Hypertension

EPIDEMIOLOGY/POPULATION SCIENCE

Isolated Diastolic Hypertension in the IDACO Study: An Age-Stratified Analysis Using 24-Hour Ambulatory Blood Pressure Measurements

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ABSTRACT: The prognostic implications of isolated diastolic hypertension (IDH), as defined by 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, have not been tested using ambulatory blood pressure (BP) monitor thresholds (ie, 24-hour mean systolic BP <125 mm Hg and diastolic BP ≥75 mm Hg). We analyzed data from 11 135 participants in the IDACO (International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes). Using 24-hour mean ambulatory BP monitor values, we performed Cox regression testing independent associations of IDH with death or cardiovascular events. Analyses were conducted in the cohort overall, as well as after age stratification (<50 years versus ≥50 years). The median age at baseline was 54.7 years and 49% were female. Over a median follow-up of 13.8 years, 2836 participants died, and 2049 experienced a cardiovascular event. Overall, irrespective of age, IDH on 24-hour ambulatory BP monitor defined by 2017 American College of Cardiology/American Heart Association criteria was not significantly associated with death (hazard ratio, 0.95 [95% CI, 0.79–1.13]) or cardiovascular events (hazard ratio, 1.14 [95% CI, 0.94–1.40]), compared with normotension. However, among the subgroup <50 years old, IDH was associated with excess risk for cardiovascular events (2.87 [95% CI, 1.72–4.80]), with evidence for effect modification based on age (*P* interaction <0.001). In conclusion, using ambulatory BP monitor data, this study suggests that IDH defined by 2017 American College of Cardiology/American Heart Association criteria is not a risk factor for cardiovascular disease in adults aged 50 years or older but is a risk factor among younger adults. Thus, age is an important consideration in the clinical management of adults with IDH. **(*Hypertension*. 2021;78:1222–1231. DOI: 10.1161/HYPERTENSIONAHA.121.17766.)** • **Data Supplement**

Key Words: blood pressure ■ hypertension ■ morbidity ■ mortality ■ risk

Ambulatory blood pressure (BP) monitor (ABPM) recordings are considered superior to office BP recordings in quantifying cardiovascular disease risk.[1,2] This is because 24-hour ABPM provides multiple recordings and gives a more precise estimate of physiological BP levels during normal activity than once-off measurements obtained in the clinic. In addition, ABPM recordings offer the opportunity to determine BP values during sleep, which have been shown to impart prognostic information.[3] Consequently, our understanding of a given BP phenotype is incomplete without data from 24-hour ABPM studies.

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Novelty and Significance

What Is New?

- Using 24-hour ambulatory blood pressure monitor recordings, we found no statistically significant association between isolated diastolic hypertension (IDH) by 2017 American College of Cardiology (ACC)/American Heart Association (AHA) criteria and increased risk for outcomes in the IDACO (International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes) cohort overall.
- By contrast, when the cohort was stratified by age, risk for cardiovascular events was higher among persons younger than 50 years who had IDH by 2017 ACC/AHA criteria; but was not increased among older adults with IDH.

What Is Relevant?

- Our data indicate that IDH by the 2017 ACC/AHA definition is not benign for adults younger than 50 years. These 24-hour ambulatory blood pressure monitor data help to settle an open question raised in prior registries using less rigorous recording of blood pressure, which indicated that age is an important consideration in the management of patients with IDH.

Summary

These 24-hour ambulatory blood pressure monitor data confirm prior reports that IDH by the 2017 ACC/AHA definition is not associated with events in adults overall, irrespective of their age. Our IDACO data also confirm the known association between IDH by the 2018 European Society of Cardiology definition and events. As such, the 2018 European Society of Cardiology definition of IDH appears to be a stronger risk factor for cardiovascular events than the 2017 ACC/AHA definition. The null association between the 2017 ACC/AHA definition of IDH and events in adults over 50 years suggests that older adults with mild IDH do not need treatment as long as systolic BP is controlled. However, our data also indicate that the 2017 ACC/AHA definition of IDH is not completely benign for adults younger than 50 years. However, because young adults are at low absolute risk for events, future studies are needed to test whether pharmacological treatment of IDH in younger persons is efficacious and cost-effective. For now, lifestyle management is indicated among persons with IDH.

Nonstandard Abbreviations and Acronyms

ABPM	ambulatory BP monitor
ACC	American College of Cardiology
AHA	American Heart Association
BP	blood pressure
ICD	*International Classification of Diseases*
ICD-10	*ICD, Tenth Revision*
ICD-8	*ICD, Eighth Revision*
ICD-9	*ICD, Ninth Revision*
IDACO	International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes
IDH	isolated diastolic hypertension
ISH	isolated systolic hypertension

One such phenotype, isolated diastolic hypertension (IDH), is less common than combined systolic-diastolic hypertension or isolated systolic hypertension (ISH).[4] However, depending on the definition applied, IDH can be seen in ≥6% of the adult population.[5] There are 2 definitions of IDH currently in widespread use; the 2018 European Society of Cardiology (ESC) guideline defines IDH as diastolic BP ≥90 mm Hg and systolic BP <140 mm Hg,[6] and the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guideline defines IDH as diastolic BP ≥80 mm Hg with a systolic BP <130 mm Hg (note that both of these definitions assume office measurement of BP).[7]

There have been conflicting reports on the association of IDH with adverse cardiovascular outcomes, especially using the 2017 ACC/AHA definition.[4,5,8-11] Analyses suggesting a modest association between the ACC/AHA definition of IDH and events have come from large clinical registries that comprised of routine clinical recordings of BP, whereas analyses finding no association have analyzed BP values obtained under more rigorous research conditions.[5,11,12] In addition, one of the clinical registries reporting a modest association between the ACC/AHA definition of IDH and events demonstrated clear evidence for interaction on the basis of age, with a stronger association between IDH and events among young versus old participants.[10] By contrast, the null studies reported to date using standardized BP values obtained under rigorous research conditions have found no interaction by age.[5,11] To clarify this uncertainty, we studied cardiovascular outcomes in the IDACO (International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes) cohort among participants with IDH that was confirmed using 24-hour ABPM, focusing primarily on the 2017 ACC/AHA definition. Analyses were conducted in the IDACO sample overall and after stratification based on age.

METHODS

The IDACO database is not publicly available; however, the authors declare that all supporting data are available within the article (and its Data Supplement).

Study Population

Previous publications describe the IDACO database in more detail.[3,13,14] Participating population studies qualified for inclusion if office and ambulatory BP measures and cardiovascular risk factors were available at baseline and if follow-up included both fatal and nonfatal outcomes. Of 13 111 people included in the database, we excluded 1976, either because they were teenagers (<18 years) without events (n=493) or because they had an ambulatory BP recording with fewer than 6 daytime or 3 nighttime readings (n=1483).[15] Thus, the number of individuals analyzed was 11 135. We did not exclude persons on antihypertensive therapy in the main analysis, although we excluded them in a sensitivity analysis. The expanded methods section and Table S1 in the Data Supplement provide detailed information on the population sampling methods, timelines, and country of recruitment. All of the included studies received ethical approval from the responsible institutional review boards in their country of origin and all participants provided written informed consent.

BP Measurement

Nurses or physicians obtained the conventional office BP clinical readings with standard auscultation using a mercury sphygmomanometer or with validated microphone or oscillometric automated BP measurement devices (see Expanded Methods in the Data Supplement). For ambulatory BP monitoring (Table S2), portable monitors were programmed to obtain ambulatory readings at 30-minute intervals throughout the whole day or at intervals of 15 to 30 minutes during daytime and at intervals ranging from 20 to 60 minutes during the nighttime.[16] Daytime readings ranged from 10 AM to 8 PM in European and South American countries and from 8 AM to 6 PM in Asian countries. The corresponding nighttime intervals ranged from midnight to 6 AM in European and South American countries and from 10 PM to 4 AM in Asian countries. The Expanded Methods section in the Data Supplement further describes the collection of questionnaire and biochemical data.

Ascertainment of End Points

We ascertained vital status and the incidence of fatal and nonfatal events from the appropriate sources in each country.[14] All events were prespecified and coded according to the *International Classification of Diseases* (*ICD*). The coprimary end points were total mortality and a composite cardiovascular event consisting of cardiovascular mortality (*ICD-8* [*ICD, Eighth Revision*], 390–448; *ICD-9* [*ICD, Ninth Revision*], 390.0–459.9; and *ICD-10* [*ICD, Tenth Revision*], I00–I79 and R96), coronary events (death from ischemic heart disease [*ICD-8*, 411–412; *ICD-9*, 411 and 414; and *ICD-10*, I20 and I24–I25], sudden death [*ICD-8*, 427.2 and 795; *ICD-9*, 427.5 and 798; and *ICD-10*, I46 and R96], nonfatal myocardial infarction [*ICD-8* or *ICD-9*, 410 and *ICD-10*, I21-I22], and coronary revascularization), stroke (*ICD-8* or *ICD-9*, 430–434 and 436; and *ICD-10*, I60–I64 and I67–I68, not including transient ischemic attack), and heart failure (*ICD-8*, 427.0, 427.1, 427.2, 428, 429, 519.1, and 782.4, *ICD-9*, 429, and *ICD-10*, I50 and J81). Secondary outcomes included each of the individual outcomes included in the composite cardiovascular event end point. All outcomes were validated against hospital files or medical records held by participants' primary care physicians or specialists. In analyses of composite outcomes, we only considered the first event.

Statistical Analysis

We used the Kolmogorov-Smirnov test for assessing the normality of distributions. For comparison of means and proportions, we applied the large-sample Z test and Fisher exact test, respectively. After stratification by cohort and sex, we interpolated missing values of body mass index and serum cholesterol levels from the regression slopes on age. In participants with unknown status of smoking, drinking, antihypertensive treatment, diabetes, or unknown history of cardiovascular disease, we set the indicator (dummy) variable to the cohort- and sex-specific mean of the codes (0, 1). Missing values were interpolated for body mass index (n=33), serum cholesterol level (n=806), smoking status (n=56), drinking status (n=805), antihypertensive treatment (n=16), diabetes (n=5), and history of cardiovascular disease (n=1).

Our analysis modeled 4 categorical exposures: normotension, IDH, ISH, and combined systolic-diastolic hypertension. Conversion of clinic BP thresholds to their respective ABPM equivalents was performed as recommended in 2017 ACC/AHA[7] and in 2018 ESC hypertension guidelines.[17] Specifically, the 24-hour systolic/diastolic ABPM thresholds for a diagnosis of IDH were 125/75 mm Hg by AHA/ACC and 130/80 mm Hg by ESC criteria. Similarly, the nighttime systolic/diastolic ABPM thresholds for a diagnosis of IDH were 110/65 mm Hg by 2017 AHA/ACC and 120/70 mm Hg by 2018 ESC criteria.

We compared the cumulative incidence of the primary and secondary outcomes by hypertension category, after adjusting for age and sex. In multivariable-adjusted Cox regression, we adjusted for cohort (random effect), sex, and baseline characteristics including age, body mass index, smoking and drinking status, serum cholesterol level, antihypertensive drug intake, diabetes, and history of cardiovascular disease. We checked the proportional hazards assumption by the Kolmogorov-type supremum test. We prespecified that all Cox regression analyses were conducted in the IDACO sample overall and after stratification on the basis of age (<50 years versus ≥50 years) and sex. In these stratified analyses, we tested for effect modification using multiplicative interaction terms.

Sensitivity analyses excluded individuals either on baseline antihypertensive medications or those with a baseline history of cardiovascular disease from the models. Finally, we also performed sensitivity analyses of our 4 main categorical exposures with further adjustment for either systolic BP or for diastolic BP as continuous covariables at baseline.

For the statistical analysis, we used SAS software, version 9.4. Statistical significance was a 2-tailed α of ≤0.05.

RESULTS

Characteristics of Participants

The study sample analyzed (n=11 135) included 5494 women (49.3%) and consisted of 6929 White Europeans (62.2%), 1887 Asians (17.0%), and 2319 South

Americans (20.8%). The median age at baseline was 54.7 years. Study participants included 3022 (27.3%) smokers, 849 (7.6%) diabetics, and 1291 (11.6%) persons with a history of cardiovascular disease.

When applying the 2017 ACC/AHA hypertension criteria using 24-hour ambulatory BP thresholds, our sample comprised of 5418 (48.7%) participants with normal BP values, 1129 (10.1%) with BP values meeting criteria for IDH, 1325 (11.9%) with BP values meeting criteria for ISH, and 3263 (29.3%) with combined systolic-diastolic hypertension (Table 1). In comparison to those with normal BP values, persons with IDH by ACC/AHA criteria were numerically more likely to be South American and male. Otherwise, the baseline characteristics of normotensive participants and those with IDH appeared similar, as summarized in Table 1.

Primary Analyses on the Whole Study Population

Median follow-up was 13.8 years (5th–95th percentile interval, 2.5–25.1 years). During 153 140 person-years of follow-up, 2836 participants died (incidence rate of 18.5 per 1000 person-years) and 2049 experienced a composite cardiovascular event (13.4 per 1000 person-years), overall. When applying the 2017 ACC/AHA hypertension criteria, crude incidence rates (per 1000 person-years) for death and cardiovascular events were 12.0 and 7.8 among normotensive participants, 9.7 and 8.4 among those with IDH, 34.1 and 26.3 among those with ISH, and 27.2 and 23.5 among participants with combined hypertension. Age and sex-standardized cumulative incidence curves, for both outcomes and among each BP category, are presented in the Figure. Using the 2017 ACC/AHA criteria for IDH, there was no statistically significant crude excess in either mortality or cardiovascular events relative to the normal BP category. However, IDH according to 2018 ESC criteria was associated with an increased cumulative incidence of cardiovascular events (but not death). Irrespective of the guideline criteria applied, both ISH and combined systolic-diastolic hypertension were associated with an excess in death and cardiovascular events.

Table 1. Baseline Characteristics of Participants by Hypertension Categories According to 24-Hour Ambulatory BP Thresholds in 2017 ACC/AHA Guidelines

Characteristic	Normotensive	Isolated diastolic	Isolated systolic	Combined hypertension
N (%) of participants	5418	1129	1325	3263
European	3352 (61.9)	649 (57.5)	863 (65.1)	2065 (63.3)
Asian	999 (18.4)	140 (12.4)	209 (15.8)	539 (16.5)
South American	1067 (19.7)	340 (30.1)	253 (19.1)	659 (20.2)
Women	3239 (59.8)	485 (43.0)	599 (45.2)	1171 (35.9)
Current smoking	1430 (26.4)	331 (29.3)	317 (23.9)	944 (28.9)
Drinking alcohol	2422 (44.7)	569 (50.4)	755 (57.0)	2069 (63.4)
On antihypertensive treatment	671 (12.4)	152 (13.5)	407 (30.7)	1032 (31.6)
Diabetes	293 (5.4)	37 (3.3)	170 (12.8)	349 (10.7)
History of CVD	452 (8.3)	114 (10.1)	253 (19.1)	472 (14.5)
Mean (SD) characteristic				
Age, y	48.6 (16.0)	49.8 (12.6)	63.2 (14.6)	58.9 (12.7)
Body mass index, kg/m^2	24.5 (4.1)	26 (4.2)	26.4 (4.7)	26.8 (4.3)
Serum total cholesterol, mmol/L	5.4 (1.1)	5.6 (1.2)	5.8 (1.2)	5.8 (1.2)
Blood pressure, mm Hg				
Conventional systolic	120.8 (16.6)	127.0 (14.5)	145.4 (23.6)	148.3 (22.4)
Conventional diastolic	74.0 (9.1)	82.5 (9.2)	79.7 (10.5)	88.6 (11.4)
24-h systolic	113.0 (6.9)	119.8 (4.0)	132.8 (8.0)	138.9 (11.3)
24-h diastolic	67.7 (4.4)	78.3 (2.9)	70.7 (3.5)	83.3 (6.4)
Daytime systolic	119.0 (8.5)	126.0 (6.3)	138.8 (9.7)	145.1 (12.3)
Daytime diastolic	72.8 (5.7)	83.8 (4.7)	74.9 (5.2)	88.2 (7.4)
Nighttime systolic	102.6 (8.3)	108.4 (7.3)	121.4 (12.5)	127.1 (14.6)
Nighttime diastolic	58.9 (5.6)	68.1 (6.0)	62.7 (5.6)	74.0 (8.7)

The 24-h systolic/diastolic BP threshold for hypertension was 125/75 mm Hg by 2017 AHA/ACC criteria. Normotension refers to those with both systolic/diastolic BPs lower than the cutoff values, whereas combined hypertension refers to those with both systolic/diastolic BPs equal to or higher than the cutoff values. Isolated systolic and diastolic hypertension refers to those with only systolic or diastolic BP elevated. Diabetes was a fasting plasma glucose level of ≥7.0 mmol/L or use of antidiabetic agents. ACC indicates American College of Cardiology; AHA, American Heart Association; BP, blood pressure; and CVD, cardiovascular disease.

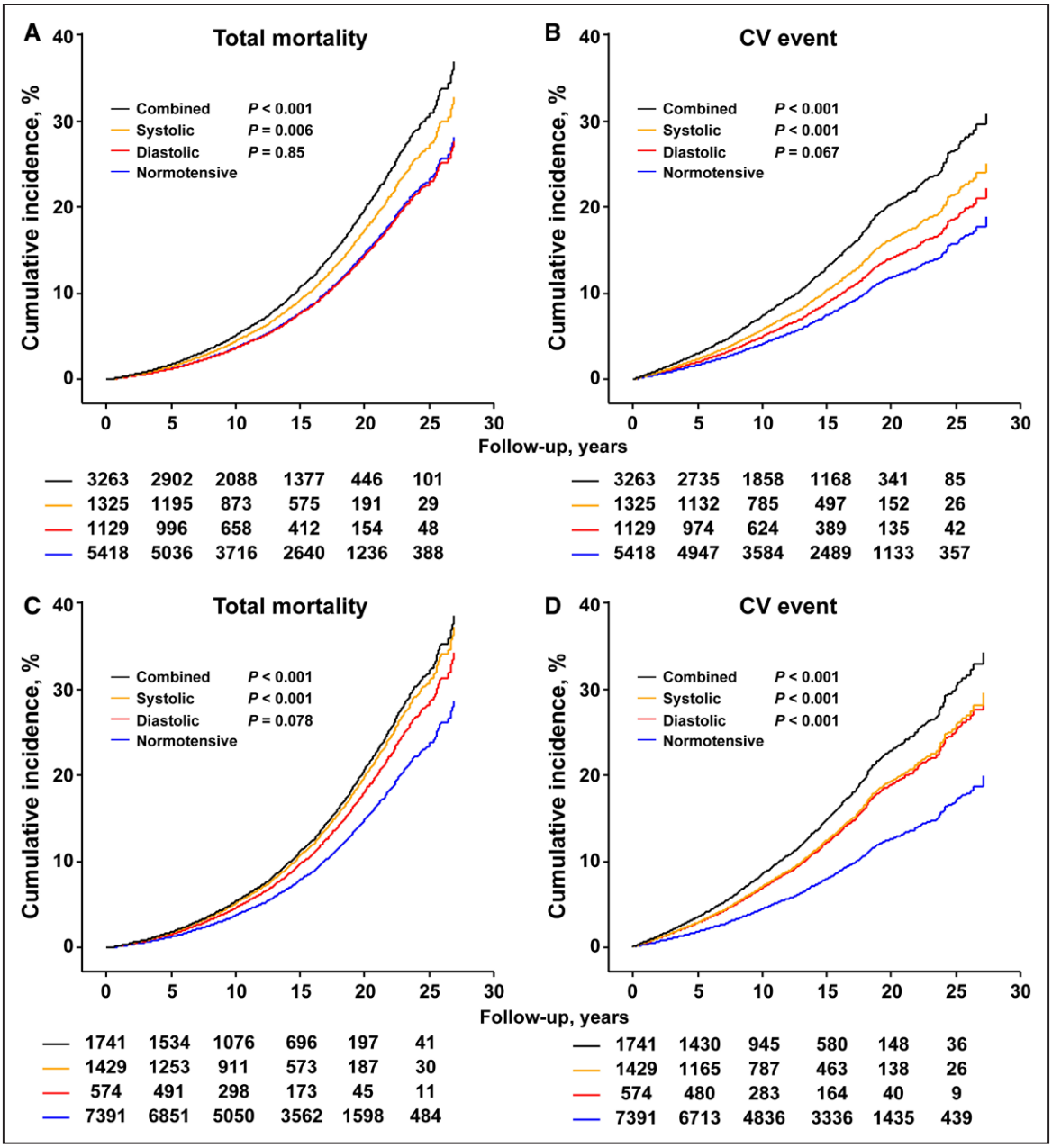

Figure. Sex- and age-standardized cumulative incidence of total mortality and cardiovascular (CV) event by hypertensive categories. Relative to normotension, isolated diastolic hypertension was not associated with increased risk of death or CV events when defined according to 2017 American Heart Association/American College of Cardiology criteria. The 24-h systolic/diastolic ambulatory blood pressure (BP) thresholds were 125/75 mm Hg by 2017 American Heart Association/American College of Cardiology (**A** and **B**) and 130/80 mm Hg by 2018 European Society of Cardiology (**C** and **D**) definitions. Normotension refers to those with both systolic/diastolic BPs lower than the cutoff values, whereas combined hypertension refers to those with both systolic/diastolic BPs equal to or higher than the cutoff levels. Isolated systolic and diastolic hypertension refers to those with only systolic or diastolic BP elevated. Tabulated data are the number of participants at risk by hypertensive categories at 5-y intervals. *P* values show significance for comparison with the normotensive group.

In Cox regression analyses adjusted for cohort, sex, age, body mass index, smoking status, alcohol drinking status, serum cholesterol levels, antihypertensive drug treatment use, diabetes, and history of cardiovascular disease (Table 2), there was no independent association in the sample overall between IDH by the 2017 ACC/AHA criteria and either death (hazard ratio, 0.95 [95% CI, 0.79–1.13]) or cardiovascular events (hazard ratio, 1.14 [95% CI, 0.94–1.40]), compared with normotension. By contrast, IDH by the 2018 ESC criteria was independently associated with risk for cardiovascular events (hazard ratio, 1.44 [95% CI, 1.12–1.85]; Table 2), but not death. Consistent with the above-described excesses in crude events and cumulative incidence rates, ISH and combined hypertension by both sets of diagnostic criteria also demonstrated excess adjusted risk in the Cox models, relative to normotension.

Table 2. Multivariable-Adjusted HR in Relation to Hypertension Categories by 24-Hour BP

Characteristic	Total mortality (n=2836)		CV event (n=2049)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
2017 AHA/ACC criteria				
Normotensive (n=5418)	Reference		Reference	
Isolated diastolic (n=1129)	0.95 (0.79–1.13)	0.55	1.14 (0.94–1.40)	0.19
Isolated systolic (n=1325)	1.16 (1.04–1.29)	0.008	1.35 (1.18–1.53)	<0.001
Combined (n=3263)	1.35 (1.23–1.48)	<0.001	1.73 (1.55–1.93)	<0.001
2018 ESC criteria				
Normotensive (n=7391)	Reference		Reference	
Isolated diastolic (n=574)	1.22 (0.96–1.56)	0.11	1.44 (1.12–1.85)	0.004
Isolated systolic (n=1429)	1.36 (1.24–1.50)	<0.001	1.53 (1.37–1.71)	<0.001
Combined (n=1741)	1.39 (1.26–1.53)	<0.001	1.86 (1.66–2.08)	<0.001

The 24-h systolic/diastolic BP thresholds were 125/75 mm Hg by 2017 AHA/ACC and 130/80 mm Hg by 2018 ESC definitions. Normotension refers to those with both systolic/diastolic BPs lower than the cutoff values, while combined hypertension refers to those with both systolic/diastolic BPs equal to or higher than the cutoff values. Isolated systolic and diastolic hypertension refers to those with only systolic or diastolic BP elevated. HRs express the relative risk compared with the normotensive group as reference and were adjusted for cohort (random effect), sex, age, body mass index, smoking and drinking, serum total cholesterol, antihypertensive drug intake, history of cardiovascular disease, and diabetes. ACC indicates American College of Cardiology; AHA, American Heart Association; BP, blood pressure; CV, cardiovascular; CVD, CV disease; ESC, European Society of Cardiology; and HR, hazard ratio.

The above results were almost identical in analyses of the subgroup of 8873 IDACO participants who were not on BP medication at baseline (Table S3). Similarly, when modeling participants on the basis of ABPM values at night, the results were again almost identical as for 24-hour readings, except that nocturnal IDH by the 2018 ESC criteria was no longer associated with cardiovascular events (results for full cohort in Table 3 and for the subgroup not on BP medication at baseline in Table S4).

Further Sensitivity Analyses

In sensitivity analyses, we further adjusted the categorical BP exposures (ie, IDH, ISH, and combined hypertension) for either diastolic BP or systolic BP values as baseline continuous covariables (Table S5 and Table S6). With further adjustment for diastolic BP as a continuous baseline covariable, the results from the categorical analyses were consistent with the main results presented in Tables 2 and 3. By contrast, with further adjustment for systolic BP as a continuous baseline covariable, there was no longer an association between IDH by the 2018 ESC definition and cardiovascular events. Second, for each of the individual outcomes that comprised the composite cardiovascular event end point, we repeated all of the analyses described above and found that IDH according to 24-hour ABPM criteria (by either guideline) was also not associated with any of these individual outcomes

Table 3. Multivariable-Adjusted HR in Relation to Hypertension Categories by Nighttime BP

Characteristic	Total mortality (n=2836)		CV event (n=2049)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
2017 AHA/ACC criteria				
Normotensive (n=4766)	Reference		Reference	
Isolated diastolic (n=772)	0.99 (0.81–1.21)	0.94	1.15 (0.92–1.45)	0.22
Isolated systolic (n=1542)	1.14 (1.02–1.27)	0.025	1.35 (1.18–1.55)	<0.001
Combined (n=4055)	1.28 (1.17–1.40)	<0.001	1.62 (1.45–1.80)	<0.001
2018 ESC criteria				
Normotensive (n=7362)	Reference		Reference	
Isolated diastolic (n=834)	1.08 (0.91–1.28)	0.38	1.12 (0.92–1.36)	0.26
Isolated systolic (n=979)	1.29 (1.15–1.43)	<0.001	1.44 (1.36–1.64)	<0.001
Combined (n=1960)	1.43 (1.31–1.57)	<0.001	1.76 (1.58–1.96)	<0.001

The nighttime systolic/diastolic BP thresholds were 110/65 mm Hg by 2017 AHA/ACC and 120/70 mm Hg by 2018 ESC definitions. Normotension refers to those with both systolic/diastolic BPs lower than the cutoff values, while combined hypertension refers to those with both systolic/diastolic BPs equal to or higher than the cutoff levels. Isolated systolic and diastolic hypertension refers to those with only systolic or diastolic BP elevated. HRs express the relative risk compared with the normotensive group as reference and were adjusted for cohort (random effect), sex, age, body mass index, smoking and drinking, serum total cholesterol, antihypertensive drug intake, history of cardiovascular disease, and diabetes. ACC indicates American College of Cardiology; AHA, American Heart Association; BP, blood pressure; CV, cardiovascular; ESC, European Society of Cardiology; and HR, hazard ratio.

in isolation (Tables S7 and S8). Finally, third, analyses among the 9844 participants without a baseline history of cardiovascular disease produced consistent results (Tables S9 and S10).

Analyses Stratified by Age and Sex

After stratification of the whole IDACO cohort into participants younger than 50 and participants of 50 years or older, there was evidence for higher crude rates of cardiovascular events among younger persons with IDH using 2017 ACC/AHA criteria (3.71 per 1000 person-years) compared with younger persons with normal BP (1.08 per 1000 person-years). By contrast, crude cardiovascular event rates among those aged 50 or more appeared lower in the IDH subgroup versus normotension (Table S11).

In adjusted Cox models, there was a statistically significant 3-fold increase in adjusted relative risk for cardiovascular events among IDACO participants younger than 50 who had IDH on 24-hour ABPM by 2017 ACC/AHA criteria, relative to young participants with normotension (Table 4). Furthermore, there was strong evidence of effect modification on the basis of age (*P* interaction <0.001) and IDACO participants 50 years or older with IDH had no excess cardiovascular risk compared to normotension. There was also a suggestion of effect modification by age on the association between IDH using the 2018 ESC criteria and cardiovascular events; with marginal evidence for higher risk in younger adults than older adults (*P* interaction =0.06). In contrast to cardiovascular events, IDH on 24-hour ABPM (either by 2017 ACC/AHA or by 2018 ESC criteria) was not significantly associated with mortality at any age and there was no evidence of interaction on the basis of age (Table 4). Similarly, for both the 2018 ESC or 2017 ACC/AHA criteria, the risks of total mortality and cardiovascular events associated with IDH were similar among men and women in the whole IDACO cohort (*P* interaction =0.10, Tables S12 and S13).

DISCUSSION

In this international study of adults with 24-hour ABPM recordings, 2 interesting and novel findings become evident. First, we found no association of IDH, as defined by the 2017 ACC/AHA guideline and using 24-hour ABPM readings, with adverse outcomes in the sample overall. By contrast and concordant with prior IDACO reports,[18] IDH on 24-hour ABPM as defined by the 2018 ESC guideline was associated with cardiovascular events, although not with death. The second observation, which addresses an issue of controversy[12], was that after stratifying the study sample by age, IDH on 24-hour ABPM was associated with increased risk for cardiovascular events (both for the 2017 ACC/AHA and the 2018 ESC definitions of IDH) among participants younger than 50 years only.

ACC/AHA Versus ESC Definitions of IDH Among Adults of All Ages

The first main finding from this IDACO report is consistent with prior research.[5,11] By using 24-hour and nocturnal ABPM recordings, the current results are an important validation of the report by McEvoy et al,[5] which analyzed adults of all ages participating in a number of US cohorts who had BP values collected at a single point in time as part of a research study visit. The IDACO

Table 4. Multivariable-Adjusted HR in Relation to Hypertension Categories After Stratification by Age

	Total mortality				P_{int}	CV events				P_{int}
	Age<50		Age≥50			Age<50		Age≥50		
Characteristic	HR (95% CI)	*P* value	HR (95% CI)	*P* value		HR (95% CI)	*P* value	HR (95% CI)	*P* value	
2017 AHA/ACC criteria										
Normotensive	Reference		Reference			Reference		Reference		
Isolated diastolic	1.66 (0.96–2.86)	0.068	0.91 (0.75–1.10)	0.31	0.076	2.87 (1.72–4.80)	<0.001	0.98 (0.78–1.23)	0.87	<0.001
Isolated systolic	0.68 (0.21–2.20)	0.52	1.14 (1.03–1.28)	0.015	0.28	0.74 (0.22–2.43)	0.62	1.33 (1.17–1.52)	<0.001	0.45
Combined	2.08 (1.33–3.25)	0.0013	1.33 (1.21–1.46)	<0.001	0.15	2.39 (1.47–3.89)	<0.001	1.68 (1.50–1.88)	<0.001	0.092
ESC 2018 criteria										
Normotensive	Reference		Reference			Reference		Reference		
Isolated diastolic	1.82 (0.93–3.57)	0.080	0.91 (0.75–1.10)	0.22	0.31	2.41 (1.30–4.45)	0.0052	1.31 (0.99–1.72)	0.058	0.058
Isolated systolic	0.98 (0.39–2.46)	0.97	1.36 (1.24–1.49)	<0.001	0.39	1.48 (0.66–3.31)	0.34	1.52 (1.35–1.70)	<0.001	0.76
Combined	2.28 (1.38–3.78)	0.0013	1.37 (1.24–1.51)	<0.001	0.097	2.34 (1.38–4.00)	0.0017	1.82 (1.63–2.04)	<0.001	0.24

The 24-h systolic/diastolic BP thresholds were 125/75 mm Hg by 2017 AHA/ACC and 130/80 mm Hg by 2018 ESC definitions. Normotension refers to those with both systolic/diastolic BPs lower than the cutoff values, while combined hypertension refers to those with both systolic/diastolic BPs equal to or higher than the cutoff levels. Isolated systolic and diastolic hypertension refers to those with only systolic or diastolic BP elevated. HRs express the relative risk compared with the normotensive group in the age stratification as reference and were adjusted for cohort (random effect), sex, age, body mass index, smoking and drinking, serum total cholesterol, antihypertensive drug intake, history of cardiovascular disease and diabetes. P_{int} is for the interaction between hypertension classifications and age group. ACC indicates American College of Cardiology; AHA, American Heart Association; BP, blood pressure; CV, cardiovascular; ESC, European Society of Cardiology; HR, hazard ratio; and P_{int}, *P* interaction.

results presented here also align with findings from the UK Biobank.[11] In all of these reports, there was no excess cardiovascular risk associated with IDH by the 2017 ACC/AHA definition when all participants, irrespective of age, were included in analyses. An advantage of our IDACO data is that the use of 24-hour ABPM values allows for a more precise measurement of the IDH exposure than has previously been possible, even allowing for the rigorous methods used to record BP in the prior analyses.[5,11]

Therefore, these IDACO data challenge prior reports from four large clinical registries, which have suggested a modest increase in adjusted risk for IDH by the 2017 ACC/AHA definition among adults of all ages.[4,10,19,20] These registries studied adults attending routine clinical care visits (thereby introducing the possibility of some confounding by indication) and who had routine, nonstandardized, clinical measurement, and documentation of BP. It is known that routine clinical measurement of BP and recording in electronic health records are not as accurate as standardized assessments undertaken as part of rigorous epidemiological studies like IDACO (this is true in particular for diastolic BP).[21]

This IDACO analysis also confirms data from UK Biobank,[11] and elsewhere,[8] demonstrating an increased risk for events among adults of all ages with IDH as defined by the 2018 ESC criteria. The apparent conflict between the 2017 ACC/AHA and 2018 ESC definitions of IDH can be explained by the former definition requiring a diastolic BP ≥80 mm Hg, whereas the latter requires a diastolic BP ≥90 mm Hg. This suggests that, among all adults with controlled systolic BP, risk for cardiovascular events is low when diastolic BP is between 80 and 89 mm Hg but increases once diastolic BP is ≥90 mm Hg.

ACC/AHA Definition of IDH and Outcomes in Young Versus Old Adults

The second main finding from this IDACO analysis suggests that, by contrast to adults of all ages, the 2017 ACC/AHA definition of IDH may be a specific prognostically adverse feature in young adults aged <50 years. This question is important for several reasons. First, IDH is more common in younger adults,[22] and about half of those newly eligible for a diagnosis of IDH since 2017 ACC/AHA guidelines are aged <50 years.[5] Second, the only prior report suggesting interaction by age in the association between the 2017 ACC/AHA definition of IDH and events comprised of routinely collected BP data from a large clinical registry and may have consequently had methodological biases for the reasons outlined above.[9,10] Prior reports of cohorts with rigorous BP measurements that looked for age interaction in the association between the 2017 ACC/AHA IDH definition and events have suggested that young adults were not at increased risk, although these same cohorts included few younger adults and so may have been underpowered.[11] Therefore, it has been unclear whether young adults have increased risk for events when IDH by the 2017 ACC/AHA definition is ascertained using research-quality BP measurements.

In IDACO, we found that younger adults with IDH by the 2017 ACC/AHA definition and measured using 24-hour ABPM did indeed have increased risk for cardiovascular events (but not death). This finding utilizing rigorous ascertainment of BP with ABPM confirms suggestions from prior studies (which used less valid routine clinical assessment of BP)[9,10] that there is an age-related interaction in the association between the 2017 ACC/AHA definition of IDH and events, with far stronger excesses in relative risk among young adults aged less than 50 years compared with older adults. The physiological reasons for this age interaction are not fully known; however, a few considerations are worth noting; (1) diastolic BP has been shown to have more prognostic significance in the young versus the old[18] and (2) the prevalence of elevated diastolic BP is as low as 10% (or less) among adults over 70 years,[4] and, therefore, some cases of IDH in older IDACO adults may have been misclassified due to BP measurement error on both office and 24-hour ABPM (noting that increased vascular stiffness with aging increases the likelihood of the fifth Korotkoff sound being absent, which could result in falsely elevated diastolic BP readings and, therefore, false positive IDH ascertainments).

Finally, several factors might help to explain why this IDACO age-stratified finding contrasts with the prior epidemiological studies using research-grade BP measurements,[5,11] none of which have found an age interaction for the 2017 ACC/AHA definition of IDH. First, the very large IDACO dataset is well powered to test this interaction effect, whereas prior studies may not have been; second, the IDACO sample is younger on average than some of the prior analyses[5] testing the 2017 ACC/AHA definition of IDH; and, third, by using 24-hour ABPM readings, our IDACO data were less likely to include spurious or artifactual readings of elevated diastolic BP that may be more commonly seen in BP assessments at a single point in time.

Limitations

This observational analysis has limitations. First, we cannot exclude residual confounding, including but not limited to lipid-lowering and antiplatelet therapies. Second, 24-hour BP and antihypertensive drug treatment status were only recorded at baseline and could therefore not be adjusted for as a time-dependent covariables. Furthermore, our sensitivity analysis excluding persons on antihypertensives at baseline may have included some persons subsequently started on therapy. Third, our prespecified adjustment model did not control for baseline

heart rate; however, in further sensitivity analyses adding heart rate to this model, the results remained quantitatively and qualitatively very similar (data not shown). Fourth, there might be misclassification bias in the assessment of the cardiovascular study end points.[23] However, all-cause mortality does not require any adjudication and is therefore not subject to this bias. Fifth, diastolic BP levels as assessed using automated oscillometric ABPM devices can sometimes overestimate true diastolic BP as measured using intra-arterial transducers. In addition, although categorical analyses of diastolic BP have implications for clinical care (given the use of specific BP thresholds to define hypertension), it is also worth noting that BP is a continuous pathophysiologic exposure variable. Sixth, our findings of interaction by age could represent the play of chance; however, they were prespecified and the highly significant *P* interaction values also make this less likely, as do prior data from registry studies suggesting significant interaction by age on the association between IDH (by both 2017 ACC/AHA and by 2018 ESC criteria) and cardiovascular events.[10] Finally, eighth, no Black participants were included in the IDACO database, and caution should be taken when extrapolating our results to races and ethnicities that were not included.

Perspectives

This prospective cohort analysis of 24-hour ambulatory BP data did not demonstrate an association between the 2017 ACC/AHA definition of IDH and outcomes in the IDACO sample overall. However, significant effect modification was noted on the basis of age and persons younger than 50 years with IDH as defined by the 2017 ACC/AHA criteria for 24-hour ABPM readings did have evidence for increased risk of cardiovascular events. These data, using rigorous 24-hour ABPM assessments, indicate that the clinical implications of IDH differ greatly based on the patient's age. Older persons (>50 years) with evidence of IDH appear to be a little risk as long as systolic BPs are controlled. However, younger persons with IDH do have elevated relative risk for cardiovascular events and may therefore benefit from intensive lifestyle interventions and, where clinically appropriate, antihypertensive medications.

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