Journal of the American Heart Association

ORIGINAL RESEARCH

Association of Isolated Diastolic Hypertension Based on the Cutoff Value in the 2017 American College of Cardiology/American Heart Association Blood Pressure Guidelines With Subsequent Cardiovascular Events in the General Population

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BACKGROUND: The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines lowered the threshold of blood pressure (BP) for hypertension to 130/80 mm Hg. However, the clinical significance of isolated diastolic hypertension (IDH) according to the cutoff value of the 2017 ACC/AHA guidelines was uncertain.

METHODS AND RESULTS: We analyzed the claims database of Japan Medical Data Center (a nationwide epidemiological database). We excluded individuals who were aged <20 years, had systolic hypertension, were taking antihypertensive medication, or had prevalent cardiovascular disease, and studied 1746493 individuals (mean age, 42.9±10.7 years; 961 097 men [55.0%]). The average observational period was 1107±855 days. Stage 1 IDH, defined as diastolic BP 80 to 89 mm Hg, and stage 2 IDH, defined as diastolic BP ≥90 mm Hg, were found in 230513 (13.2%) and 16 159 (0.9%) individuals, respectively. Compared with individuals with normal diastolic BP, individuals with stage 1 and stage 2 IDH were older and more likely to be men. Prevalence of classic risk factors was higher in patients with IDH. Kaplan–Meier curves showed that stage 1 and stage 2 IDH were associated with a higher incidence of cardiovascular events, defined as myocardial infarction, angina pectoris, and stroke. Multivariable analysis showed that stage 1 (hazard ratio [HR], 1.17) and stage 2 (HR, 1.28) IDH were independently associated with a higher incidence of cardiovascular events. Subgroup analyses showed that the association of IDH with cardiovascular events was seen irrespective of age and sex.

CONCLUSIONS: The analysis of a nationwide epidemiological database showed that IDH based on the cutoff value in the 2017 ACC/AHA BP guidelines was associated with an elevated risk of subsequent cardiovascular events.

Key Words: cardiovascular disease ■ epidemiology ■ isolated diastolic hypertension ■ prevention

Hypertension is a major cause of cardiovascular disease (CVD)[1–3] and is diagnosed based on both systolic blood pressure (SBP) and diastolic blood pressure (DBP). The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for hypertension lowered the threshold of blood pressure (BP) from 140/90 mm Hg to 130/80 mm Hg.[4] However, the 2018 European Society

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Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.017963

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Our comprehensive analysis of a nationwide epidemiological database including individuals without prevalent cardiovascular disease (CVD) showed that stage 1 and stage 2 isolated diastolic hypertension (IDH) based on the cutoff value of diastolic blood pressure in the 2017 American College of Cardiology/American Heart Association guidelines independently increased the risk of subsequent CVD.
- The association of IDH and incident CVD was observed regardless of age and sex.
- This is the first large-scale epidemiological study demonstrating the association of IDH with incident CVD among the general population.

What Are the Clinical Implications?

- Our study suggests the potential clinical significance of IDH according to the cutoff value of diastolic blood pressure in the 2017 American College of Cardiology/American Heart Association guidelines in the development of CVD.
- Further studies are warranted to establish the optimal management strategy for IDH based on the latest American College of Cardiology/American Heart Association guidelines.

Nonstandard Abbreviations and Acronyms

ACC	American College of Cardiology
AHA	American Heart Association
BPLTTC	Blood Pressure Lowering Treatment Trialists' Collaboration
CARDIA	Coronary Artery Risk Development in Young Adults
DBP	diastolic blood pressure
IDH	isolated diastolic hypertension
JMDC	the Japan Medical Data Center
JPHC	Japan Public Health Center-based Prospective Study
SBP	systolic blood pressure
SPRINT	Systolic Blood Pressure Intervention Trial

of Cardiology/European Society of Hypertension guidelines for the management of arterial hypertension retained the cutoff value of BP for hypertension at 140/90 mm Hg.[5] Although several studies confirmed the validity of the updated ACC/AHA classification of BP,[6,7] lowering the threshold of diastolic BP to 80 mm Hg was based on expert opinion.[8] Further, there have been conflicting data regarding the influence of DBP on subsequent cardiovascular events.[9–14] Particularly, McEvoy et al[9] recently indicated that isolated diastolic hypertension (IDH) according to the cutoff value of DBP, which the 2017 ACC/AHA guidelines suggested was not significantly associated with an increased risk for cardiovascular events. Therefore, the cutoff value of DBP in the 2017 ACC/AHA guidelines is still under debate, and further investigation is warranted to verify the validity of these guidelines. In this study, we sought to explore the association of IDH based on the cutoff value of DBP, which the 2017 ACC/AHA guidelines indicated with the risk of subsequent cardiovascular events among the general population without a prevalent history of CVD using a nationwide epidemiological database.

METHODS

Study Design and Data Source

We conducted this retrospective observational analysis using the health claims database of the Japan Medical Data Center (JMDC; Tokyo, Japan), which has been described in detail in previous reports.[15–17] The JMDC collects data from >60 insurers and includes data for health insurance claims on insured individuals. More than 5 million individuals were registered in this database. Most individuals registered in the JMDC database are employees of relatively large companies in Japan. The JMDC database includes annual health checkup data including a questionnaire regarding medical history and status of medications and laboratory data. Data of clinical follow-up from the first health checkup obtained by claim records are also included in the JMDC database. This database is available for anyone who purchases it from the JMDC (https://www.jmdc.co.jp/en/index).

Ethics

This study was approved by the institutional review board of the University of Tokyo (2018-10862) in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because of the anonymous nature of the JMDC database.

Definition

Incidence of CVD including myocardial infarction, angina pectoris, and stroke was evaluated using the *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnosis codes recorded in the claim records of each individual.[18] The primary end point was defined as a composite end point including myocardial infarction, angina pectoris, and stroke.

Generally, healthcare professionals such as nurses measured the BP of resting individuals twice at health checkups according to the procedure recommended by the Ministry of Health, Labour and Welfare, and the Japanese Society of Cardiovascular Disease Prevention. The average of 2 measurements was recorded. We defined normal DBP as <80 mm Hg (and SBP <130 mmHg) stage 1 IDH as 80 mm Hg ≤ DBP <90 mm Hg (and SBP <130 mm Hg), and stage 2 IDH as DBP ≥90 mm Hg (and SBP <130 mm Hg). Obesity was defined as body mass index ≥25 kg/m^2 according to the criteria of the Japan Society for the Study of Obesity (http://www.jasso.or.jp/contents/english/index.html#e1).[19] Abdominal obesity was defined as a waist circumference ≥85 cm for men and ≥90 cm for women.[20] Diabetes mellitus was defined as a fasting glucose level ≥126 mg/dL or ongoing antidiabetic therapy. Dyslipidemia was defined as low-density lipoprotein cholesterol ≥140 mg/dL or high-density lipoprotein cholesterol <40 mg/dL or triglycerides ≥150 mg/dL or ongoing lipid-lowering therapy.

Statistical Analysis

We presented categorical and continuous data as number (percentage) and mean (SD). We compared categorical and continuous variables between groups using chi-square test and 1-way ANOVA. The long-term event rate was estimated using Kaplan–Meier curves and log-rank test to assess the differences in the event rate. We conducted multivariable Cox regression analysis including category of DBP, and established CVD risk factors at study entry (health checkup) including SBP, age, sex, obesity, high waist circumference, diabetes mellitus, dyslipidemia, and current cigarette smoking to identify the association of IDH with subsequent risk of composite end point. We additionally performed multivariable Cox regression analysis for heart failure, atrial fibrillation, and composite end point, defined as myocardial infarction, angina pectoris, and stroke. We performed multiple imputation for missing values (obesity, high waist circumference, diabetes mellitus, dyslipidemia, and current cigarette smoking), as previously described.[21] Multiple imputation is a statistical procedure to replace missing values in the original database with other plausible values by creating multiple filling-in patterns to avoid bias caused by missing values in the original database. Multiple imputation is considered as an alternative procedure to analyze incomplete data as well.[22] Using multiple imputation by chained equation method, we replaced each missing value with a set of substituted plausible values by creating 20 filled-in complete data sets.[23] We calculated hazard ratio and standard errors using Rubin rules. We also performed multivariable Cox regression analysis for the composite end point including population with all available measurements of confounding factors. The study population was divided into subgroups by age (≥50 years and 20–49 years) or sex. Incidence of composite end point was evaluated using Kaplan–Meier curves and log-rank (Mantel–Cox) test in each subgroup. A $P<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS software (version 25, SPSS Inc) and STATA (version 16, StataCorp LLC).

RESULTS

Study Population

We studied 2943563 individuals included in the JMDC database between January 2005 and August 2018. We excluded individuals with the following criteria: (1) age <20 years (n=36788), (2) prior history of CVD and hemodialysis (obtained from the information including the patients' questionnaire, recorded data on coronary artery revascularization, and recorded diagnosis of myocardial infarction, angina pectoris, and stroke before study enrollment) (n=101934), (3) taking antihypertensive medication (n=202303), (4) missing information about antihypertensive medication (n=391975), (5) missing data on BP (n=3028), and (6) SBP ≥130 mm Hg (n=461042). Finally, we included 1746493 individuals in this study. Of these, 1499821 individuals (85.9%) were classified as the normal DBP group, while 230513 individuals (13.2%) and 16159 individuals (0.9%) were classified as the stage 1 and stage 2 IDH groups, respectively. The average observational period was 1107±855 days.

Characteristics of the Study Population

Characteristics of the study population are shown in Table 1. Patients with IDH were older and more likely to be men. Patients with IDH had higher body mass index and waist circumference. SBP was higher in individuals with IDH. The prevalence of classic CVD risk factors such as dyslipidemia, diabetes mellitus, and current cigarette smoking were higher among those with high DBP.

IDH and CVD Events

The number of CVD events is shown in Table 2. The actual rate of primary outcome was overall 0.57 (per 100 patient-years). Actual rates of primary outcome of each group were 0.52 (per 100 patient-years) in the normal DBP group, 0.81 (per 100 patient-years) in the stage 1 IDH group, and 0.96 (per 100 patient-years) in the stage 2 IDH group. Kaplan–Meier curves and the log-rank test showed that the incidence of reaching the composite end point of

Table 1. Characteristics of the Study Population

	Missing	Normal DBP (1 499 821)	Stage 1 IDH (230 513)	Stage 2 IDH (16 159)	*P* Value
Age, y	0 (0.0)	42.3±10.8	46.8±9.2	47.9±8.1	<0.001
20–29	0 (0.0)	222 284 (14.8)	10 056 (4.4)	322 (2.0)	
30–39	0 (0.0)	301 871 (20.1)	28 899 (12.5)	1453 (9.0)	
40–49	0 (0.0)	603 724 (40.3)	103 223 (44.8)	7533 (46.6)	
50–59	0 (0.0)	277 066 (18.5)	67 678 (29.4)	5565 (34.4)	
≥60	0 (0.0)	94 876 (6.3)	20 657 (9.0)	1286 (8.0)	
Men	0 (0.0)	781 285 (52.1)	167 018 (72.5)	12 794 (79.2)	<0.001
Body mass index, kg/m^2	785 (0.0)	21.9±3.1	23.5±3.5	24.2±3.8	<0.001
Obesity	785 (0.0)	220 805 (14.7)	69 007 (29.9)	5944 (36.8)	<0.001
Waist circumference, cm	184 513 (10.6)	78.3±8.8	83.1±9.4	84.9±9.6	<0.001
High waist circumference	184 513 (10.6)	236 623 (17.8)	79 705 (36.4)	6945 (44.4)	<0.001
SBP, mm Hg	0 (0.0)	110.5±10.4	122.1±5.5	124.7±4.0	<0.001
Diabetes mellitus	353 033 (20.2)	26 517 (2.2)	8381 (4.3)	710 (5.1)	<0.001
Dyslipidemia	68 443 (3.9)	452 217 (31.5)	108 858 (48.0)	8687 (54.3)	<0.001
Current cigarette smoking	12 966 (0.7)	383 493 (25.8)	67 471 (29.4)	4691 (29.1)	<0.001
Laboratory data					
Glucose, mg/dL	355 924 (20.4)	91.4±13.6	95.9±17.4	97.9±17.8	<0.001
HbA_{1c}, %	343 510 (19.7)	5.4±0.5	5.5±0.6	5.6±0.7	<0.001
LDL-C, mg/dL	68 462 (3.9)	116.5±30.8	125.6±31.8	128.5±31.9	<0.001
HDL-C, mg/dL	63 352 (3.6)	64.9±16.4	61.6±16.6	60.3±16.4	<0.001
Triglycerides, mg/dL	63 678 (3.6)	92.3±68.6	121.8±96.4	137.6±113.6	<0.001

Data are expressed as mean±SD or number (percentage). DBP indicates diastolic blood pressure; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IDH, isolated diastolic hypertension; LDL-C, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

myocardial infarction, angina pectoris, and stroke increased with higher DBP (Figure 1). Multivariable Cox regression analysis after multiple imputation showed that high DBP was independently associated with reaching the composite end point (Table 3). Multivariable Cox regression analysis after multiple imputation showed that high DBP was independently associated with elevated risk of heart failure, atrial fibrillation, and composite end point including myocardial infarction and stroke (Tables S1 through S3). Multivariable Cox regression analysis including population with all available measurements of confounding factors also showed that high DBP was independently associated with higher incidence of composite end point including myocardial infarction, angina pectors, and stroke (Table S4).

Subgroup Analyses

Results of the subgroup analyses are shown in Figure 2. Kaplan–Meier curves and the log-rank test presented that the association of high DBP with the incidence of CVD was seen in individuals aged ≥50 years (Figure 2A), aged <50 years (Figure 2B), men (Figure 2C), and women (Figure 2D).

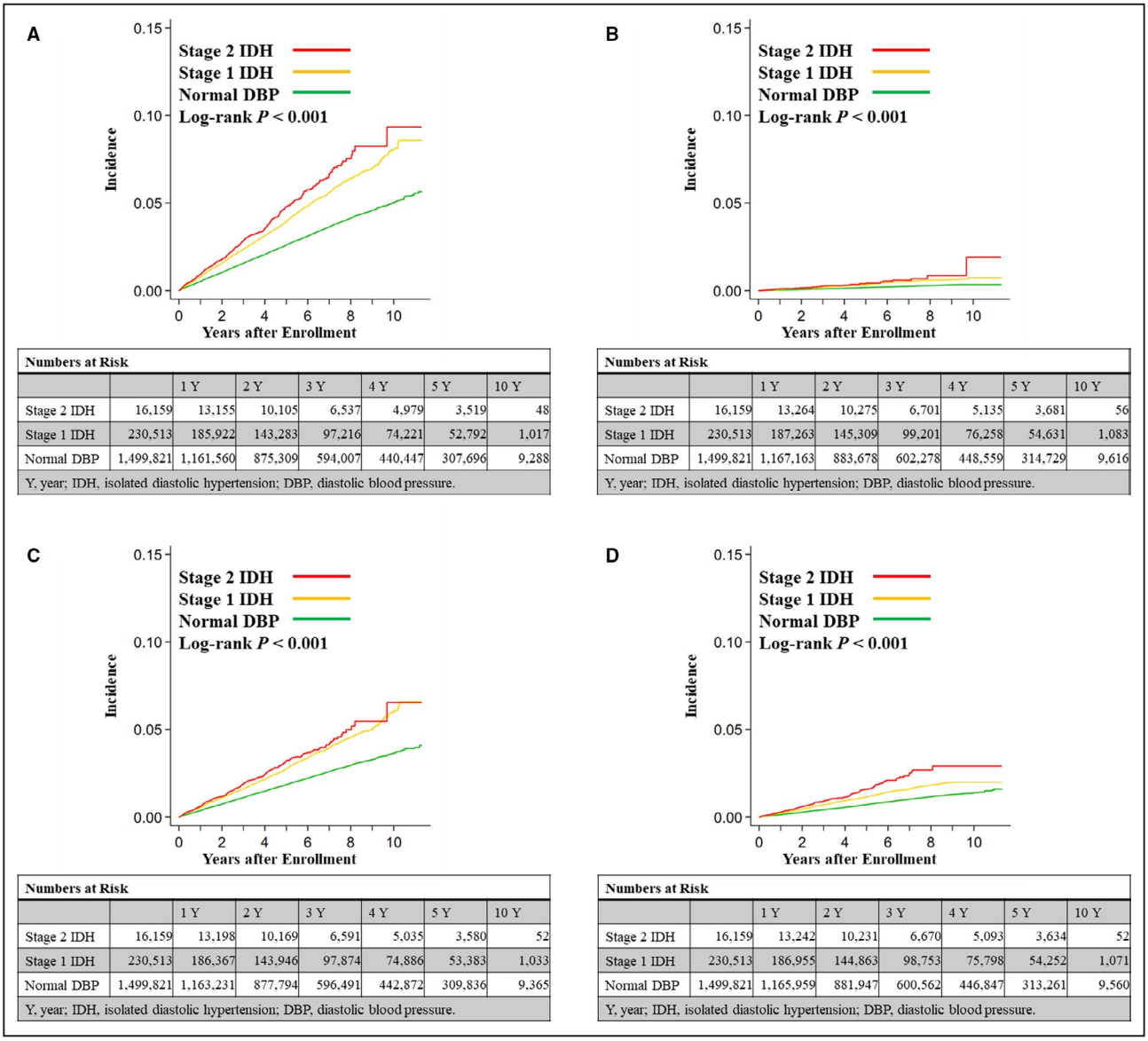
DISCUSSION

Our analysis of a nationwide epidemiological database including 1 746 493 individuals who had normal SBP and no prior history of prevalent CVD demonstrated that the stage 1 and stage 2 IDH groups according to the cutoff value of DBP in the

Table 2. Cardiovascular Disease Events

	Missing	Normal DBP (1 499 821)	Stage 1 IDH (230 513)	Stage 2 IDH (16 159)	*P* Value
Myocardial infarction	0 (0.0)	1564 (0.1)	514 (0.2)	45 (0.3)	<0.001
Angina pectoris	0 (0.0)	16 826 (1.1)	4133 (1.8)	318 (2.0)	<0.001
Stroke	0 (0.0)	6416 (0.4)	1699 (0.7)	163 (1.0)	<0.001
Composite end point	0 (0.0)	23 563 (1.6)	5903 (2.6)	482 (3.0)	<0.001

Data are expressed as number (percentage). DBP indicates diastolic blood pressure; and IDH, isolated diastolic hypertension.



Numbers at Risk

		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
Stage 2 IDH	16,159	13,155	10,105	6,537	4,979	3,519	48
Stage 1 IDH	230,513	185,922	143,283	97,216	74,221	52,792	1,017
Normal DBP	1,499,821	1,161,560	875,309	594,007	440,447	307,696	9,288

Y, year; IDH, isolated diastolic hypertension; DBP, diastolic blood pressure.

Numbers at Risk

		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
Stage 2 IDH	16,159	13,264	10,275	6,701	5,135	3,681	56
Stage 1 IDH	230,513	187,263	145,309	99,201	76,258	54,631	1,083
Normal DBP	1,499,821	1,167,163	883,678	602,278	448,559	314,729	9,616

Y, year; IDH, isolated diastolic hypertension; DBP, diastolic blood pressure.

Numbers at Risk

		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
Stage 2 IDH	16,159	13,198	10,169	6,591	5,035	3,580	52
Stage 1 IDH	230,513	186,367	143,946	97,874	74,886	53,383	1,033
Normal DBP	1,499,821	1,163,231	877,794	596,491	442,872	309,836	9,365

Y, year; IDH, isolated diastolic hypertension; DBP, diastolic blood pressure.

Numbers at Risk

		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
Stage 2 IDH	16,159	13,242	10,231	6,670	5,093	3,634	52
Stage 1 IDH	230,513	186,955	144,863	98,753	75,798	54,252	1,071
Normal DBP	1,499,821	1,165,959	881,947	600,562	446,847	313,261	9,560

Y, year; IDH, isolated diastolic hypertension; DBP, diastolic blood pressure.

Figure 1. Crude cumulative incidences of composite end point including myocardial infarction, angina pectoris, and stroke (A); myocardial infarction (B); angina pectoris (C); and stroke (D).
DBP indicates diastolic blood pressure; and IDH, isolated diastolic hypertension.

2017 ACC/AHA guidelines were associated with an elevated risk of subsequent cardiovascular events. Individuals with stage 1 and stage 2 IDH had more compromised baseline parameters than individuals with normal DBP. However, even after adjustment for covariates, both stage 1 and stage 2 hypertension were associated with a higher incidence of subsequent cardiovascular events. The association of IDH and incident CVD was observed regardless of age and sex. To the best of our knowledge, this is the first large-scale study uncovering the relationship between IDH based on the cutoff value of DBP in the 2017 ACC/AHA guidelines for BP and the development of CVD among the general population without prevalent CVD.

Reducing the threshold of BP for hypertension from 140/90 mm Hg to 130/80 mm Hg in the 2017 ACC/AHA guidelines[4] has attracted great clinical interest and has led to much debate. However, 2 large-scale studies validated the 2017 ACC/AHA guidelines.[6,7] The analysis of the prospective cohort CARDIA (Coronary Artery Risk Development in Young Adults) study including 4851 young adults presented that patients with 1 stage hypertension and stage 2 hypertension as defined by the 2017 ACC/AHA guidelines had increased risk for subsequent CVD events compared with those with normal BP.[6] Similarly, the population-based cohort study from the Korean National Health Insurance Service consisting of 2 488 101 young adults showed that individuals

Table 3. Multivariable Cox Regression Analysis for the Composite End Point After Multiple Imputation

	Hazard Ratio	95% CI	*P* Value
Category of DBP			
Normal	Reference		
Stage 1 IDH	1.17	1.13–1.20	<0.001
Stage 2 IDH	1.28	1.17–1.41	<0.001
SBP (per 10 mm Hg)	1.04	1.03–1.05	<0.001
Age, y	1.06	1.06–1.06	<0.001
Men	0.99	0.96–1.01	0.348
Obesity	1.06	1.02–1.10	0.002
High waist circumference	1.14	1.10–1.18	<0.001
Diabetes mellitus	1.45	1.38–1.53	<0.001
Dyslipidemia	1.19	1.16–1.22	<0.001
Current cigarette smoking	1.02	0.99–1.05	0.165

DBP indicates diastolic blood pressure; IDH, isolated diastolic hypertension; and SBP, systolic blood pressure.

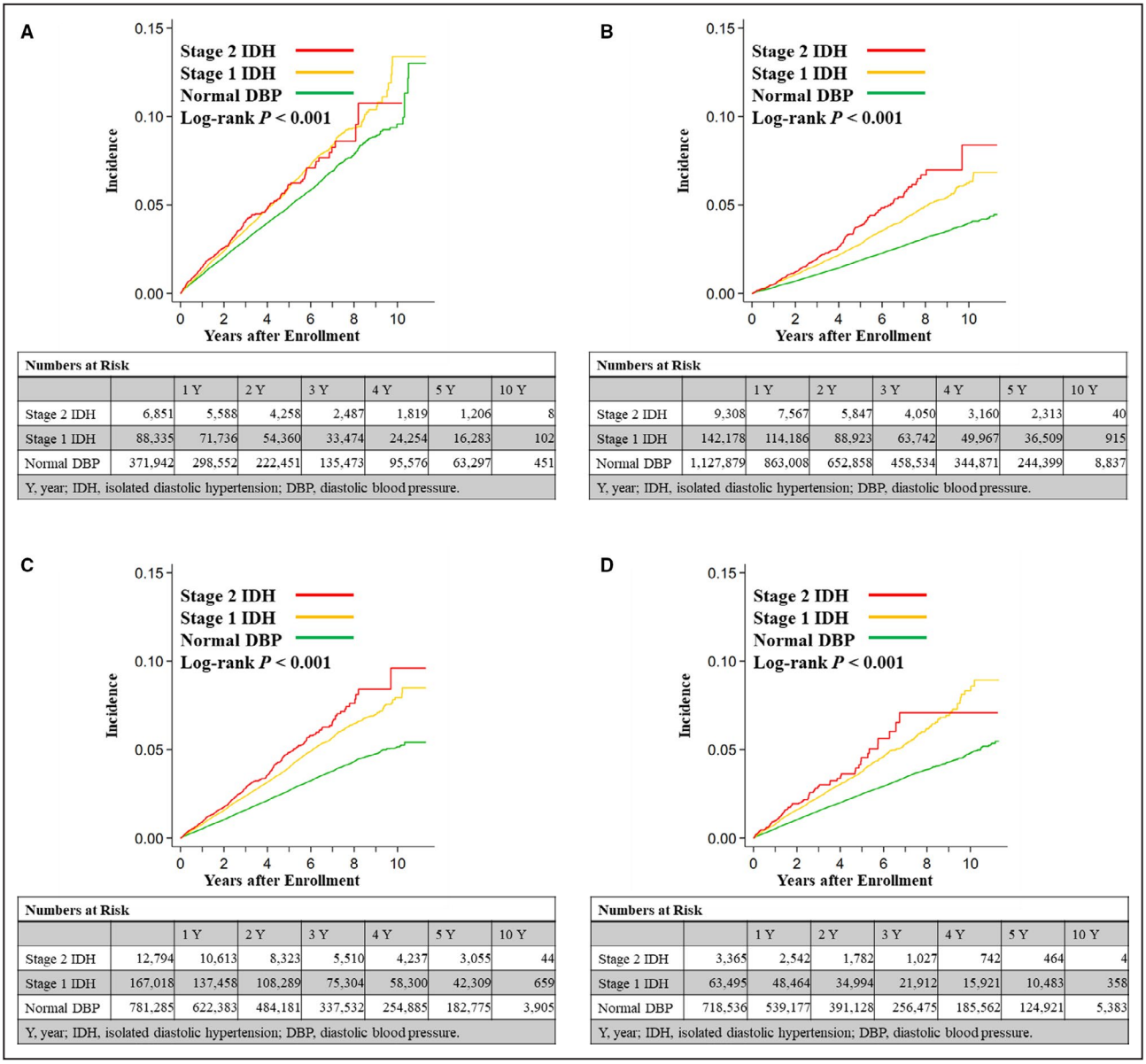
with baseline stage 1 and stage 2 hypertension compared with those with normal BP had a higher risk of cardiovascular events.[7]

We earlier explored the relationship between stage 1/stage 2 hypertension and subclinical atherosclerosis. Our analysis including individuals undergoing voluntary health checkups showed that increased thickness of carotid intima-media within the general population was seen in not only stage 2 but also stage 1 hypertension, suggesting the possible association between hypertension as defined by the 2017 ACC/AHA guidelines and subclinical atherosclerosis among the general population.[24] Further, we also reported that the prevalence of high cardio-ankle vascular index increased in stage 1 hypertension, and further increased in stage 2 hypertension in men.[25] These studies imply the potential pathophysiological significance of stage 1 and stage 2 hypertension, which the 2017 ACC/AHA guidelines suggested among the general population.

However, the validity of IDH defined by the 2017 ACC/AHA guidelines has not yet been well established. Further, contrary to the robust evidence supporting the clinical significance of SBP, there are conflicting data on the clinical importance of DBP and IDH.[9–14] McEvoy et al[9] reported that IDH based on the 2017 ACC/AHA guidelines was not related to incident cardiovascular events. Difference in study population, analyzed outcomes, treatment status (the study by McEvoy et al included patients taking antihypertensive medications), and races might contribute to the difference in results of our study and the study by McEvoy et al. Although further studies are required to confirm our results, we believe that our findings presenting the association between IDH and incident CVD among the general population without prevalent CVD are informative for the optimal management of BP and the primary prevention of subsequent CVD.

The clinical significance of DBP is influenced by multiple factors including race, age, baseline CVD risk, medication status, duration of the study, and clinical end points analyzed, which results in conflicting clinical outcomes. For example, Yano et al[26] reported the potential racial difference in the prognostic significance of DBP. Further, DBP usually decreases with age because of reduced compliance of blood vessels, which can complicate the association of DBP with the risk of CVD. However, our subgroup analyses showed that a higher incidence of subsequent CVD in stage 1 and stage 2 IDH was seen in young as well as old individuals. Further, a similar relationship was observed in both men and women. Therefore, the pathological significance of IDH did not seemingly depend on age and sex in our study population. Analyzed end point could also influence the study results. Preceding studies showed that lower DBP was associated with elevated risk of coronary artery disease.[27,28] Peri-Okonny et al reported that DBP was significantly associated with angina with a J-shaped relationship.[27] Therefore, both low DBP and high DBP could increase the risk of angina pectoris. Further investigations are needed to determine the optimal value of DBP for the prevention of coronary artery disease. Taking these into consideration, the clinical significance of DBP might be diverse, and the risk of IDH should be assessed from various perspectives such as genetic variation, racial difference, comparison between short- and long-term observation, and targeted clinical outcomes.

Another important issue is whether pharmacological intervention could lower the risk of CVD among patients with stage 1 IDH. Regarding this critical point, Son et al[7] reported that patients with stage 1 hypertension not taking antihypertensive medications had an elevated incidence of CVD, whereas patients with stage 1 hypertension taking antihypertensive medications had a similar risk of CVD compared with those with normal BP, suggesting the efficacy of pharmacological intervention for patients with stage 1 hypertension. Further, the SPRINT (Systolic Blood Pressure Intervention Trial) strongly supports the importance of strict BP control in patients with hypertension.[29] Recent meta-analyses of randomized trials showed that BP-lowering treatment for individuals with SBP/DBP values in the ranges of 120 to 139/80 to 89 mm Hg was found to significantly reduce CVD risk. However, BP-lowering treatment showed no significant benefits among individuals at low-moderate risk.[30] Furthermore, the BPLTTC (Blood Pressure Lowering Treatment Trialists' Collaboration) presented that protective effects of BP-lowering treatments increased with baseline cardiovascular risk. In



Numbers at Risk

		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
Stage 2 IDH	6,851	5,588	4,258	2,487	1,819	1,206	8
Stage 1 IDH	88,335	71,736	54,360	33,474	24,254	16,283	102
Normal DBP	371,942	298,552	222,451	135,473	95,576	63,297	451

Y, year; IDH, isolated diastolic hypertension; DBP, diastolic blood pressure.

Numbers at Risk

		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
Stage 2 IDH	9,308	7,567	5,847	4,050	3,160	2,313	40
Stage 1 IDH	142,178	114,186	88,923	63,742	49,967	36,509	915
Normal DBP	1,127,879	863,008	652,858	458,534	344,871	244,399	8,837

Y, year; IDH, isolated diastolic hypertension; DBP, diastolic blood pressure.

Numbers at Risk

		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
Stage 2 IDH	12,794	10,613	8,323	5,510	4,237	3,055	44
Stage 1 IDH	167,018	137,458	108,289	75,304	58,300	42,309	659
Normal DBP	781,285	622,383	484,181	337,532	254,885	182,775	3,905

Y, year; IDH, isolated diastolic hypertension; DBP, diastolic blood pressure.

Numbers at Risk

		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
Stage 2 IDH	3,365	2,542	1,782	1,027	742	464	4
Stage 1 IDH	63,495	48,464	34,994	21,912	15,921	10,483	358
Normal DBP	718,536	539,177	391,128	256,475	185,562	124,921	5,383

Y, year; IDH, isolated diastolic hypertension; DBP, diastolic blood pressure.

Figure 2. Crude cumulative incidences of composite end point including myocardial infarction, angina pectoris, and stroke in individuals aged ≥50 years (A), individuals aged <50 years (B), men (C), and women (D).
DBP indicates diastolic blood pressure; and IDH, isolated diastolic hypertension.

addition, BP-lowering therapy according to estimated cardiovascular risk is more effective than that according to BP levels alone, supporting the use of cardiovascular risk assessment to guide BP management decision-making in moderate- to high-risk patients, particularly for primary prevention.[31,32] Therefore, well-designed prospective studies or randomized controlled trials are needed to conclude the efficacy and the safety of pharmacological therapy for patients with stage 1 and stage 2 IDH. Body weight reduction is an alternative option for the management of BP.[33–37] We previously reported that body weight reduction (≥5%) could lower BP in the Japanese general population with body mass index ≥22 kg/m^2 without any pharmacological intervention.[38] Therefore, it may be beneficial to recommend body weight reduction for individuals with elevated DBP and body mass index ≥22 kg/m^2.

There are several limitations to this study. The category of BP was determined by BP measured at the initial health checkup, and measurements based on rigorous contemporary standards were not conducted. Therefore, misclassification could have occurred. Although we conducted a multivariable analysis, there could be unmeasured confounders and residual bias. Individuals registered in the JMDC

database mainly comprised an employed, working-age population, and there could be a "healthy worker" bias. Therefore, we need further investigations to generalize our results with other populations of different ethnicities, races, educational levels, and incomes. The incidence of CVD in our study is almost comparable to that in other nationwide epidemiological data in Japan (JPHC [Japan Public Health Center-based Prospective Study] https://epi.ncc.go.jp/en/jphc/index.html).[39] Therefore, we believe that our data could have reflected real-world clinical practice. However, recorded diagnoses are generally considered less well validated because of the nature of the retrospective design and administrative database. The data on CVD-related deaths cannot be assessed in this database. We did not track the status of drug treatment during follow-up. Although we excluded patients with a prior history of CVD as described in the Methods section, we are unable to eliminate the risk of misclassification, and, therefore, individuals with a prior history of CVD could be included in the analysis of this study. We also excluded patients taking antihypertensive medication. However, medications other than antihypertensives such as statins could have influenced BP values and affected the results.

CONCLUSIONS

IDH based on the cutoff value of DBP in the 2017 ACC/AHA BP guidelines was associated with a higher risk of CVD in the general population without prevalent CVD, suggesting the potential clinical significance of IDH in the development of CVD.

ARTICLE INFORMATION

Received June 15, 2020; accepted August 31, 2020.

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Sources 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).

Disclosures

Hidehiro Kaneko and Katsuhito Fujiu report research funding and scholarship funds from Medtronic Japan CO., LTD; Abbott Medical Japan CO., LTD; Boston Scientific Japan CO., LTD; and Fukuda Denshi, Central Tokyo CO., LTD. The remaining authors have no disclosures to report.

Supplementary Materials

Tables S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Multivariable Cox Regression Analysis for Heart Failure after Multiple Imputation.

	Hazard Ratio	95% Confidence Interval	*P* Value
Category of Diastolic Blood Pressure			
Normal	Reference		
Stage 1 Isolated Diastolic Hypertension	1.16	1.12-1.21	< 0.001
Stage 2 Isolated Diastolic Hypertension	1.41	1.26-1.58	< 0.001
Systolic Blood Pressure (per 10 mmHg)	1.02	1.00-1.03	0.064
Age, years	1.06	1.05-1.06	< 0.001
Male Sex	0.96	0.92-0.99	0.011
Obesity	1.14	1.09-1.20	< 0.001
High Waist Circumference	1.17	1.11-1.22	< 0.001
Diabetes Mellitus	1.52	1.42-1.63	< 0.001
Dyslipidemia	1.08	1.05-1.12	< 0.001
Current Cigarette Smoking	1.00	0.97-1.04	0.867

Table S2. Multivariable Cox Regression Analysis for Atrial Fibrillation after Multiple Imputation.

	Hazard Ratio	95% Confidence Interval	*P* Value
Category of Diastolic Blood Pressure			
Normal	Reference		
Stage 1 Isolated Diastolic Hypertension	1.20	1.11-1.29	< 0.001
Stage 2 Isolated Diastolic Hypertension	1.26	1.02-1.56	0.032
Systolic Blood Pressure (per 10 mmHg)	0.98	0.95-1.01	0.141
Age, years	1.08	1.08-1.09	< 0.001
Male Sex	2.40	2.23-2.58	< 0.001
Obesity	1.08	0.99-1.17	0.086
High Waist Circumference	1.38	1.28-1.50	< 0.001
Diabetes Mellitus	1.13	0.99-1.29	0.079
Dyslipidemia	0.84	0.80-0.89	< 0.001
Current Cigarette Smoking	0.94	0.89-1.01	0.073

Table S3. Multivariable Cox Regression Analysis for Composite Endpoint defined as Myocardial Infarction and Stroke after Multiple Imputation.

	Hazard Ratio	95% Confidence Interval	*P* Value
Category of Diastolic Blood Pressure			
Normal	Reference		
Stage 1 Isolated Diastolic Hypertension	1.23	1.17-1.30	< 0.001
Stage 2 Isolated Diastolic Hypertension	1.55	1.35-1.79	< 0.001
Systolic Blood Pressure (per 10 mmHg)	1.06	1.03-1.08	< 0.001
Age, years	1.08	1.08-1.08	< 0.001
Male Sex	0.98	0.94-1.03	0.475
Obesity	1.04	0.98-1.10	0.245
High Waist Circumference	1.10	1.04-1.17	0.001
Diabetes Mellitus	1.55	1.42-1.69	< 0.001
Dyslipidemia	1.19	1.15-1.24	< 0.001
Current Cigarette Smoking	1.26	1.21-1.32	< 0.001

Table S4. Multivariable Cox Regression Analysis for Composite Endpoint.

	Hazard Ratio	95% Confidence Interval	*P* Value
Category of Diastolic Blood Pressure			
Normal	Reference		
Stage 1 Isolated Diastolic Hypertension	1.16	1.12-1.20	< 0.001
Stage 2 Isolated Diastolic Hypertension	1.29	1.17-1.42	< 0.001
Systolic Blood Pressure (per 10 mmHg)	1.04	1.03-1.05	< 0.001
Age, years	1.06	1.06-1.06	< 0.001
Male Sex	1.00	0.97-1.03	0.779
Obesity	1.06	1.02-1.11	0.002
High Waist Circumference	1.12	1.08-1.17	< 0.001
Diabetes Mellitus	1.46	1.38-1.54	< 0.001
Dyslipidemia	1.20	1.17-1.23	< 0.001
Current Cigarette Smoking	1.04	1.01-1.07	0.019