Isolated Diastolic Hypotension and Incident Heart Failure in Older Adults

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Abstract—Aging is often associated with increased systolic blood pressure and decreased diastolic blood pressure. Isolated systolic hypertension or an elevated systolic blood pressure without an elevated diastolic blood pressure is a known risk factor for incident heart failure in older adults. In the current study, we examined whether isolated diastolic hypotension, defined as a diastolic blood pressure <60 mm Hg and a systolic blood pressure ≥100 mm Hg, is associated with incident heart failure. Of the 5795 Medicare-eligible community-dwelling adults age ≥65 years in the Cardiovascular Health Study, 5521 were free of prevalent heart failure at baseline. After excluding 145 individuals with baseline systolic blood pressure <100 mm Hg, the final sample included 5376 participants, of whom 751 (14%) had isolated diastolic hypotension. Propensity scores for isolated diastolic hypotension were calculated for each of the 5376 participants and used to match 545 and 2348 participants with and without isolated diastolic hypotension, respectively, who were balanced on 58 baseline characteristics. During >12 years of median follow-up, centrally adjudicated incident heart failure developed in 25% and 20% of matched participants with and without isolated diastolic hypotension, respectively (hazard ratio associated with isolated diastolic hypotension: 1.33 [95% CI: 1.10–1.61]; *P*=0.004). Among the 5376 prematch individuals, multivariable-adjusted hazard ratio for incident heart failure associated with isolated diastolic hypotension was 1.29 (95% CI: 1.09–1.53; *P*=0.003). As in isolated systolic hypertension, among community-dwelling older adults without prevalent heart failure, isolated diastolic hypotension is also a significant independent risk factor for incident heart failure. **(*Hypertension*. 2011;58:895-901.)**

Key Words: aging ■ blood pressure ■ diastolic ■ heart failure ■ pulse pressure

Arterial stiffening is common in older adults and may contribute to the elevation of systolic blood pressure (SBP) and the depression of diastolic blood pressure (DBP), as well as a resultant widening of the pulse pressure (PP), all commonly observed in this population.[1] Although isolated systolic hypertension (ISH), defined as isolated elevation of SBP without a concomitant elevation of DBP, is a known risk factor for incident heart failure (HF) in older adults,[2,3] little is known about the effect of an isolated diastolic hypotension (IDH), where DBP is decreased without a concomitant decrease in SBP. The purpose of this study was to examine the association between IDH and incident HF in community-dwelling older adults.

Methods

Study Design and Participants

The Cardiovascular Health Study (CHS) is a National Heart, Lung, and Blood Institute–funded population-based prospective study of cardiovascular disease in older adults, the details of which have been reported previously.[4–6] Briefly, 5888 Medicare-eligible community-dwelling older adults (≥65 years of age) were recruited in 2 phases; an original cohort of 5201 participants recruited during 1989–1990 was later supplemented with a second cohort of 687 black participants recruited during 1992–1993. For the purpose of the current study, we used a deidentified public-use copy of the CHS data obtained from the National Heart, Lung, and Blood Institute. These data, prepared by the CHS Central Coordinating Center at the University of Washington, Seattle, are identical to the original CHS data except that they contain data on 5795 participants (93 did not consent to be included in the public-use copy of the data).

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Table 1. Baseline Characteristics of Older Adults Without Prevalent Heart Failure by IDH*, Before and After Propensity Score Matching

	Before Matching			After Matching		
n (%) or Mean (±SD)	No IDH (n=4625)	IDH (n=751)	*P*	No IDH (n=2348)	IDH (n=545)	*P*
Demographics						
Age ≥75 y	1458 (32)	337 (45)	<0.001	890 (38)	221 (41)	0.253
Female	2609 (56)	486 (65)	<0.001	1452 (62)	338 (62)	0.938
Nonwhite	798 (17)	60 (8)	<0.001	237 (10)	48 (9)	0.364
Education college or higher	1992 (43)	320 (43)	0.813	1026 (44)	238 (434)	0.991
Past medical history						
Coronary artery disease	757 (16)	181 (24)	<0.001	441 (19)	113 (21)	0.297
Hypertension	2870 (62)	321 (43)	<0.001	1169 (50)	252 (46)	0.135
Diabetes mellitus	717 (16)	134 (18)	0.103	374 (16)	92 (17)	0.586
Stroke	180 (4)	31 (4)	0.757	91 (4)	24 (4)	0.570
Peripheral artery disease	568 (12)	116 (15)	0.016	459 (18)	86 (24)	0.007
Loss of balance	1041 (23)	200 (27)	0.013	574 (24)	145 (27)	0.293
Dizzy or light headed on standing up	939 (20)	153 (20)	0.965	480 (20)	110 (20)	0.892
Frequent falls	147 (3)	28 (4)	0.431	79 (3)	20 (4)	0.724
Self-reported fair-to-poor general health	1089 (24)	178 (24)	0.926	509 (22)	126 (23)	0.464
Current smoker	537 (12)	110 (15)	0.018	313 (13)	70 (13)	0.763
Alcohol, units per week	2.7 (±6.7)	1.6 (±4.2)	<0.001	1.8 (±4.5)	1.9 (±4.6)	0.633
Physical examination						
Body mass index, kg/m^2	26.7 (±4.1)	25.9 (±3.9)	<0.001	26.3 (±4.0)	26.2 (±3.8)	0.582
Heart rate, bpm	68 (±11)	66 (±11)	<0.001	67 (±10)	67 (±11)	0.672
Systolic blood pressure, mm Hg	139 (±21)	126 (±18)	<0.001	131 (±17)	130 (±18)	0.028
Diastolic blood pressure, mm Hg†	74 (±9)	53 (±5)	<0.001	71 (±8)	54 (±5)	<0.001
Pulse pressure, mm Hg†	66 (±11)	73 (±11)	<0.001	60 (±16)	76 (±20)	<0.001
Mini-mental state examination	27.6 (±2.7)	27.3 (±2.9)	0.008	27.6 (±2.8)	27.4 (±2.6)	0.423
Depression score	4.6 (±4.5)	4.9 (±4.8)	0.036	4.6 (±4.6)	4.7 (±4.7)	0.624
Cardiopulmonary testing						
Atrial fibrillation by electrocardiogram	99 (2)	11 (2)	0.225	39 (2)	11 (32)	0.564
Left ventricular hypertrophy by electrocardiogram	200 (4)	35 (5)	0.676	100 (4)	24 (54)	0.881
Borderline or abnormal left ventricular systolic function	336 (7)	66 (9)	0.141	184 (8)	44 (8)	0.853
Medications						
Angiotensin-converting enzyme inhibitors	319 (7)	28 (4)	0.001	131 (6)	21 (4)	0.104
β-blockers	593 (13)	96 (13)	0.977	324 (14)	63 (12)	0.166
Calcium channel blockers	568 (12)	106 (14)	0.159	291 (12)	62 (11)	0.513
Diuretics	1263 (27)	208 (28)	0.825	637 (27)	150 (28)	0.852
Any antihypertensive drug	2133 (46)	331 (44)	0.297	1055 (45)	235 (43)	0.443
Laboratory values						
Serum creatinine, mg/dL	0.96 (±0.38)	0.94 (±0.33)	0.106	0.94 (±0.36)	0.94 (±0.34)	0.922
Serum uric acid, mg/dL	5.67 (±1.51)	5.57 (±1.49)	0.090	5.61 (±1.50)	5.60 (±1.50)	0.850
Serum glucose, mg/dL	111 (±36)	112 (±38)	0.658	110 (±37)	111 (±35)	0.766
Serum insulin, μU/mL	17 (±24)	16 (±24)	0.606	16 (±23)	17 (±27)	0.593
Serum potassium, mEq/L	4.16 (±0.38)	4.19 (±0.38)	0.020	4.17 (±0.37)	4.17 (±0.38)	0.994
Total cholesterol, mg/dL	212 (±39)	209 (±40)	0.057	212 (±38)	211 (±40)	0.424
Serum albumin, g/dL	4.00 (±0.28)	3.98 (±0.31)	0.059	3.99 (±0.28)	3.98 (±0.32)	0.200
Serum C-reactive protein, mg/L	4.6 (±7.7)	5.0 (±9.7)	0.217	4.6 (±7.4)	4.5 (±8.6)	0.767
Hemoglobin, g/dL	14.1 (±1.3)	13.7 (±1.3)	<0.001	13.9 (±1.3)	13.8 (±1.3)	0.357

*IDH indicates isolated diastolic hypotension defined as a diastolic blood pressure <60 mm Hg and a systolic blood pressure ≥100 mm Hg.

†Diastolic blood pressure and pulse pressure are related to the exposure variable, IDH; are expected to be imbalanced; and are presented as baseline descriptive purposes only.

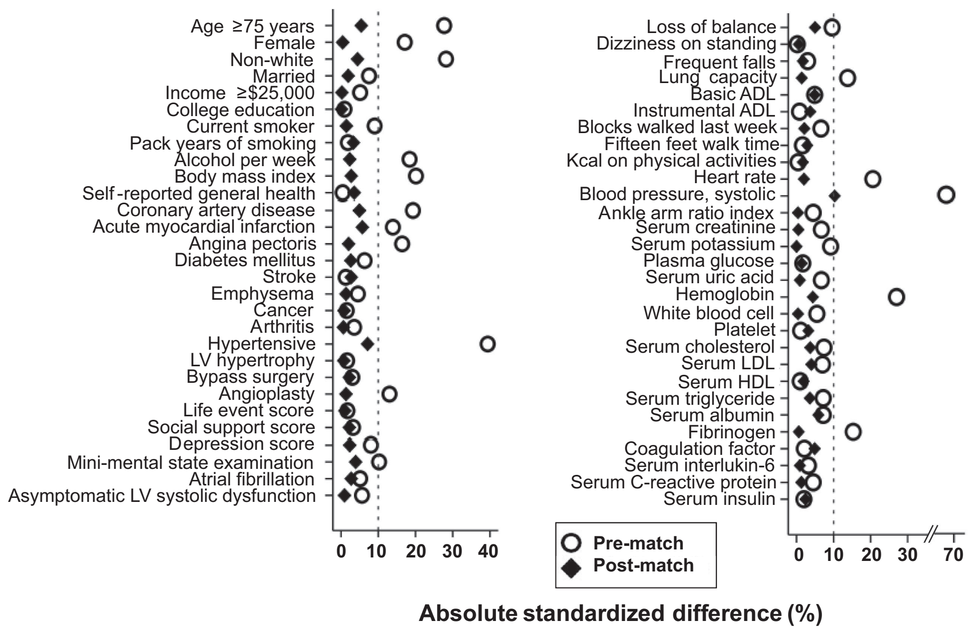


Figure 1. Love plot displaying absolute standardized differences in baseline characteristics between older adults with and without isolated diastolic hypotension (IDH), before and after propensity score matching.

Of the 5795 participants, 274 had centrally adjudicated prevalent HF at baseline and, hence, were excluded from the current analysis. Of the remaining 5521 participants, data on baseline SBP and DBP were available on 5504 participants. Because our definition of IDH excludes patients with SBP <100 mm Hg, we excluded 128 participants with SBP <100 mm Hg. Thus, the final sample size was composed of 5376 participants without baseline HF and with SBP ≥100 mm Hg. We included participants with and without treated hypertension to determine whether the effect of IDH on incident HF varied by antihypertensive therapy.

Baseline IDH and Other Measurements

Seated SBP and DBP were measured at baseline in the right arm after a 5-minute rest with a Hawksley random-zero sphygmomanometer, and the average of 2 measurements corrected for 0 values was used.[2] IDH was defined as DBP <60 mm Hg (and SBP ≥100 mm Hg), and, of the 5376 participants, 751 (14%) had IDH. Because blood pressure is a continuous variable and our definition of IDH is categorical, to understand the clinical characteristics of those with IDH better, we also categorized those with IDH into the following SBP categories: 100 to 109, 110 to 119, 120 to 129, 130 to 139, and ≥140 mm Hg. Data

Table 2. Baseline Characteristics of the 751 Prematch Participants With IDH, by Baseline SBP

		SBP, mm Hg					
Variable	IDH (Total)	100–109	110–119	120–129	130–139	≥140	*P*
Mean, n (%)	751 (100)	126 (17)	184 (25)	158 (21)	126 (17)	157 (21)	
Mean age, y	75	73	74	74	75	77	<0.001
Female, n (%)	486 (65)	81 (64)	105 (57)	105 (67)	82 (65)	113 (72)	0.073
Hypertension, n (%)	321 (43)	24 (19)	44 (24)	52 (33)	44 (35)	157 (100)	<0.001
Coronary artery disease, n (%)	181 (24)	33 (26)	42 (23)	43 (27)	26 (21)	37 (24)	0.707
Diabetes mellitus, n (%)	134 (18)	18 (14)	27 (15)	28 (18)	21 (17)	40 (26)	0.069
Mean blood pressure in persons not receiving any antihypertensive drug, mm Hg							
SBP	125	105	115	124	134	155	<0.001
DBP	54	55	54	54	54	53	0.197
PP	71	50	61	70	80	102	<0.001
Any antihypertensive drugs, n (%)	331 (44)	45 (36)	68 (37)	74 (47)	61 (48)	83 (53)	0.008
Mean blood pressure in persons receiving any antihypertensive drug, mm Hg							
SBP	129	106	115	124	134	152	<0.001
DBP	54	54	53	54	54	54	0.200
PP	75	52	62	70	80	99	<0.001

IDH indicates isolated diastolic hypotension; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

Table 3. Association of IDH* With Incident Heart Failure and All-Cause Mortality

Outcomes	No. of Events (%) No IDH	IDH	Absolute Risk Difference†	Hazard Ratio (95% CI)	*P*
Incident heart failure					
Before matching (n=5376)	n=4625	n=751			
Unadjusted	929 (20)	189 (25)	+5%	1.28 (1.10–1.50)	0.002
Multivariable adjusted				1.29 (1.09–1.53)	0.003
After matching (n=2893)	n=2348	n=545			
Propensity matched	459 (20)	137 (25)	+5%	1.33 (1.10–1.61)	0.004
All-cause mortality					
Before matching (n=5376)	n=4625	n=751			
Unadjusted	1997 (43)	381 (51)	+8%	1.19 (1.07–1.33)	0.002
Multivariable adjusted				1.14 (1.01–1.29)	0.031
After matching (n=2893)	n=2348	n=545			
Propensity matched	1039 (44)	266 (49)	+5%	1.12 (0.98–1.28)	0.096

*IDH indicates isolated diastolic hypotension defined as a diastolic blood pressure <60 mm Hg and a systolic blood pressure ≥100 mm Hg.

†Absolute risk differences were calculated by subtracting the percentage of events in the IDH group from the percentage of events in the no-IDH group (before values were rounded).

on demographics, past medical history, clinical findings, and laboratory variables were collected at baseline and have been described in detail previously.[2,4,5] Missing values for continuous variables were imputed based on values predicted by age, sex, and race.

Assembly of the Balanced Cohort

Considering significant imbalances in baseline characteristics between participants with and without IDH (Table 1 and Figure 1), we used propensity score matching to assemble a population in which those with and without IDH would be well balanced in all of the measured baseline characteristics.[7,8] Propensity scores for IDH were estimated for each of the 5376 participants using a nonparsimonious multivariable logistic regression model, in which IDH was the dependent variable and 58 baseline characteristics (Figure 1) were used as covariates.[3,9–13] Using a greedy matching protocol we matched each IDH participant with ≤5 no-IDH participants who had similar propensity scores, thus matching 545 IDH participants with 2348 no-IDH participants.[3,9–13] Absolute standardized differences for all of the 58 covariates were estimated and presented as Love plots.

Incident HF and Other Outcomes

The primary outcome for this study was centrally adjudicated incident HF during a median follow-up of >12 years, which has been described previously.[5,14–19] Briefly, self-reports of physician-diagnosed HF ascertained during semiannual visits were adjudicated by CHS Events Committee through the examination of participant's medical charts for clinical symptoms, physical signs, and other supporting evidence, including medications commonly used for HF and follow-up surveillances. Secondary outcomes were all-cause mortality and other incident cardiovascular events.

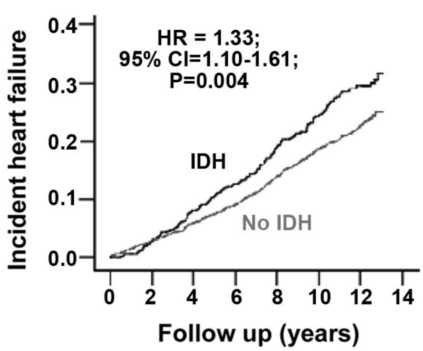
Statistical Analysis

For descriptive analyses, the Pearson χ^2 test, Student *t* test, ANOVA, Wilcoxon rank-sum test, and paired sample *t* test were used as appropriate for between-group comparisons. We used Kaplan-Meier and Cox proportional hazard analyses to estimate the associations between IDH and outcomes. Subgroup analyses were performed to determine the homogeneity of this association. Sensitivity analyses were performed as follows: (1) to quantify the degree of a hidden bias that would need to be present to invalidate our conclusions based on the propensity-matched cohort[20]; (2) to estimate the multivariable-adjusted association of IDH with incident HF in the 5376 prematch participants using the 58 covariates used in the propensity model; and (3) to estimate the effect of IDH in 3141 prematch participants without hypertension (after excluding 157 and 2078 participants with and without IDH who had SBP ≥140 mm Hg). All of the statistical tests were 2 tailed with 95% confidence levels, and a *P* value <0.05 was considered significant. SPSS for Windows version 15 (Chicago, IL) was used for all of the data analysis.

Results

Baseline Characteristics

Compared with participants without IDH, those with IDH were more likely to be older, female, white, current smokers, and to have coronary artery disease but less likely to have hypertension and similar orthostatic symptoms, all of which were balanced after matching (Table 1 and Figure 1). Overall, 267 (5%) had DBP ≥90 mm Hg, and among the remaining 5109 participants, 1995 (39%) had ISH and 3114 (61%) had normal SBP. Among the 751 older adults with IDH, 41% had normal SBP, 38% had prehypertension, and 21% had ISH, of whom, respectively, 37%, 48%, and 53% received antihypertensive therapy (Table 2). Mean DBP was similar across SBP



Number of patients at risk:				
No-IDH	2348	2050	1621	1125
IDH	545	472	354	231

Figure 2. Kaplan-Meier plot for incident heart failure by isolated diastolic hypotension (IDH). HR indicates hazard ratio.

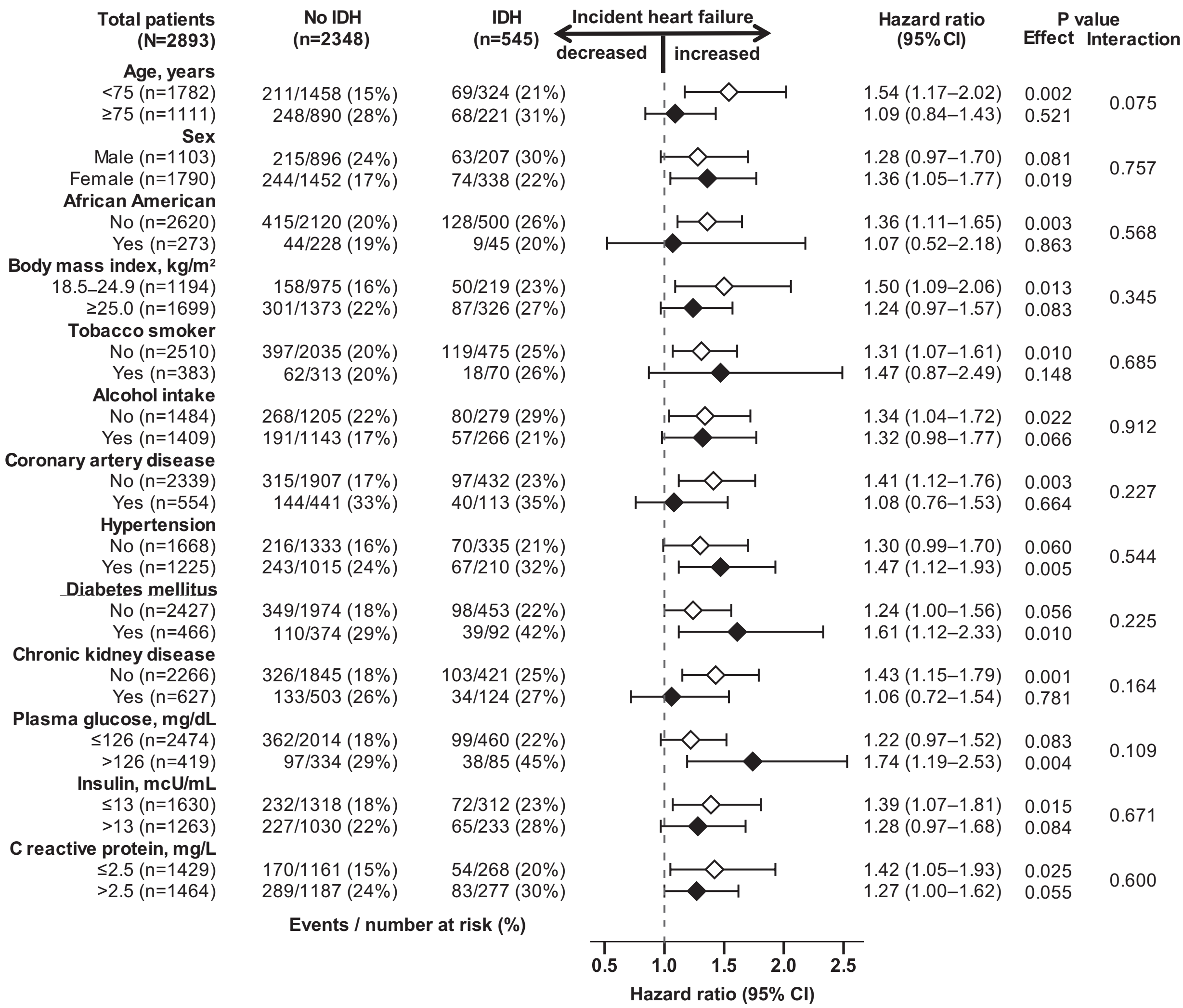


Figure 3. Association of baseline isolated diastolic hypotension (IDH) with incident heart failure in subgroups of propensity score-matched older adults.

categories regardless of the use of antihypertensive drugs (Table 2).

Association of IDH With Incident HF

During >12 years of median follow-up, incident HF developed in 25% and 20% of matched participants with and without IDH, respectively (hazard ratio [HR] when IDH was compared with no-IDH: 1.33 [95% CI: 1.10–1.61]; P=0.004; Table 3 and Figure 2). A hidden binary covariate that is a near-perfect predictor of incident HF would need to increase the odds of IDH by 17% to explain away this association. This association was homogenous across a wide spectrum of matched participants (Figure 3). Prematch associations of IDH with incident HF are displayed in Table 3. The multivariable-adjusted HR for IDH-associated incident HF in prematch participants with SBP <140 mm Hg was 1.43 (95% CI: 1.16–1.77; P=0.001).

Association of IDH With Other Outcomes

All-cause mortality occurred in 49% and 44% of matched participants with and without IDH, respectively (HR associated with IDH: 1.12 [95% CI: 0.98–1.28]; P=0.096; Table 3). IDH had no significant association with acute myocardial infarction (HR: 0.94 [95% CI: 0.69–1.27]; P=0.664), angina pectoris (HR: 1.04 [95% CI: 0.83–1.32]; P=0.724), stroke (HR: 0.95 [95% CI: 0.74–1.24]; P=0.720), transient ischemic attack (HR: 1.21 [95% CI: 0.72–2.04]; P=0.475), and peripheral arterial disease (HR: 0.81 [95% CI: 0.48–1.36]; P=0.420).

Discussion

The results of the current analysis demonstrate that IDH was an independent risk factor for incident HF among community-dwelling older adults, which was similar in magnitude to the effect of ISH on incident HF in this cohort.[3] We also demonstrate that the effect of IDH on incident HF was homogeneous across a wide spectrum of older adults, including those with SBP <140 mm Hg. Although diastolic hypotension has been shown to be associated with adverse cardiovascular outcomes,[21] to the best of our knowledge, this is the first report of a propensity-matched study identifying IDH as a significant independent risk factor for centrally adjudicated incident HF in community-dwelling older adults.

As in ISH and wide PP, IDH is also primarily a manifestation of impaired aortic compliance associated with aging, which results in a rise in SBP and a fall in DBP, thus widening the PP.[22–27] The resultant increased afterload and myocardial oxygen demand may result in myocardial ischemia and subsequent systolic and diastolic dysfunction.[28,29] Poor outcomes associated with a DBP ≤60 mm Hg in frail older adults has been reported to be independent of aortic compliance and left ventricular ejection fraction.[30] Hypertension or uncontrolled SBP is unlikely to explain the association between IDH and incident HF, because the association persisted after excluding those with SBP ≥140 mm Hg. In addition, the use of antihypertensive drugs is unlikely to explain this association, because the mean SBP and DBP were similar regardless of the use of antihypertensive drugs. Although both ISH and IDH are associated with wide PP, the roles of SBP and DBP in these 2 conditions may differ. For example, despite a similar PP (70 mm Hg), DBP may not play a role in the development of incident HF in ISH (150/80 mm Hg), whereas SBP may not play a role in the development of incident HF in IDH (120/50 mm Hg).[31] Further studies are needed to elucidate the detailed mechanisms by which IDH is associated with incident HF.

In patients with hypertension and coronary artery disease, a low DBP has been shown to be associated with poor outcomes, and it has been suggested that excessive reduction in DBP should be avoided in these patients.[30,32] Despite the fact that, in our study, the mean SBP and DBP were similar regardless of antihypertensive therapy, data from ISH suggest that antihypertensive therapy is often associated with concomitant lowering of DBP.[33] Because intensive lowering of SBP may not reduce major cardiovascular events,[34] taken together with the findings of the current study, it may be reasonable to keep DBP ≥60 mm Hg in older adults with ISH. Future hypertension guidelines need to focus on optimal DBP parameters for older adults receiving antihypertensive therapy.

Several limitations of our study need to be acknowledged. We had no data on dosages of antihypertensive drugs used to determine whether those with IDH were receiving higher doses. It is possible that participants without IDH at baseline may have developed IDH during follow-up, and this regression dilution may have underestimated the associations observed in our study.[35] The association of IDH with outcomes may vary across various subsets of SBP, which needs to be examined in the future. Despite the displayed balance in all of the measured baseline covariates, bias because of residual imbalance or imbalance in an unmeasured covariate is possible. However, findings from our sensitivity analysis suggest that the association of IDH with incident HF was rather insensitive to an unmeasured covariate.

Perspectives

IDH, defined as a DBP <60 mm Hg with an SBP ≥100 mm Hg, is an independent risk factor for incident HF in community-dwelling older adults, the magnitude of which is similar to the effect of ISH on incident HF.

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Disclosures

None.

References

1. Franklin SS, Gustin Wt, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure: the Framingham Heart Study. *Circulation*. 1997;96:308–315.
2. Psaty BM, Furberg CD, Kuller LH, Borhani NO, Rautaharju PM, O'Leary DH, Bild DE, Robbins J, Fried LP, Reid C. Isolated systolic hypertension and subclinical cardiovascular disease in the elderly: initial findings from the cardiovascular health study. *JAMA*. 1992;268:1287–1291.
3. Ekundayo OJ, Allman RM, Sanders PW, Aban I, Love TE, Arnett D, Ahmed A. Isolated systolic hypertension and incident heart failure in older adults: a propensity-matched study. *Hypertension*. 2009;53:458–465.
4. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A, O'Leary DH, Psaty B, Rautaharju P, Tracy RP, Weiler PG. The cardiovascular health study: design and rationale. *Ann Epidemiol*. 1991;1:263–276.
5. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW, Gardin JM, Rutledge JE, Boineau RC. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol*. 2000;35:1628–1637.
6. Gottdiener JS, McClelland RL, Marshall R, Shemanski L, Furberg CD, Kitzman DW, Cushman M, Polak J, Gardin JM, Gersh BJ, Aurigemma GP, Manolio TA. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function–the Cardiovascular Health Study. *Ann Intern Med*. 2002;137:631–639.
7. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70:41–55.
8. Rubin DB. Using propensity score to help design observational studies: application to the tobacco litigation. *Health Serv Outcomes Res Methodol*. 2001;2:169–188.
9. Ahmed A, Husain A, Love TE, Gambassi G, Dell'Italia LJ, Francis GS, Gheorghiade M, Allman RM, Meleth S, Bourge RC. Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. *Eur Heart J*. 2006;27:1431–1439.
10. Ekundayo OJ, Dell'italia LJ, Sanders PW, Arnett D, Aban I, Love TE, Filippatos G, Anker SD, Lloyd-Jones DM, Bakris G, Mujib M, Ahmed A. Association between hyperuricemia and incident heart failure among older adults: a propensity-matched study. *Int J Cardiol*. 2009;142:279–287.
11. Filippatos GS, Ahmed MI, Gladden JD, Mujib M, Aban IB, Love TE, Sanders PW, Pitt B, Anker SD, Ahmed A. Hyperuricaemia, chronic kidney disease, and outcomes in heart failure: potential mechanistic insights from epidemiological data. *Eur Heart J*. 2011;32:712–720.
12. Pitt B, Ahmed A, Love TE, Krum H, Nicolau J, Cardoso JS, Parkhomenko A, Aschermann M, Corbalan R, Solomon H, Shi H, Zannad F. History of hypertension and eplerenone in patients with acute myocardial infarction complicated by heart failure. *Hypertension*. 2008;52:271–278.
13. Bowling CB, Pitt B, Ahmed MI, Aban IB, Sanders PW, Mujib M, Campbell RC, Love TE, Aronow WS, Allman RM, Bakris GL, Ahmed A. Hypokalemia and outcomes in patients with chronic heart failure and chronic kidney disease: findings from propensity-matched studies. *Circ Heart Fail*. 2010;3:253–260.
14. Ives DG, Fitzpatrick AL, Bild DE, Psaty BM, Kuller LH, Crowley PM, Cruise RG, Theroux S. Surveillance and ascertainment of cardiovascular events: the Cardiovascular Health Study. *Ann Epidemiol*. 1995;5:278–285.
15. Psaty BM, Kuller LH, Bild D, Burke GL, Kittner SJ, Mittelmark M, Price TR, Rautaharju PM, Robbins J. Methods of assessing prevalent cardio-

vascular disease in the Cardiovascular Health Study. *Ann Epidemiol*. 1995;5:270–277.
16. Aurigemma GP, Gottdiener JS, Shemanski L, Gardin J, Kitzman D. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol*. 2001;37:1042–1048.
17. Gardin JM, McClelland R, Kitzman D, Lima JA, Bommer W, Klopfenstein HS, Wong ND, Smith VE, Gottdiener J. M-mode echocardiographic predictors of six- to seven-year incidence of coronary heart disease, stroke, congestive heart failure, and mortality in an elderly cohort (the Cardiovascular Health Study). *Am J Cardiol*. 2001;87:1051–1057.
18. Schellenbaum GD, Rea TD, Heckbert SR, Smith NL, Lumley T, Roger VL, Kitzman DW, Taylor HA, Levy D, Psaty BM. Survival associated with two sets of diagnostic criteria for congestive heart failure. *Am J Epidemiol*. 2004;160:628–635.
19. Schellenbaum GD, Heckbert SR, Smith NL, Rea TD, Lumley T, Kitzman DW, Roger VL, Taylor HA, Psaty BM. Congestive heart failure incidence and prognosis: case identification using central adjudication versus hospital discharge diagnoses. *Ann Epidemiol*. 2006;16:115–122.
20. Rosenbaum PR. Sensitivity to hidden bias. In: Rosenbaum PR, ed. *Observational Studies.* New York, NY: Springer-Verlag; 2002:105–170.
21. Benetos A, Zureik M, Morcet J, Thomas F, Bean K, Safar M, Ducimetiere P, Guize L. A decrease in diastolic blood pressure combined with an increase in systolic blood pressure is associated with a higher cardiovascular mortality in men. *J Am Coll Cardiol*. 2000;35:673–680.
22. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises–part I: aging arteries–a "set up" for vascular disease. *Circulation*. 2003;107:139–146.
23. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, Havlik R, Lakatta EG, Spurgeon H, Kritchevsky S, Pahor M, Bauer D, Newman A. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation*. 2005;111:3384–3390.
24. Dart AM, Kingwell BA. Pulse pressure: a review of mechanisms and clinical relevance. *J Am Coll Cardiol*. 2001;37:975–984.
25. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol*. 2005;25: 932–943.
26. Schlatmann TJ, Becker AE. Histologic changes in the normal aging aorta: implications for dissecting aortic aneurysm. *Am J Cardiol*. 1977;39: 13–20.
27. Chae CU, Pfeffer MA, Glynn RJ, Mitchell GF, Taylor JO, Hennekens CH. Increased pulse pressure and risk of heart failure in the elderly. *JAMA*. 1999;281:634–639.
28. Milnor WR. Arterial impedance as ventricular afterload. *Circ Res*. 1975; 36:565–570.
29. Urschel CW, Covell JW, Sonnenblick EH, Ross J Jr, Braunwald E. Effects of decreased aortic compliance on performance of the left ventricle. *Am J Physiol*. 1968;214:298–304.
30. Protogerou AD, Safar ME, Iaria P, Safar H, Le Dudal K, Filipovsky J, Henry O, Ducimetiere P, Blacher J. Diastolic blood pressure and mortality in the elderly with cardiovascular disease. *Hypertension*. 2007;50: 172–180.
31. Domanski M, Mitchell G, Pfeffer M, Neaton JD, Norman J, Svendsen K, Grimm R, Cohen J, Stamler J. Pulse pressure and cardiovascular disease-related mortality: follow-up study of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA*. 2002;287:2677–2683.
32. Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, Kolloch R, Benetos A, Pepine CJ. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med*. 2006;144:884–893.
33. Somes GW, Pahor M, Shorr RI, Cushman WC, Applegate WB. The role of diastolic blood pressure when treating isolated systolic hypertension. *Arch Intern Med*. 1999;159:2004–2009.
34. Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575–1585.
35. Clarke R, Shipley M, Lewington S, Youngman L, Collins R, Marmot M, Peto R. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol*. 1999;150: 341–353.