)	3,573 (45.6)	25,905 (49.9)	2,444 (54.6)	14,583 (56.8)	3,537 (59.3)	<0.001
Cigarette Smoking, n (%)	42,824 (21.9)	1,738 (22.2)	13,180 (25.4)	1,038 (23.2)	6,025 (23.4)	1,444 (24.2)	<0.001
Laboratory Data							
Glucose, mg/dL	91 (86-97)	94 (88-101)	95 (89-102)	97 (91-105)	97 (91-106)	99 (92-108)	<0.001
LDL-C, mg/dL	117 (97-139)	125 (104-145)	127 (106-148)	129 (108-150)	131 (109-153)	132 (110-154)	<0.001
HDL-C, mg/dL	65 (54-77)	63 (52-77)	60 (50-73)	60 (50-72)	60 (50-73)	60 (50-72)	<0.001
Triglycerides, mg/dL	72 (53-105)	83 (60-120)	95 (66-142)	98 (69-145)	105 (73-155)	108 (76-162)	<0.001

Data are expressed as median (interquartile range) or number (percentage). *P* values were calculated using chi-square tests for categorical variables and the analysis of variance for continuous variables. Normal blood pressure is defined as untreated systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg. Elevated blood pressure is defined as untreated systolic blood pressure 120-129 mm Hg and diastolic blood pressure <80 mm Hg. Stage 1 hypertension is defined as untreated systolic blood pressure 130-139 mm Hg or diastolic blood pressure 80-89 mm Hg. Stage 2 hypertension is defined as untreated systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg. Retinal arteriolosclerosis is defined as Keith-Wagener-Barker system grade ≥ 1. ACC; American College of Cardiology, AHA; American Heart Association, LDL-C; low-density lipoprotein cholesterol, HDL-C; high-density lipoprotein cholesterol.

(HR 1.45, 95% CI 1.22–1.72) or stage 2 hypertension (HR 2.27, 95% CI 2.00–2.57) with RA **(Fig. 2D)**.

After multiple imputation for missing data, we analyzed 317,655 participants. During a mean follow-up period of 1,255±854 days, 595 MI, 6,272 AP, 3,212 stroke, and 5,945 HF events were observed. The association of stratification based on BP classification and RA with incident CVD, including MI **(Fig. 3A)**, AP **(Fig. 3B)**, stroke **(Fig. 3C)**, and HF **(Fig. 3D)**, was similar to that in participants without multiple imputation, as presented in **Fig. 2**.

The results of subgroup analyses are summarized in **Table 2**. Compared with participants having normal or elevated BP without RA, the risk of CVD was generally higher in participants having stage 1 hypertension or stage 2 hypertension without RA, and this association was pronounced in those having stage 1 hypertension or stage 2 hypertension with RA who were aged ≥ 50 years **(Table 2A)**, aged <50 years **(Table 2B)**, men **(Table 2C)**, and women **(Table 2D)**. Further, in participants having normal or elevated BP, RA was associated with a higher incidence of stroke in those aged ≥ 50 years **(Table 2A)**, HF in those aged <50 years **(Table 2B)**, and stroke and HF in men **(Table 2C)**.

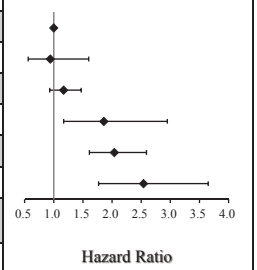
Discussion

The current analyses using a nationwide epidemiological database, including a general population of approximately 300,000 adults without prior history of CVD and not taking any BP-lowering mediations, revealed that the association between BP category based on the 2017 ACC/AHA BP guideline and future CVD events could be pronounced by the presence of RA assessed using the Keith–Wagener–Barker system.

According to the 2017 ACC/AHA BP guideline, approximately 30 million individuals are newly diagnosed with hypertension in the United States[31].

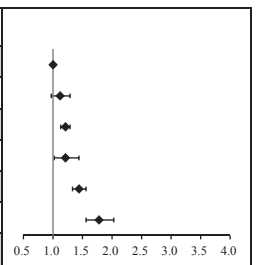
(A) Myocardial Infarction

BP Classification	RA	Number	No. of events	Incidence Rate (95% CI)	Model 1	Model 2	Model 3
Normal Blood Pressure /Elevated Blood Pressure	-	195678	241	3.7 (3.2-4.2)	1 [Ref]	1 [Ref]	1 [Ref]
	+	7830	15	5.6 (3.4-9.2)	1.53 (0.91-2.58)	0.98 (0.58-1.66)	0.94 (0.56-1.60)
Stage 1 Hypertension	-	51884	111	6.4 (5.3-7.6)	1.73 (1.38-2.16)	1.28 (1.02-1.60)	1.17 (0.93-1.47)
	+	4473	20	13.2 (8.6-20.4)	3.60 (2.28-5.67)	1.99 (1.25-3.16)	1.86 (1.17-2.95)
Stage 2 Hypertension	-	25693	104	12.4 (10.2-15.0)	3.38 (2.68-4.25)	2.31 (1.83-2.92)	2.04 (1.61-2.59)
	+	5964	36	18.4 (13.3-25.5)	5.04 (3.55-7.16)	2.97 (2.08-4.25)	2.54 (1.77-3.65)
P for trend					< 0.001	< 0.001	< 0.001



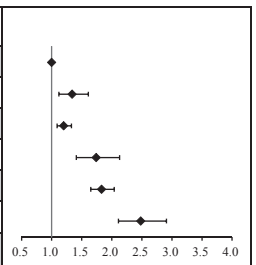
(B) Angina Pectoris

BP Classification	RA	Number	No. of events	Incidence Rate (95% CI)	Model 1	Model 2	Model 3
Normal Blood Pressure /Elevated Blood Pressure	-	195678	3101	47.9 (46.2-49.6)	1 [Ref]	1 [Ref]	1 [Ref]
	+	7830	203	77.0 (67.1-88.3)	1.61 (1.40-1.86)	1.14 (0.99-1.32)	1.12 (0.97-1.29)
Stage 1 Hypertension	-	51884	1228	71.4 (67.5-75.5)	1.49 (1.40-1.59)	1.29 (1.21-1.38)	1.21 (1.13-1.29)
	+	4473	135	90.6 (76.5-107.2)	1.89 (1.59-2.25)	1.29 (1.09-1.54)	1.21 (1.02-1.44)
Stage 2 Hypertension	-	25693	793	96.6 (90.1-103.5)	2.02 (1.87-2.18)	1.60 (1.48-1.73)	1.44 (1.33-1.56)
	+	5964	258	135.6 (120.0-153.2)	2.84 (2.50-3.22)	2.01 (1.77-2.29)	1.78 (1.56-2.03)
P for trend					< 0.001	< 0.001	< 0.001



(C) Stroke

BP Classification	RA	Number	No. of events	Incidence Rate (95% CI)	Model 1	Model 2	Model 3
Normal Blood Pressure /Elevated Blood Pressure	-	195678	1421	21.8 (20.7-23.0)	1 [Ref]	1 [Ref]	1 [Ref]
	+	7830	131	49.3 (41.5-58.5)	2.27 (1.90-2.72)	1.36 (1.13-1.63)	1.34 (1.12-1.61)
Stage 1 Hypertension	-	51884	574	33.1 (30.5-35.9)	1.52 (1.38-1.67)	1.23 (1.12-1.36)	1.20 (1.09-1.33)
	+	4473	101	67.5 (55.6-82.0)	3.10 (2.53-3.79)	1.78 (1.45-2.18)	1.74 (1.41-2.13)
Stage 2 Hypertension	-	25693	484	58.2 (53.3-63.7)	2.67 (2.41-2.96)	1.91 (1.72-2.12)	1.83 (1.65-2.04)
	+	5964	179	93.2 (80.5-107.9)	4.29 (3.67-5.01)	2.61 (2.22-3.05)	2.48 (2.11-2.91)
P for trend					< 0.001	< 0.001	< 0.001



(D) Heart Failure

BP Classification	RA	Number	No. of events	Incidence Rate (95% CI)	Model 1	Model 2	Model 3
Normal Blood Pressure /Elevated Blood Pressure	-	195678	2702	41.6 (40.0-43.2)	1 [Ref]	1 [Ref]	1 [Ref]
	+	7830	179	67.6 (58.4-78.3)	1.63 (1.40-1.90)	1.14 (0.98-1.33)	1.11 (0.95-1.30)
Stage 1 Hypertension	-	51884	1140	66.1 (62.4-70.0)	1.59 (1.48-1.70)	1.36 (1.27-1.46)	1.28 (1.19-1.37)
	+	4473	143	96.3 (81.7-113.4)	2.32 (1.96-2.74)	1.55 (1.31-1.84)	1.45 (1.22-1.72)
Stage 2 Hypertension	-	25693	921	112.3 (105.3-119.8)	2.70 (2.50-2.91)	2.11 (1.96-2.28)	1.91 (1.76-2.06)
	+	5964	290	153.0 (136.4-171.6)	3.69 (3.27-4.16)	2.57 (2.27-2.90)	2.27 (2.00-2.57)
P for trend					< 0.001	< 0.001	< 0.001

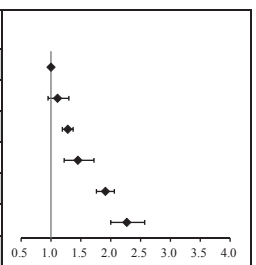
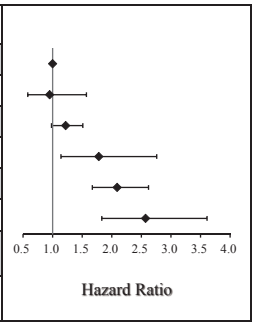


Fig. 2. The Frequency of Events, Corresponding Incidence Rates, and HRs for CVD Events

The incidence rate was per 10000 person-years. Unadjusted and adjusted hazard ratios (95% CI) are presented. Model 1 is unadjusted. Model 2 includes adjustment for age and sex. Model 3 includes adjustment for age, sex, obesity, high waist circumference, diabetes mellitus, dyslipidemia, and cigarette smoking. Each participant is classified into six groups: (1) normal BP or elevated BP without RA, (2) normal BP or elevated BP with RA, (3) stage 1 hypertension without RA, (4) stage 1 hypertension with RA, (5) stage 2 hypertension without RA, and (6) stage 2 hypertension with RA. (A) Myocardial infarction. (B) Angina pectoris. (C) Stroke. (D) Heart failure. Normal BP is defined as untreated systolic BP <120 mm Hg and diastolic BP <80 mm Hg. Elevated BP is defined as untreated systolic BP of 120–129 mm Hg and diastolic BP <80 mm Hg. Stage 1 hypertension is defined as untreated systolic BP of 130–139 mm Hg or diastolic BP of 80–89 mm Hg. Stage 2 hypertension is defined as untreated systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg. RA is defined as Keith–Wagener–Barker system grade ≥ 1. BP, blood pressure; RA, retinal arteriolosclerosis.

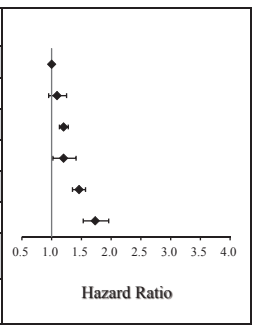
(A) Myocardial Infarction

BP Classification	RA	Number	No. of events	Incidence Rate (95% CI)	Model 1	Model 2	Model 3
Normal Blood Pressure /Elevated Blood Pressure	-	211996	265	3.6 (3.2-4.1)	1 [Ref]	1 [Ref]	1 [Ref]
	+	8521	17	5.7 (3.5-9.1)	1.56 (0.95-2.54)	1.00 (0.61-1.64)	0.95 (0.58-1.57)
Stage 1 Hypertension	-	57230	130	6.5 (5.5-7.7)	1.79 (1.45-2.20)	1.34 (1.08-1.65)	1.22 (0.98-1.51)
	+	4990	22	12.6 (8.3-19.0)	3.44 (2.23-5.32)	1.92 (1.23-2.98)	1.78 (1.14-2.76)
Stage 2 Hypertension	-	28402	120	12.6 (10.5-15.0)	3.45 (2.78-4.28)	2.39 (1.92-2.98)	2.09 (1.67-2.62)
	+	6516	41	18.7 (13.8-25.4)	5.15 (3.71-7.16)	3.05 (2.18-4.27)	2.57 (1.83-3.61)
P for trend					< 0.001	< 0.001	< 0.001



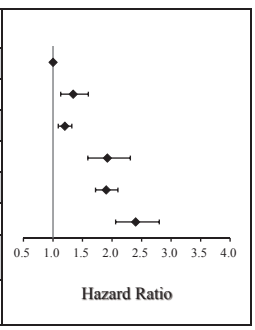
(B) Angina Pectoris

BP Classification	RA	Number	No. of events	Incidence Rate (95% CI)	Model 1	Model 2	Model 3
Normal Blood Pressure /Elevated Blood Pressure	-	211996	3369	46.9 (45.3-48.5)	1 [Ref]	1 [Ref]	1 [Ref]
	+	8521	219	74.0 (64.9-84.5)	1.58 (1.38-1.81)	1.11 (0.97-1.28)	1.09 (0.95-1.25)
Stage 1 Hypertension	-	57230	1359	69.2 (65.6-73.0)	1.48 (1.39-1.57)	1.29 (1.21-1.37)	1.20 (1.13-1.28)
	+	4990	153	88.6 (75.6-103.8)	1.89 (1.60-2.22)	1.28 (1.09-1.51)	1.20 (1.02-1.41)
Stage 2 Hypertension	-	28402	892	95.4 (89.4-101.9)	2.03(1.89-2.19)	1.62 (1.50-1.75)	1.46 (1.35-1.57)
	+	6516	280	131.1 (116.6-147.4)	2.79 (2.47-3.16)	1.96 (1.73-2.22)	1.73 (1.53-1.96)
P for trend					< 0.001	< 0.001	< 0.001



(C) Stroke

BP Classification	RA	Number	No. of events	Incidence Rate (95% CI)	Model 1	Model 2	Model 3
Normal Blood Pressure /Elevated Blood Pressure	-	211996	1552	21.5 (20.4-22.6)	1 [Ref]	1 [Ref]	1 [Ref]
	+	8521	145	48.6 (41.3-57.2)	2.27 (1.92-2.69)	1.36 (1.14-1.62)	1.34 (1.13-1.60)
Stage 1 Hypertension	-	57230	637	32.1 (29.7-34.7)	1.49 (1.36-1.64)	1.24 (1.13-1.36)	1.20 (1.09-1.32)
	+	4990	127	73.4 (61,7-87.4)	3.42 (2.85-4.09)	1.97 (1.64-2.37)	1.92 (1.59-2.31)
Stage 2 Hypertension	-	28402	556	58.8 (54.1-63.9)	2.73 (2.48-3.01)	1.99 (1.80-2.19)	1.90 (1.72-2.10)
	+	6516	195	90.5 (78.6-104.1)	4.21 (3.63-4.89)	2.55 (2.19-2.96)	2.40 (2.06-2.80)
P for trend					< 0.001	< 0.001	< 0.001



(D) Heart Failure

BP Classification	RA	Number	No. of events	Incidence Rate (95% CI)	Model 1	Model 2	Model 3
Normal Blood Pressure /Elevated Blood Pressure	-	211996	2948	40.9 (39.5-42.4)	1 [Ref]	1 [Ref]	1 [Ref]
	+	8521	197	66.4 (57.7-76.3)	1.63 (1.41-1.88)	1.12 (0.97-1.30)	1.10 (0.95-1.27)
Stage 1 Hypertension	-	57230	1268	64.4 (60.9-68.0)	1.57 (1.47-1.68)	1.36 (1.27-1.45)	1.27 (1.19-1.36)
	+	4990	164	95.3 (81.8-111.1)	2.33 (1.99-2.72)	1.55 (1.32-1.82)	1.45 (1.23-1.70)
Stage 2 Hypertension	-	28402	1038	111.2 (104.6-118.1)	2.71 (2.53-2.91)	2.14 (1.99-2.30)	1.92 (1.79-2.07)
	+	6516	330	155.6 (139.7-173.3)	3.80 (3.39-4.26)	2.62 (2.33-2.94)	2.31 (2.05-2.60)
P for trend					< 0.001	< 0.001	< 0.001

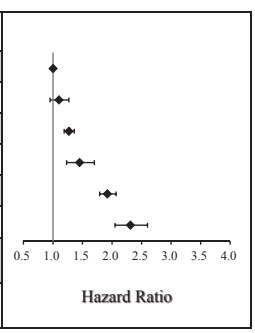


Fig. 3. The Frequency of Events, Corresponding Incidence Rates, and HRs for CVD Events After Multiple Imputation for Missing Data

The incidence rate was per 10000 person-years. Unadjusted and adjusted hazard ratios (95% CI) are presented. Model 1 is unadjusted. Model 2 includes adjustment for age and sex. Model 3 includes adjustment for age, sex, obesity, high waist circumference, diabetes mellitus, dyslipidemia, and cigarette smoking. Each participant is classified into six groups: (1) normal BP or elevated BP without RA, (2) normal BP or elevated BP with RA, (3) stage 1 hypertension without RA, (4) stage 1 hypertension with RA, (5) stage 2 hypertension without RA, and (6) stage 2 hypertension with RA. (A) Myocardial infarction. (B) Angina pectoris. (C) Stroke. (D) Heart failure. Normal BP is defined as untreated systolic BP <120 mm Hg and diastolic BP <80 mm Hg. Elevated BP is defined as untreated systolic BP of 120–129 mm Hg and diastolic BP <80 mm Hg. Stage 1 hypertension is defined as untreated systolic BP of 130–139 mm Hg or diastolic BP of 80–89 mm Hg. Stage 2 hypertension is defined as untreated systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg. RA is defined as Keith–Wagener–Barker system grade ≥ 1. BP, blood pressure; RA, retinal arteriolosclerosis.

Table 2. Subgroup Analysis

(A) Age ≥ 50 years									
		Myocardial Infarction		Angina Pectoris		Stroke		Heart Failure	
BP Classification	RA	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)
Normal BP/Elevated BP	(-)	109	1 [Reference]	1435	1 [Reference]	774	1 [Reference]	1281	1 [Reference]
	(+)	12	0.97 (0.53-1.77)	151	1.04 (0.88-1.24)	107	1.29 (1.06-1.59)	127	0.94 (0.78-1.12)
Stage 1 Hypertension	(-)	65	1.22 (0.90-1.67)	678	1.14 (1.03-1.25)	361	1.12 (0.99-1.28)	648	1.18 (1.07-1.30)
	(+)	14	1.65 (0.94-2.89)	112	1.26 (1.04-1.53)	75	1.50 (1.18-1.90)	112	1.32 (1.09-1.61)
Stage 2 Hypertension	(-)	58	1.81 (1.31-2.51)	450	1.23 (1.11-1.38)	327	1.67 (1.46-1.90)	514	1.53 (1.37-1.70)
	(+)	24	2.27 (1.45-3.56)	170	1.53 (1.30-1.80)	129	2.13 (1.77-2.58)	185	1.77 (1.51-2.07)
P for trend			<0.001		<0.001		<0.001		<0.001
(B) Age <50 years									
		Myocardial Infarction		Angina Pectoris		Stroke		Heart Failure	
BP Classification	RA	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)
Normal BP/Elevated BP	(-)	132	1 [Reference]	1666	1 [Reference]	647	1 [Reference]	1421	1 [Reference]
	(+)	3	0.82 (0.26-2.57)	52	1.26 (0.95-1.66)	24	1.40 (0.93-2.10)	52	1.51 (1.15-2.00)
Stage 1 Hypertension	(-)	46	1.09 (0.77-1.54)	550	1.26 (1.14-1.39)	213	1.29 (1.10-1.51)	492	1.37 (1.23-1.53)
	(+)	6	2.37 (1.04-5.41)	23	0.91 (0.60-1.38)	26	2.67 (1.80-3.97)	31	1.54 (1.07-2.20)
Stage 2 Hypertension	(-)	46	2.30 (1.61-3.29)	343	1.74 (1.54-1.97)	157	2.12 (1.76-2.55)	407	2.54 (2.26-2.85)
	(+)	12	3.06 (1.67-5.63)	88	2.41 (1.94-3.00)	50	3.62 (2.69-4.86)	105	3.58 (2.92-4.40)
P for trend			<0.001		<0.001		<0.001		<0.001
(C) Men									
		Myocardial Infarction		Angina Pectoris		Stroke		Heart Failure	
BP Classification	RA	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)
Normal BP/Elevated BP	(-)	159	1 [Reference]	1455	1 [Reference]	651	1 [Reference]	1287	1 [Reference]
	(+)	13	1.07 (0.60-1.90)	116	1.18 (0.98-1.43)	74	1.43 (1.12-1.82)	112	1.23 (1.01-1.49)
Stage 1 Hypertension	(-)	94	1.24 (0.96-1.61)	818	1.24 (1.14-1.35)	384	1.30 (1.14-1.47)	752	1.29 (1.17-1.41)
	(+)	17	1.84 (1.11-3.06)	91	1.19 (0.96-1.48)	74	1.93 (1.51-2.46)	106	1.52 (1.25-1.86)
Stage 2 Hypertension	(-)	89	2.19 (1.67-2.86)	521	1.52 (1.37-1.69)	333	2.12 (1.85-2.43)	605	1.98 (1.79-2.19)
	(+)	34	2.85 (1.94-4.17)	183	1.93 (1.65-2.26)	124	2.71 (2.22-3.30)	216	2.51 (2.17-2.91)
P for trend			<0.001		<0.001		<0.001		<0.001
(D) Women									
		Myocardial Infarction		Angina Pectoris		Stroke		Heart Failure	
BP Classification	RA	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)
Normal BP/Elevated BP	(-)	82	1 [Reference]	1646	1 [Reference]	770	1 [Reference]	1415	1 [Reference]
	(+)	2	0.57 (0.14-2.35)	87	1.04 (0.84-1.30)	57	1.26 (0.96-1.65)	67	0.97 (0.76-1.24)
Stage 1 Hypertension	(-)	17	1.08 (0.64-1.85)	410	1.16 (1.04-1.30)	190	1.10 (0.93-1.29)	388	1.29 (1.15-1.45)
	(+)	3	2.25 (0.70-7.25)	44	1.30 (0.96-1.76)	27	1.47 (1.00-2.17)	37	1.29 (0.93-1.80)
Stage 2 Hypertension	(-)	15	1.80 (1.01-3.22)	272	1.34 (1.17-1.53)	151	1.49 (1.24-1.79)	316	1.82 (1.60-2.07)
	(+)	2	1.05 (0.25-4.33)	75	1.55 (1.23-1.97)	55	2.22 (1.68-2.94)	74	1.81 (1.43-2.31)
P for trend			0.083		<0.001		<0.001		<0.001

Subgroup analyses are performed as follows: (A) Aged ≥ 50 years; (B) Age <50 years; (C) Men; (D) Women. Results of analyses are shown in tables (A, B, C, and D). HRs (95% CI) are adjusted for age, sex, obesity, high waist circumference, diabetes mellitus, dyslipidemia, and cigarette smoking in subgroups stratified by age (A, B), or for age, obesity, high waist circumference, diabetes mellitus, dyslipidemia, and cigarette smoking in subgroups stratified by sex (C, D). BP classification and the definition of RA are the same as in table 1. BP; blood pressure, RA; retinal arteriolosclerosis, HR; hazard ratio, CI; confidence interval.

Similarly, the analysis of the US National Health and Nutrition Examination Survey and China Health and Retirement Longitudinal Study reported that the prevalence of hypertension would increase by 26.8% in the USA and by 45.1% in China and that more than half of the population aged 45–75 years in both countries would be diagnosed with hypertension according to this guideline[32]. Due to the great clinical and epidemiological impact of this guideline, the accurate risk stratification of population classified using this guideline is essential for determining the management strategy with this guideline. Particularly, identifying the subpopulation at a higher risk of future CVD among the population categorized in stage 1 hypertension is important because the necessity of proactive BP-lowering efforts using pharmacological treatment would depend on the subsequent CVD risk of each individual.

Our results including population without a prevalent history of CVD indicated that subjects with RA defined as Keith–Wagener–Barker system grade ≥ 1 were associated with a greater risk of MI, AP, stroke, and HF than those without RA among participants with stage 1 or stage 2 hypertension. Furthermore, subjects with RA were associated with a higher incidence of stroke than those without RA even among participants categorized in the normal/elevated BP group. These results may suggest that detecting subclinical atherosclerosis would be helpful for identifying population at a high risk of future CVD.

Although our study is the first to suggest the potential benefit of the assessment of RA for CVD risk stratification of subjects classified using the 2017 ACC/AHA BP guideline, preceding studies focusing on coronary artery calcium yielded similar results. The analysis of Multi-Ethnic Study of Atherosclerosis (MESA), Coronary Artery Risk Development in Young Adults study, and Jackson Heart Study including 6,461 subjects revealed that coronary artery calcium score of >0 was associated with a higher incidence of CVD including MI and revascularization or resuscitated cardiac arrest due to cardiac causes in subjects categorized in elevated BP/stage 1 hypertension or stage 2 hypertension[33]. Similarly, McEvoy *et al.* reported that a higher coronary artery calcium score was associated with a higher CVD risk among participants with baseline low CVD risk and SBP of either 120–139 mmHg or 140–159 mmHg[34]. Uddin *et al.* also reported that an increase in coronary artery calcium score was associated with increased coronary heart disease and CVD mortality among hypertensive subjects[35].

A biomarker-based strategy is another option for facilitating BP management. The analysis of Atherosclerosis Risk in Communities Study, Dallas Heart Study, and MESA study including 12,987 subjects revealed that elevated biomarker (high-sensitivity cardiac troponin or N-terminal pro-B-type natriuretic peptide) was associated with a higher incidence of cardiovascular events defined as atherosclerotic CVD or HF in subjects with elevated BP or hypertension[36]. Similarly, Pokharel *et al.* reported that higher troponin T was associated with increasing cardiovascular events, including HF hospitalization, coronary heart disease, and stroke, across most SBP categories[37].

Taking our results and these previous studies into consideration, detecting subclinical atherosclerosis or measuring biomarker could be clinically useful strategies for identifying population at a high risk of future CVD. However, given that RA can be evaluated in a minimally invasive and inexpensive manner, the assessment of RA could be the most useful strategy for the risk stratification for subsequent CVD events in the general population. Further investigations are required to determine the optimal approach to facilitate the management strategy for people diagnosed with hypertension according to the 2017 ACC/AHA BP guideline.

The strengths of this study include the large nationwide longitudinal population-based database including the general population without a prior history of CVD, the fact that participants were not taking any BP-lowering medications at baseline, and the high ascertainment rate of the study participants. As previously described[38], since the JMDC Claims Database contains medical claims records using ICD-10 codes of employee health insurance, it is theoretically possible to track all clinical events, such as the onset of CVD, as long as he or she has the same insurance, even if he or she visits multiple healthcare providers or institutions.

This study has several limitations. Although we categorized study population using BP measurements at a health check-up, BP classification based on a single-visit assessment may not represent the BP phenotype of each individual. The Japanese Ministry of Health, Labour and Welfare recommends healthcare professionals to measure BP and to conduct nonmydriatic retinal photography using the standardized protocol[25]. However, in a real-world health check-up environment on a nationwide scale, adherence to the recommended protocols might be limited. Only data from the retinoscopy findings of one eye (right or left eye) were available. The risk of CVD could be different between Keith–Wagener–Barker system grade 1 and Keith–Wagener–Barker system grade 2 or higher. However, due to the limited

sample size, we could not analyze these subjects separately. Because the occurrence of CVD events was identified based on diagnostic codes registered in the JMDC Claims Database, uncertainty could remain regarding the accuracy of the diagnoses. Selection bias (e.g., healthy worker bias) might be present because the JMDC Claims Database obtained data mainly from an employed population of the working age. Therefore, further investigations are required to generalize our results. Although we conducted multivariable analyses, there could be unmeasured confounders or residual bias. For example, data on socioeconomic status could not be analyzed in this study.

Conclusion

Our analysis of a nationwide epidemiological database including adults not taking any BP-lowering medications and with no prevalent history of CVD revealed that the risk of CVD events increased depending on the BP category according to the 2017 ACC/AHA BP guideline, and this association was pronounced in participants with RA defined as Keith–Wagener–Barker system grade ≥ 1. The assessment of RA would be helpful for the CVD risk stratification of people classified based on the 2017 ACC/AHA BP guideline.

Source of Funding

This work was supported by grants from the Ministry of Health, Labour and Welfare, Japan (19AA2007 and H30-Policy-Designated-004) and the Ministry of Education, Culture, Sports, Science and Technology, Japan (17H04141). This study was funded by a grant from the Pfizer Health Research Foundation (in 2019).

Disclosures

Research funding and scholarship funds (Hidehiro Kaneko and Katsuhito Fujiu) from Medtronic Japan CO., LTD, Boston Scientific Japan CO., LTD, Biotronik Japan, Simplex QUANTUM CO., LTD, and Fukuda Denshi, Central Tokyo CO., LTD.

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