Can the Absence of Hypertension Refine the Risk Assessment of Older Adults for Future Cardiovascular Events?

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We sought to determine if the absence of hypertension in older adults can be used to identify those at lower risk of atherosclerotic cardiovascular disease (ASCVD). We identified participants ≥75 years old free of cardiovascular disease (CVD) in the National Institutes of Health Pooled Cohorts with and without hypertension. We assessed the association between systolic blood pressure (BP), diastolic BP, and cardiovascular events using multivariable modeling. The association between predicted ASCVD risk and observed events was compared. Of 2,667 adults aged ≥75 years, 67.9% had hypertension. Lower systolic BP correlated with lower CVD event rates. ASCVD predicted risk score and systolic BP were both independently associated with ASCVD event rates. Among adults with similar ASCVD predicted risk estimates, those without (vs with) hypertension had lower observed event rates across the predicted risk spectrum. The absence of hypertension may help refine the risk stratification of older adults, particularly those with intermediate predicted risk. **(Am J Cardiol 2021;142:83−90)**

Systolic blood pressure (BP) rises with advancing age, [1] largely due to progressive atherosclerosis and increased vascular stiffening.[2, 3] We hypothesized that the absence of hypertension in older adults may be a marker for healthy underlying vasculature which, in turn, may be a marker for those at lower risk of future atherosclerotic cardiovascular disease (ASCVD) events. To test this hypothesis, we utilized data from the National Heart, Lung, and Blood Institute's (NHLBI's) Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) Pooled Cohorts Study program, including data from the Cardiovascular Health Study (CHS), the Framingham Heart Study (Framingham Original), the Framingham Offspring Study (FOS), and the Multi-Ethnic Study of Atherosclerosis (MESA). Using this data, we sought to (1) demonstrate the associations between systolic BP, diastolic BP, and CVD events in a closely followed US population of older adults ≥75 years old and free of CVD; and (2) assess whether normotensive older adult patients are at significantly lower risk compared with hypertensive patients when predicted ASCVD risk is otherwise similar.

Methods

We identified individuals ≥75 years old without known CVD using data from the following cohort studies obtained from the NHLBI's BioLINCC program: CHS,[4] Framingham Original,[5] FOS,[6] and MESA.[7] Within each cohort, we identified a baseline exam chosen to maximize the number of older adult patients with at least 5 years of follow-up: CHS visit 3 (1992−1993), Framingham Exam 24 (1995−1998), FOS Exam 7 (1998−2001), and MESA Exam 1 (2000−2002). Previous CVD was defined as a history of cerebrovascular disease, coronary heart disease, peripheral arterial disease, or heart failure. We evaluated baseline variables including the participants' age, sex, race, systolic BP, diastolic BP, BP lowering medication, lipid levels, the presence of lipid-lowering therapy, diabetes, smoking, body mass index, and estimated glomerular filtration rate. BP was ascertained with a sphygmomanometer through an average of 2 or 3 seated measurements. For the majority of our analyses, hypertension was defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg per the more liberal definition from Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7),[8] or the use of BP lowering medication regardless of BP recorded. A BP of ≥140/90 was selected as the primary definition of hypertension for this study to optimize the number of patients qualifying as "normotensive" who may benefit from derisking, and to utilize a definition where patients are universally recommended for antihypertensive therapy. In sensitivity analysis, hypertension was defined as systolic BP ≥130 mm Hg or diastolic BP ≥80 mm Hg per the most recent 2017 American College of Cardiology/American Heart Association guideline definition.[9] The use of BP lowering medications was self-reported in all 4 cohorts. Of note, for the univariable cox proportional hazards modeling of the relationship between systolic BP and CVD events and diastolic BP and CVD events, patients on BP lowering medications were excluded from the primary analysis as we determined that BP lower medications are likely an intermediary step

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Dr. Nanna was supported during the conduct of this study by the NIH training grant T32-HL069749. Dr. Navar is funded by NIH K01HL133416-01.

See page 89 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2020.11.027

in the causal pathway between the exposure of interest (hypertension) and the outcome of interest (5-year CVD events). Patients on BP lowering medications were included in a sensitivity analysis. Among the identified subjects ≥75 years old, 390 of 3,057 (12.8%) were excluded, due to missing values for hypertension status, diabetes status, lipid-lowering medication or low-density lipoprotein cholesterol level, or smoking. Within the final cohort of 2,667 patients, missingness was rare−−1 patient on lipid-lowering therapy was missing a low-density lipoprotein cholesterol level and 4 patients on antihypertensive medications were missing data on BP. The primary outcome of interest was CVD events, defined as a composite of CVD, myocardial infarction, and stroke at 5 years. Within each of the cohorts, events were ascertained prospectively and adjudicated using each cohort's specific protocol.

Baseline characteristics were assessed in the individuals with versus without hypertension. Continuous variables are summarized with medians and quartiles and compared with the Wilcoxon test. Categorical variables are presented as frequencies and percentages and compared using chi-square tests. In order to calculate the 5-year risk of first occurrence of myocardial infarction, stroke (including fatal and nonfatal), and coronary heart disease death, we used the previously described ASCVD pooled cohort equations (PCE) 5-year risk calculation.[10] Chronologic age was used in the formula for individuals older than 79 years of age. Using univariable Cox proportional hazards modeling, we assessed the relationship between: (1) Systolic BP and CVD events at 5 years; and (2) Diastolic BP and CVD events in patients not on BP lowering medications. Linearity was assessed and nonlinearity was addressed using restricted cubic splines. Adjusted results were derived using multivariable Cox proportional hazards models. Adjustment variables included age, sex, race, diabetes, smoking, body mass index, estimated glomerular filtration rate, high-density lipoprotein cholesterol and non−high-density lipoprotein cholesterol, and lipid-lowering medications. In sensitivity analyses, we included patients on BP lowering medications (4 subjects excluded for missing systolic BP and 12 for diastolic BP).

In order to determine whether the absence of hypertension decreased risk in older subjects, we estimated 5-year CVD event rates using the Kaplan-Meier method stratified by predicted risk according to the PCE and by the presence or absence of hypertension, including patients on BP medication. Patients were stratified using a predicted 5-year high-risk threshold of 10%, which roughly corresponds to a 20% 10-year risk (i.e., the high-risk threshold in the current lipid guidelines).[11] Kaplan-Meier curves were repeated using the alternative definition of hypertension (BP ≥130/80 mm Hg).

Finally, we assessed the association between 5-year predicted ASCVD risk using the PCE and CVD events at 5 years in patients with versus without hypertension as defined above and repeated using the more liberal definition of ≥130/80 mm Hg in a sensitivity analysis. In addition, we computed the deciles of the distribution of the predicted versus observed risk in the whole sample, and then split them into hypertensive and nonhypertensive groups. The performance of the 5-year predicted risk using the PCE was assessed in older adults with and without hypertension by evaluating the c-statistic and calibration Chi-squared in each population.

Analyses were approved by the Duke University Institutional Review Board (PRO 00051569), and all subjects participating in the individual studies provided informed consent to participate. All analyses were performed using SAS version 9.4 (TS1M5) (Cary, North Carolina).

Results

Overall, 2667 participants free of CVD at 75 years were included with a median follow-up time of 8.3 years (25th −75th percentile = 5.0 to 10.1 years). Of these, 1,812 (67.9%) met study criteria for our primary definition of hypertension. The primary definition of hypertension used in our analysis was patients with systolic BP ≥140 mm Hg (N = 1194, 66.0% of hypertension group) or diastolic BP ≥90 mm Hg (N = 98, 5.4%) and/or patients who were on a BP lowering medication regardless of BP (N = 1247, 68.8%). Table 1 and Supplementary Table S1 summarize the baseline characteristics of the cohort, which are stratified by the presence or absence of hypertension. The highest event rates were seen in those with BP ≥140/90, either on (15.7%) or not on medications (17.9%); event rates were lower in those on BP medications with BP <140/90 (12.9%) and those with BP <140/90 not on BP medications (8.0%) (p <0.001).

Among adults not on BP lowering treatment (N = 1420), the association between systolic BP and CVD events was statistically significant (p <0.0001; Figure 1). After multivariable adjustment, the HR per 10 mm Hg decrease in systolic BP was 0.853 (95% CI, 0.813 to 0.894, p <0.0001); Table 2). Among adults not on BP lowering treatment and with a diastolic BP measurement available (N = 1417), the association between diastolic BP and CVD events with diastolic BP was nonlinear (p-value for nonlinearity = 0.02). For diastolic BP below 80 mm Hg, we observed no statistically significant relation between diastolic BP and CVD events. A statistically significant relation was found between diastolic BP and CVD events for diastolic BP values above 80 mm Hg with an overall p-value = 0.03 (Figure 1; Table 2). The association between diastolic BP and CVD events was attenuated in multivariable modeling (HR per 10 mm Hg decrease = 0.919, 95% CI, 0.830 to 1.019, p = 0.11). Sensitivity analyses including patients on BP lowering medications for both models were performed and produced consistent results (Supplementary Figure S1, Supplementary Figure S2, and Supplementary Table S2), with the exception that the association between diastolic BP and CVD events remained significant in multivariable modeling (p = 0.01).

We assessed 5-year CVD event rates among subjects stratified above and below a predicted 5-year ASCVD risk of 10% using the PCE (N = 1958 with <10% risk; N = 705 with ≥10% risk), then further divided based on the presence or absence of hypertension (Figure 2). Among subjects with a predicted 5-year risk ≥10%, 5-year CVD event rates were lower among those without hypertension versus those with hypertension (Kaplan-Meier rate 10.5% vs 16.9%, p <0.0001). Individuals with <10% predicted risk without hypertension had lower event rates than those with, but this

Table 1
Characteristics of older adult (≥75 year old) patients in the pooled cohorts by hypertension status

Characteristic	Hypertension*		p Value
	Yes (N = 1812)	No (N = 855)	
Study cohort			0.1294
CHS	787 (43.4%)	412 (48.2%)	
Framingham Offspring	141 (7.8%)	64 (7.5%)	
Framingham Original	217 (12.0%)	98 (11.5%)	
MESA	667 (36.8%)	281 (32.9%)	
Women	1092 (60.3%)	479 (56.0%)	0.0377
Age (median, 25th−75th)	78, 76−82	78, 76−81	0.0451
Age (years)			0.0150
75−79	1168 (64.5%)	592 (69.2%)	
≥80	644 (35.5%)	263 (30.8%)	
			0.0001
White	1355 (74.8%)	690 (80.7%)	
Black	232 (12.8%)	64 (7.5%)	
Other	225 (12.4%)	101 (11.8%)	
BMI (median, 25th−75th) (Kg/m^2)	26.5, 23.7−29.3	25.4, 22.8−27.9	<0.0001
Systolic BP (median, 25th−75th)	146, 134−159	123, 114−131	<0.0001
Diastolic BP (median, 25th−75th)	71, 64−79	66, 60−71	<0.0001
Systolic BP ≥140	1194 (66.0%)	0	–
Diastolic BP ≥90	98 (5.4%)	0	–
Systolic BP ≥140 or Diastolic BP ≥90	1201 (66.3%)	0	–
On BP meds	1247 (68.8%)	0	–
Total cholesterol (median, 25th−75th) (mg/dl)	196, 173−222	198, 175−225	0.1638
HDL-C (median, 25th−75th) (mg/dl)	52, 42−62	53, 44−63	0.0256
Triglycerides (median, 25th−75th) (mg/dl)	120, 86−165	110, 78−151	<0.0001
LDL-C (median, 25th−75th) (mg/dl)	116, 96−139	119, 97−141	0.0635
LDL-C ≥130 mg/dl	615 (33.9%)	317 (37.1%)	0.0653
On lipid lowering medications	245 (13.5%)	61 (7.1%)	<0.0001
Diabetes mellitus	263 (14.5%)	68 (8.0%)	<0.0001
Current smoker	87 (4.8%)	57 (6.7%)	0.0467
eGFR (median, 25th−75th) (ml/min)	53.1, 43.4−64.4	53.4, 44.5−63.6	0.2566
On aspirin	377 (20.8%)	121 (14.2%)	<0.0001

BMI = body mass index; BP = blood pressure; CHS = Cardiovascular Health Study; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MESA = Multi-Ethnic Study of Atherosclerosis

* Defined as having a blood pressure ≥140/90 or on blood pressure lowering medications.

was not statistically significant (Kaplan-Meier rate 5.1% without hypertension vs 8.9% with hypertension, p = 0.68). Sensitivity analyses using BP ≥130/80 mm Hg or on BP lowering medication as the criteria for hypertension revealed similar results (Supplementary Figure S3).

Figure 3 demonstrates the association between PCE 5-year predicted ASCVD risk and observed 5-year event rates stratified by subjects with and without hypertension (Figure 3). In the very low predicted risk subjects (approximately 4% to 10% 5-year predicted risk) and the very high-risk subjects (>20% 5-year predicted risk), the hypertensive and normotensive groups appeared to be at similar risk for ASCVD events. Nevertheless, among those at intermediate risk with a predicted risk between 10% and 20%, those without hypertension had markedly lower 5-year observed event rates than those with hypertension. Individuals without hypertension appeared to be at lower risk compared with individuals with hypertension even when the 5-year PCE predicted risk was the same. This is further demonstrated in Supplementary Figures S4 & S5, which display predicted versus observed 5-year rates of CVD in those with and without hypertension by decile of predicted risk. This difference was attenuated using a BP cut-off of ≥130/80 mm Hg to define hypertension (Supplementary Figure S6).

Discussion

Our study found a strong and significant association between lower systolic BP and lower cardiovascular risk in adults older than 75 years. These results are consistent with longstanding evidence of the association between blood pressure and ASCVD risk[12−15]; however, our study emphasizes that most older adult patients who survive to 75 years and beyond without hypertension, or the need for BP lowering medications, are at markedly lower ASCVD risk than their peers with otherwise similar predicted risk. This finding highlights how normal BP is a simple factor that can easily identify older patients at relatively lower risk for future events; such patients may be considered for a less-aggressive primary prevention strategy.

Systolic BP elevation in our cohort was strongly associated with future cardiovascular risk, further emphasizing the importance of SBP as a modifiable cardiovascular risk factor even in an older population. Although DBP elevation

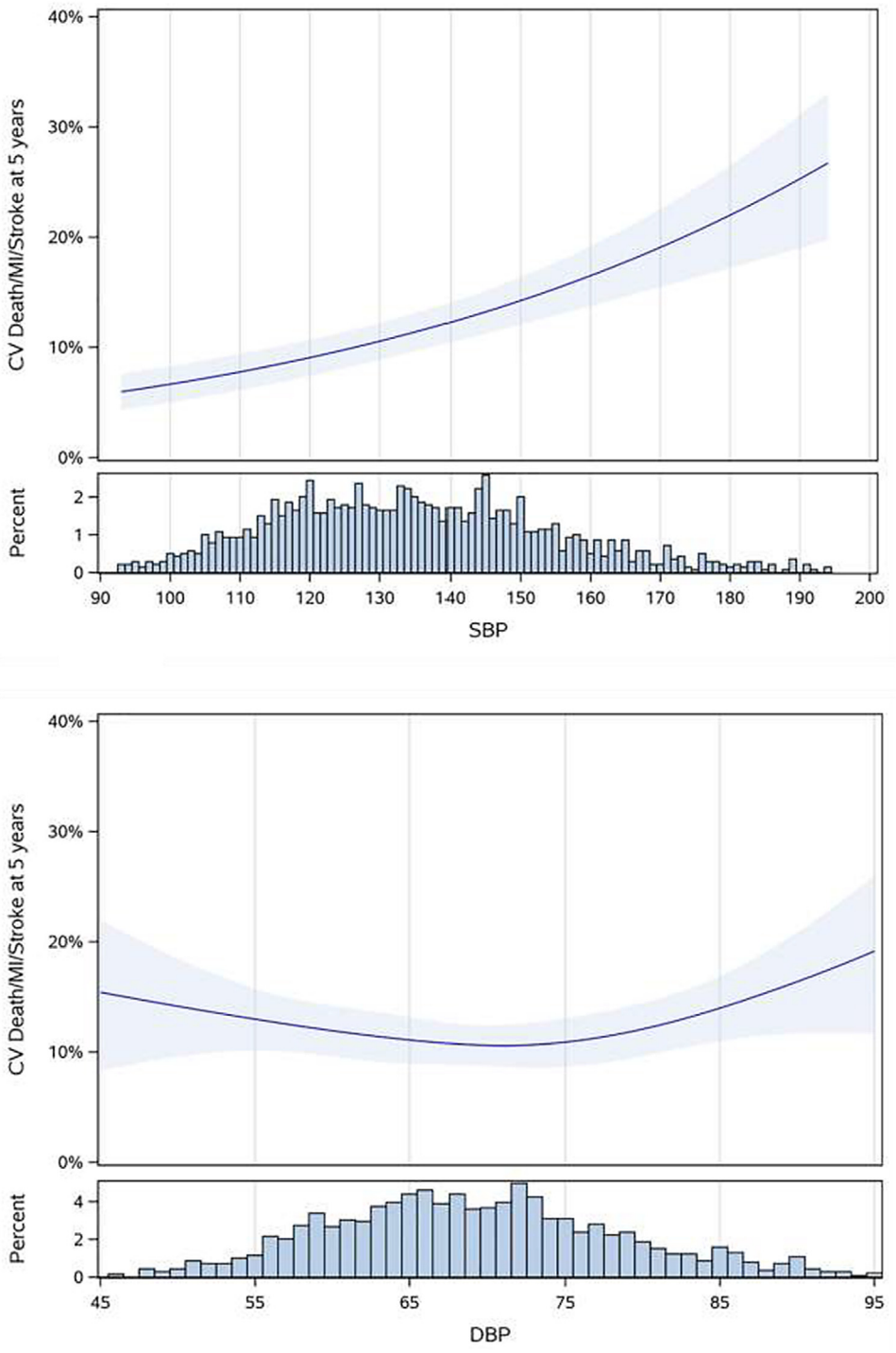

Figure 1. **A. Relationship between systolic BP and Risk of CVD in older adults (≥75 years old)** This figure exhibits the association between systolic BP and CVD events with systolic BP modeled both linearly and nonlinearly (unadjusted HR per 10 mm Hg increase was 1.174, 95% CI, 1.120 to 1.231, p <0.0001). After adjustment using multivariable modeling, HR per 10 mm Hg increase was 1.174, 95% CI, 1.119 to 1.231, p <0.0001. There was no evidence of a nonlinear relationship in the unadjusted (p-value for non-linearity = 0.31) or adjusted (p-value for nonlinearity = 0.17) models. A total of 1,247 observations on BP medications were excluded from this analysis. *(B)* **Relationship between diastolic BP and Risk of CVD in older adults** This figure exhibits the association between diastolic BP and CVD events with DBP modeled both linearly and nonlinearly, excluding patients on blood pressure medications. There was evidence of a nonlinear relationship with p-value for nonlinearity = 0.02. Modeled nonlinearly using restricted cubic splines, with the following unadjusted results per 10 mm Hg increase: at diastolic BP = 50 mm Hg: HR = 0.833 (0.608 to 1.141); at diastolic BP = 60 mm Hg: HR = 0.882 (0.736 to 1.057); at diastolic BP = 70 mm Hg: HR = 1.148 (0.995 to 1.326); at diastolic BP = 80 mm Hg: HR = 1.391 (1.071 to 1.805); at diastolic BP = 90 mm Hg: HR = 1.412 (1.068 to 1.868; p-value = 0.0285). Multivariable modeling yielded the following adjusted result per 10 mm Hg increase: HR = 1.093, 95% CI, 0.986 to 1.212, p = 0.09. There was no evidence of a nonlinear relationship between diastolic BP and CVD events with multivariable modeling (p-value for nonlinearity = 0.95). 1247 observations on BP medications were excluded from this analysis. BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio.

Table 2
Association between continuous BP and CVD risk, excluding patients on BP medications

	p Value	HR for 10 units decrease (95% CI)
Systolic BP (linear)		
Unadjusted	<0.0001	0.852 (0.813-0.893)
Adjusted*	<0.0001	0.853 (0.813-0.894)
Diastolic BP		
Unadjusted	0.0285	at Diastolic BP = 50: 1.205 (0.860-1.687) at Diastolic BP = 60: 1.201 (0.846-1.646) at Diastolic BP = 70: 1.134 (0.945-1.362) at Diastolic BP = 80: 0.869 (0.7531.003) at Diastolic BP=90: 0.720 (0.555-0.935)
Adjusted[2]	0.1091	0.919 (0.830-1.019)

BMI = body mass index; BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; Diastolic BP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; Systolic BP = systolic blood pressure.

Nonlinearity tests in unadjusted models: Systolic BP (p = 0.3092), Diastolic BP (p = 0.0162), Diastolic BP analyzed as nonlinear, HR presented at variable Diastolic BP levels.

Nonlinearity test in adjusted models: Systolic BP (p = 0.1567), Diastolic BP (p = 0.9515), Diastolic BP analyzed as linear.

N = 1420 for SBP, 1417 for Diastolic BP − 1,247 observations on BP meds excluded from this analysis.

* Adjusted by age, sex, race, diabetes, smoking, HDL-C, non−HDL-C, lipid-lowering medications, BMI, and eGFR. 19 observations not included in the adjusted analysis due to missing values in the adjustment variables.

† Adjusted by age, sex, race, diabetes, smoking, HDL-C, non−HDL-C, lipid-lowering medications, BMI, and eGFR. 19 observations not included in the adjusted analysis due to missing values in the adjustment variables.

was associated with significant risk beyond 80 mm Hg, it was no longer statistically significant following adjustment. The benefits of aggressive BP control in older adult populations ≥75 years of age and free of CVD have been previously demonstrated.[9,16–18] These benefits are noted in frail older participants, without an increased burden of serious adverse events or injurious falls.[17] This is reflected in the recent American College of Cardiology/American Heart Association guideline recommendations, which recommend a BP target of ≤130/80 mm Hg even among older adults.[9]

Hypertension is both a symptom and a cause of vascular dysfunction as patient's age.

Vascular aging occurs after upwards of 30 million pulsations/year and leads to increased intimal hyperplasia and vascular stiffening over time, with decreased elasticity and loss of arterial recoil.[19–21] These changes result in both systolic hypertension and lower diastolic BP, with increased pulse pressure creating increased arterial wall stress, thereby completing the cycle to further arterial stiffening.[20,22] Given the critical role of hypertension in the pathophysiology of vascular aging, normotension is a useful marker of relative vascular health in older adults.

Prevention treatment decisions are complex in older adult patients who may be more vulnerable to adverse effects from medications and polypharmacy.[23] In older adults at risk for harm from polypharmacy and adverse drug effects, revising the risk of individuals at borderline risk is an important consideration for clinicians to consider.[24] Our results suggest that the absence of hypertension in older adults holds promise as another possible risk refinement option for those at intermediate risk. This has the potential to impact decisions around therapeutic intensification versus de-escalation of preventive therapies such as lipid-lowering and antithrombotic therapies. Importantly, while the absence of hypertension was associated with relatively lower risk than predicted, it did not eliminate cardiovascular risk entirely; this was particularly true in those at high-predicted risk, due to other risk factors. Ultimately, broader shared decision-making requires a consideration of co-morbidities, polypharmacy, frailty, and individual patient preferences. The potential benefits of aggressive preventive therapies much be balanced with the potential harms, impact on function, and individual patient preferences.[25,26]

We acknowledge some limitations to our study. First, we were unable to capture important conditions associated with aging including atrial fibrillation, cognitive impairment, and frailty. Second, we relied on baseline BP measurements, but did not evaluate BP changes longitudinally, which may provide additional insights into the risk associated with hypertension. Third, while our findings are hypothesis-generating in highlighting normotension as a potential risk stratification identifier in older adult patients, this approach must be tested prospectively to definitively evaluate the safety, efficacy, and potential clinical utility of this marker in clinical practice. Finally, the PCE were derived and validated in subjects' ≤79 years old, but are the most widely utilized risk stratification tool in contemporary practice to inform primary prevention treatment decisions, including in older individuals in our experience; furthermore, dedicated risk stratification tools are not currently available for older adults.

In conclusion, the link between hypertension and cardiovascular risk remains strong even among those of advanced age. In the same vein, individuals who reach older age without known ASCVD or hypertension are at relatively lower cardiovascular risk compared with their peers with otherwise similar predicted risk. The presence or absence of normotension may be a simple predictor that can aid clinicians in making prevention decisions in vulnerable older adult populations.

Author Contributions

All authors have been involved in the study design, analysis, and manuscript revision. All authors read and approved the final manuscript. Dr. Nanna is the guarantor who accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

MG Nanna: Dr. Nanna had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Nanna contributed to the conception and design of the study, the data analysis, the data interpretation, the manuscript drafting, and the critical revision of the manuscript. **AM Navar:** Dr.

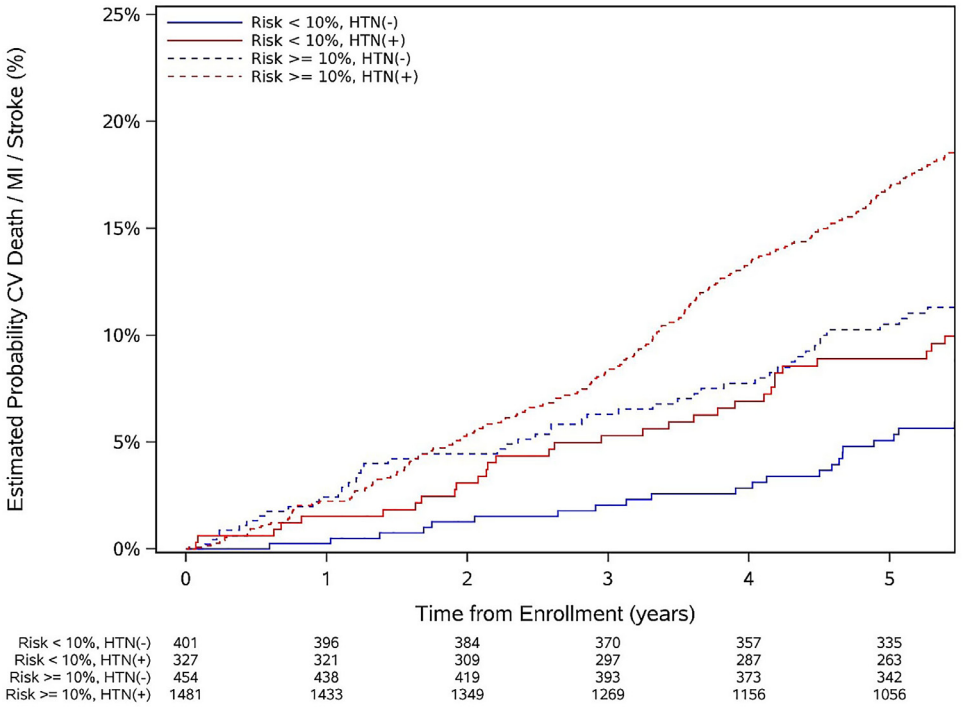

Figure 2. **CVD event rates in individuals stratified by predicted ASCVD risk (≥ or <10%) and hypertension** This figure demonstrates the observed 5-year CVD event rate of older adults (≥75 years old) across 4 separate strata: (1) predicted ASCVD risk <10% without hypertension; (2) predicted ASCVD risk <10% with hypertension; (3) predicted ASCVD risk ≥10% without hypertension; and (4) predicted ASCVD risk ≥10% with hypertension. The hypertension group includes patients on blood pressure lowering medications. ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease

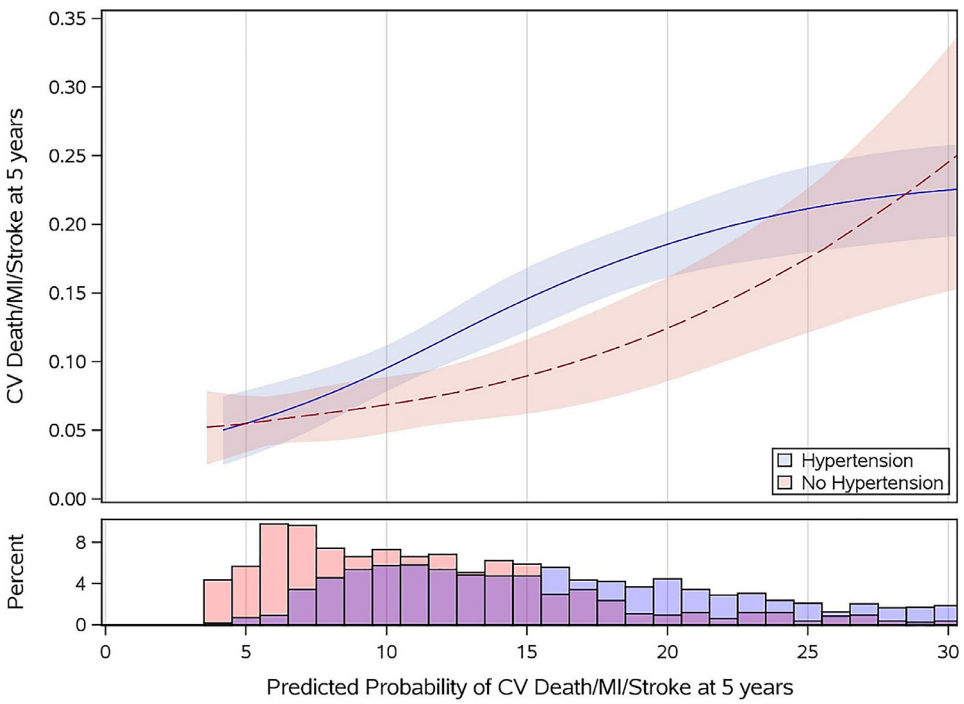

Figure 3. **Relationship between predicted risk of CVD and actual risk of CVD by hypertension status** This figure demonstrates the continuous association between the PCE 5-year predicted risk of CVD events and the actual 5-year CVD event rate in patients with versus without hypertension. Approximately 9% of the total observations at very high risk for CVD events (>30% 5-year risk) are excluded from the figure for presentation purposes; there was no significant difference between the groups above this threshold. Discrimination and Calibration: In nonhypertension: c = 0.6155, calibration chi-square = 23.8, p = 0.0046; In hypertension: c = 0.6054, calibration chi-square = 41.0, p <0.0001. CVD = cardiovascular disease.

Navar contributed to the conception and design of the study, the supervision, the data acquisition, the data analysis, the data interpretation, the manuscript drafting, and the critical revision of the manuscript. **D Wojdyla:** Mr. Wojdyla contributed to the design of study, the data analysis, the data interpretation, the manuscript drafting, and the critical revision of the manuscript. **AJ Nelson:** Dr. Nelson contributed to the data interpretation, the manuscript drafting, and the critical revision of the manuscript. **AE Sullivan:** Dr. Sullivan contributed to the data interpretation, the manuscript drafting, and the critical revision of the manuscript. **ED Peterson:** Dr. Peterson contributed to the conception and design of the study, the supervision, the data acquisition, the data analysis, the data interpretation, the manuscript drafting, and the critical revision of the manuscript.

Disclosures

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MG Nanna: Dr. Nanna is supported by NIH training grant T-32-HL069749. AM Navar: Research Grant: Significant; Amarin, Janssen, Amgen, Sanofi, and Regeneron Pharmaceuticals. Consultant/Advisory Board: Significant; Amarin, Amgen, Esperion, Janssen, The Medicines Company, Novartis, Pfizer, Novonordisk, AstraZeneca, Sanofi, and Regeneron. D Wojdyla: No relationship(s) to disclose. AJ Nelson: No relationship(s) to disclose. AE Sullivan: No relationship(s) to disclose. ED Peterson: Research Grant: Significant; Amgen, Sanofi, Astrazeneca, Merck, and Janssen. Consultant/Advisory Board; Modest; Amgen. AstraZeneca, Merck, Novartis, Pfizer, Janssen and Sanofi.

Acknowledgments

We thank Erin Campbell, MS, for her editorial contributions to this manuscript. Ms. Campbell did not receive compensation for her contributions, apart from her employment at the institution where this study was conducted.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.11.027.

1. Muntner P, Carey RM, Gidding S, Jones DW, Taler SJ, Wright JT Jr, Whelton PK. Potential US population impact of the 2017 ACC/AHA high blood pressure guideline. *Circulation* 2018;137:109–118.
2. Intengan HD, Schiffrin EL. Vascular remodeling in hypertension: roles of apoptosis, inflammation, and fibrosis. *Hypertension* 2001;38:581–587.
3. Lieb W, Larson MG, Benjamin EJ, Yin X, Tofler GH, Selhub J, Jacques PF, Wang TJ, Vita JA, Levy D, Vasan RS, Mitchell GF. Multimarker approach to evaluate correlates of vascular stiffness. *Circulation* 2009;119:37–43.
4. MPH for the Cardiovascular Health Study Research Group (CHS), 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, Weiler PG. The cardiovascular health study: design and rationale. *Ann Epidemiol* 1991;1:263–276.
5. Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: the Framingham Study. *Ann NY Acad Sci* 1963;107:539–556.
6. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The framingham offspring study. Design and preliminary data. *Prev Med* 1975;4:518–525.
7. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, Clark Nelson J, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-Ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol* 2002;156:871–881.
8. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, & National High Blood Pressure Education Program Coordinating Committee. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 Report. *JAMA* 2003;289:2560–2572.
9. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr.. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2018;138:e426–e483.
10. Muntner P, Colantonio LD, Cushman M, Goff DC Jr, Howard G, Howard VJ, Kissela B, Levitan EB, Lloyd-Jones DM, Safford MM. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. *JAMA* 2014;311:1406–1415.
11. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;139:e1082–e1143.
12. Flint AC, Conell C, Ren X, Banki NM, Chan SL, Rao VA, Melles RB, Bhatt DL. Effect of systolic and diastolic blood pressure on cardiovascular outcomes. *N Engl J Med* 2019;381:243–251.
13. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–1913.
14. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med* 1992;152:56–64.
15. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, White IR, Caulfield MJ, Deanfield JE, Smeeth L, Williams B, Hingorani A, Hemingway H. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet* 2014;383:1899–1911.
16. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ, HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008;358:1887–1898.
17. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, Fine LJ, Haley WE, Hawfield AT, Ix JH, Kitzman DW, Kostis JB, Krousel-Wood MA, Launer LJ, Oparil S, Rodriguez CJ, Roumie CL, Shorr RI, Sink KM, Wadley VG, Whelton PK, Whittle J, Woolard NF, Wright JT Jr, Pajewski NM, SPRINT Research Group. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized clinical trial. *JAMA* 2016;315:2673–2682.
18. Hakala SM, Tilvis RS, Strandberg TE. Blood pressure and mortality in an older population. A 5-year follow-up of the Helsinki Ageing Study. *Eur Heart J* 1997;18:1019–1023.

19. Dao HH, Essalihi R, Bouvet C, Moreau P. Evolution and modulation of age-related medial elastocalcinosis: impact on large artery stiffness and isolated systolic hypertension. *Cardiovasc Res* 2005; 66:307–317.
20. Lionakis N, Mendrinos D, Sanidas E, Favatas G, Georgopoulou M. Hypertension in the elderly. *World J Cardiol* 2012;4:135–147.
21. O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. *J Am Coll Cardiol* 2007;50:1–13.
22. Millar JA, Lever AF. Implications of pulse pressure as a predictor of cardiac risk in patients with hypertension. *Hypertension* 2000;36:907–911.
23. Pinto E. Blood pressure and ageing. *Postgrad Med J* 2007;83:109–114.
24. Mortensen MB, Fuster V, Muntendam P, Mehran R, Baber U, Sartori S, Falk E. A simple disease-guided approach to personalize ACC/AHA-recommended statin allocation in elderly people. The BioImage Study. *J Am Coll Cardiol* 2016;68:881–891.
25. Benetos A, Petrovic M, Strandberg T. Hypertension management in older and frail older patients. *Circ Res* 2019;124:1045–1060.
26. Strandberg TE, Kolehmainen L, Vuorio A. Evaluation and treatment of older patients with hypercholesterolemia: a clinical review. *JAMA* 2014;312:1136–1144.