ORIGINAL ARTICLE

Effect of Systolic and Diastolic Blood Pressure on Cardiovascular Outcomes

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ABSTRACT

BACKGROUND

The relationship between outpatient systolic and diastolic blood pressure and cardiovascular outcomes remains unclear and has been complicated by recently revised guidelines with two different thresholds (≥140/90 mm Hg and ≥130/80 mm Hg) for treating hypertension.

METHODS

Using data from 1.3 million adults in a general outpatient population, we performed a multivariable Cox survival analysis to determine the effect of the burden of systolic and diastolic hypertension on a composite outcome of myocardial infarction, ischemic stroke, or hemorrhagic stroke over a period of 8 years. The analysis controlled for demographic characteristics and coexisting conditions.

RESULTS

The burdens of systolic and diastolic hypertension each independently predicted adverse outcomes. In survival models, a continuous burden of systolic hypertension (≥140 mm Hg; hazard ratio per unit increase in z score, 1.18; 95% confidence interval [CI], 1.17 to 1.18) and diastolic hypertension (≥90 mm Hg; hazard ratio per unit increase in z score, 1.06; 95% CI, 1.06 to 1.07) independently predicted the composite outcome. Similar results were observed with the lower threshold of hypertension (≥130/80 mm Hg) and with systolic and diastolic blood pressures used as predictors without hypertension thresholds. A J-curve relation between diastolic blood pressure and outcomes was seen that was explained at least in part by age and other covariates and by a higher effect of systolic hypertension among persons in the lowest quartile of diastolic blood pressure.

CONCLUSIONS

Although systolic blood-pressure elevation had a greater effect on outcomes, both systolic and diastolic hypertension independently influenced the risk of adverse cardiovascular events, regardless of the definition of hypertension (≥140/90 mm Hg or ≥130/80 mm Hg). (Funded by the Kaiser Permanente Northern California Community Benefit Program.)

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Thresholds for hypertension and prevailing concepts about hypertension have shifted over time. Constructs about the consequences of isolated diastolic, isolated systolic, and combined systolic and diastolic hypertension[1] evolved in the 1960s, with a prevailing notion that only diastolic hypertension affected outcomes. The Framingham Heart Study and other research showed that systolic hypertension is actually more important as a predictor of cardiovascular outcomes,[2] bringing calls to "abandon diastole"[3] and a near-exclusive focus on systolic hypertension in the 2000 clinical advisory statement from the National High Blood Pressure Education Program.[4] The American College of Cardiology (ACC)–American Heart Association (AHA) risk estimation tool,[5] a critical choice point in the 2017 hypertension-management guidelines,[6] does not consider diastolic blood pressure in the determination of cardiovascular risk. Despite often assigning little importance to diastolic blood pressure in the management of hypertension, clinicians still record and target values for both systolic and diastolic blood pressures.

The thresholds that had been used to define hypertension were changed in the 2017 U.S. hypertension guidelines — high-risk patients now have a treatment threshold of 130/80 mm Hg, whereas others have a threshold of 140/90 mm Hg.[6] There is additional controversy regarding a possible J-curve relationship between diastolic blood pressure and outcomes; some sources have shown a higher risk of adverse outcomes at both high and low diastolic blood pressures,[7-11] which is of particular concern because the lower targets in the new hypertension guidelines might result in more patients being treated to the point of diastolic hypotension.[8,9,11,12]

We sought to determine whether the burdens of systolic and diastolic hypertension each independently predict the risk of adverse cardiovascular outcomes. We reviewed more than 36 million outpatient blood-pressure measurements from more than 1 million members of a large integrated health care system. We examined whether the relationship between systolic hypertension burden, diastolic hypertension burden, and cardiovascular outcomes was influenced by the choice of threshold for the definition of hypertension and explored the J-curve relationship between diastolic blood pressure and outcomes.

Methods

Study Design

We performed a retrospective cohort study involving outpatients from Kaiser Permanente Northern California (KPNC), a large integrated health care delivery system with more than 4 million members that reflects the diverse population of Northern California.[13] KPNC integrates data on outpatient encounters, inpatient care, pharmacy services, and laboratory services into a single electronic medical record.[14] We used a 2-year baseline period to record initial blood-pressure measurements and coexisting conditions and then recorded additional blood-pressure measurements and observed whether patients had a composite outcome event (myocardial infarction, ischemic stroke, or hemorrhagic stroke) over an 8-year observation period. The KPNC institutional review board approved this retrospective data–only study with waiver of informed consent.

Study Population

Study participants were persons 18 years of age or older who had at least one blood-pressure measurement at baseline (from January 1, 2007, through December 31, 2008) and at least two blood-pressure measurements during the observation period (from January 1, 2009, through December 31, 2016). Participants were enrolled in KPNC from January 1, 2007, through December 31, 2016, or until death, with no more than a mean of 31 days of disenrollment per year in the study. Participants who had a period of 3 years or longer between the last blood-pressure measurement in the observation period and the end of the observation period had their observations truncated before the gap. Participants were observed for the full 8-year observation period or until the occurrence of a composite outcome event or censoring of data because of death or because of truncation due to the measurement criteria as described above. The study population was selected from an adult population of 2.6 million members who were enrolled as of January 1, 2009, which was reduced to 1.7 million members after the enrollment criteria were applied and then reduced to 1.3 million members after the criteria for blood-pressure measurement were applied (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

PRIMARY PREDICTORS

We included all outpatient blood-pressure measurements for all participants, which had been obtained by means of an automated oscillometric blood-pressure cuff. Analyses included all blood-pressure measurements from both the baseline period and the observation period, up to a composite outcome event or censoring event, if one occurred (Fig. S2 in the Supplementary Appendix).

The primary predictors in our study were the burdens of systolic and diastolic hypertension, which are continuous measures of the degree of hypertension, calculated as follows. The weighted average blood pressure was first determined by performing linear interpolation over the days between measurements, including data from both the baseline and observation periods, up to an outcome event, if one occurred. Measured values and the interpolated daily values between measurements were then averaged. For weighted average hypertension burdens above specific thresholds defining hypertension (≥140/90 mm Hg vs. ≥130/80 mm Hg), linear interpolated measures were zeroed at the threshold, with values at or below the threshold set equal to 0 and values above the threshold expressed in millimeters of mercury (mm Hg) above the threshold (Fig. S3 in the Supplementary Appendix). Our hypertension-burden predictors are therefore continuous variables representing the degree of hypertension, with zero values for normal or low blood pressures. To avoid spurious blood-pressure readings, we excluded measurements with a systolic blood pressure above 240 mm Hg or below 60 mm Hg or a diastolic blood pressure above 160 mm Hg or below 30 mm Hg. To prevent systolic blood pressure from having a greater effect owing to higher values, systolic and diastolic values were standardized to z scores (±SDs from the mean) (Fig. S4 in the Supplementary Appendix).

COVARIATES

Covariates were age, sex, race or ethnic group, body-mass index, and coexisting conditions (presence of diabetes mellitus, coronary artery disease or history of myocardial infarction, hypercholesterolemia, heart failure, history of stroke, and smoking status), measured at the start of the baseline period. All multivariable models (see below) controlled for all covariates unless stated otherwise.

OUTCOMES

The primary outcome in our study was a composite of the first episode of myocardial infarction, ischemic stroke, or hemorrhagic stroke during the observation period, with an event defined as hospitalization with a discharge diagnosis matching one of the components of the composite primary outcome, as previously validated for this population.[15,16] Death was not part of the primary outcome.

STATISTICAL ANALYSIS

The primary analysis in our study was bivariate and multivariable Cox survival analysis of the composite outcome, performed using z-score–standardized hypertension-burden predictors (with both systolic and diastolic predictors in all models). All multivariable models in the study controlled for the full set of covariates (see above), with the exception of models specifically addressing the role of confounding by age in producing a J curve in bivariate analysis (see below). All Cox analyses reflect a single period of observation, and blood-pressure predictors and covariates were not time-varying in the models. Bivariate analyses were also performed to explore the tabular relationship between quantiles (cutoff points) of blood pressures and the risk of a composite outcome event at each quantile. To perform similar analyses, but with control for the full list of covariates above, multivariable logistic regression was used to generate a model estimation of event risk, with controls held at means. The same structure of predictors (including blood pressures recorded up to the point of an event, if one occurred), covariates, and outcomes that were used in Cox regression was used in logistic regression but without the time coding of outcome that was used in the Cox models. Statistical analyses were performed with the use of SAS software, version 9.3 (SAS Institute), and Stata–MP software, version 14.2 (StataCorp).

RESULTS

STUDY POPULATION, MEASUREMENTS, AND OUTCOMES

Our cohort consisted of 1,316,363 participants, with 36,784,850 blood-pressure measurements. The baseline characteristics of the participants are shown in Table 1. A total of 44,286 outcome

Table 1. Characteristics of the Study Population at Baseline.*

Characteristic	Overall Cohort (N=1,316,363)	Mean Blood Pressure ≥130/80 mm Hg (N=533,353)	Mean Blood Pressure ≥140/90 mm Hg (N=118,159)
Age — yr			
Median	53	57	60
Interquartile range	40–64	46–68	49–72
Range	18–111	18–108	18–108
Female sex — no. (%)	752,662 (57.2)	284,524 (53.3)	66,822 (56.6)
Race or ethnic group — no. (%)†			
White	722,421 (54.9)	298,710 (56.0)	65,624 (55.5)
Black	98,804 (7.5)	52,245 (9.8)	15,225 (12.9)
Hispanic	205,487 (15.6)	75,608 (14.2)	15,860 (13.4)
Asian	205,146 (15.6)	73,019 (13.7)	14,019 (11.9)
Other or unknown	84,505 (6.4)	33,771 (6.3)	7,431 (6.3)
Type 1 or type 2 diabetes mellitus — no. (%)	173,365 (13.2)	83,393 (15.6)	22,333 (18.9)
Coronary artery disease or history of myocardial infarction — no. (%)	73,723 (5.6)	30,076 (5.6)	7,912 (6.7)
History of ischemic or hemorrhagic stroke — no. (%)	78,721 (6.0)	33,955 (6.4)	8,302 (7.0)
Hyperlipidemia — no. (%)	78,960 (6.0)	39,538 (7.4)	9,582 (8.1)
Congestive heart failure — no. (%)	4,976 (0.4)	2,081 (0.4)	625 (0.5)
Current smoking — no. (%)	125,192 (9.5)	52,751 (9.9)	12,083 (10.2)
Body-mass index‡			
Median	27.2	28.8	29.1
Interquartile range	24.1–31.5	25.3–33.1	25.5–33.9

* The cohort with a mean blood pressure of 130/80 mm Hg or higher included persons who had a mean systolic blood pressure of at least 130 mm Hg or a mean diastolic blood pressure of at least 80 mm Hg (or both). The cohort with a mean blood pressure of 140/90 mm Hg or higher included persons who had a mean systolic blood pressure of at least 140 mm Hg or a mean diastolic blood pressure of at least 90 mm Hg (or both).
† Race and ethnic group were reported by the participants in the electronic medical record.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

events occurred in the 8-year observation period, including 24,681 myocardial infarctions, 16,271 ischemic strokes, and 3334 hemorrhagic strokes. The median number of measurements per participant was 22 (interquartile range, 13 to 36) (Fig. S5 in the Supplementary Appendix).

PREVALENCE OF MEASUREMENTS INDICATING HYPERTENSION

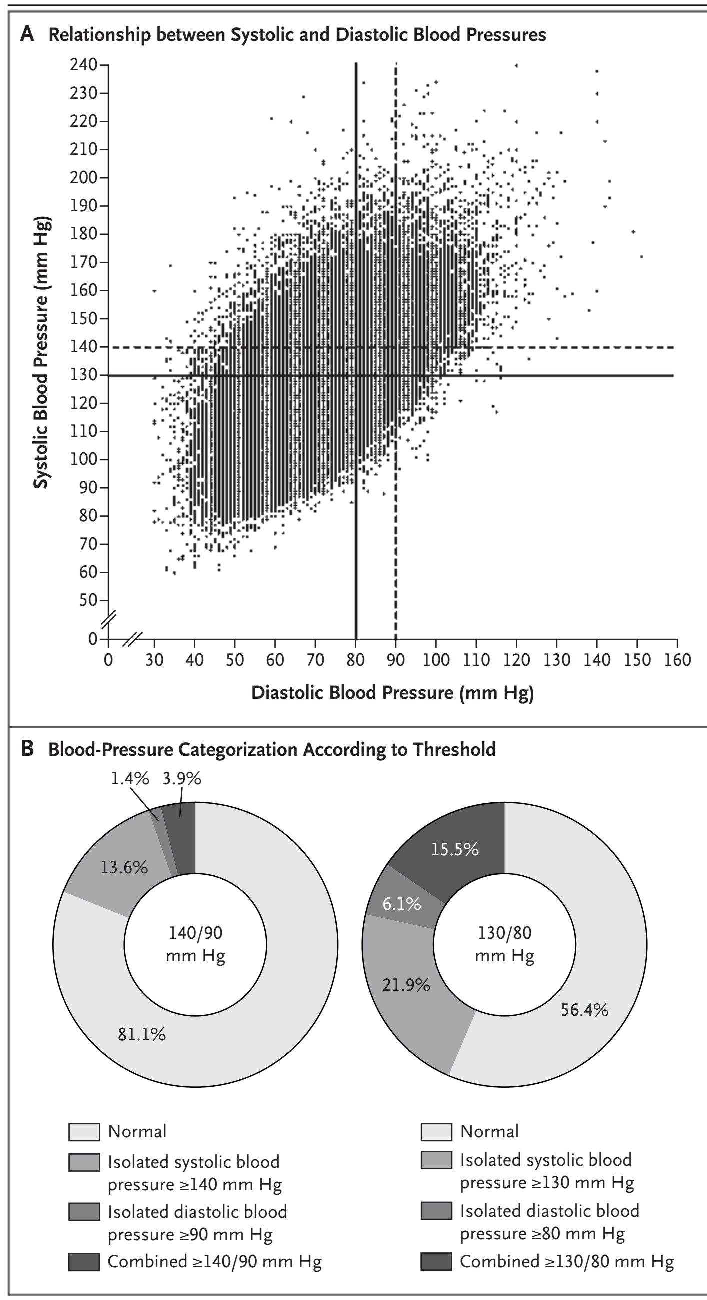
We examined the prevalence of measurements indicating hypertension using two thresholds (≥140/90 mm Hg and ≥130/80 mm Hg) from the 2017 ACC–AHA guidelines.[6] Figure 1 shows the relationship between systolic and diastolic blood-pressure measurements as well as the breakdown of measurements into four categories for the two thresholds. For the threshold of 140/90 mm Hg, 18.9% of the measurements showed hypertension, whereas for the threshold of 130/80 mm Hg, 43.5% of the measurements showed hypertension. Systolic blood-pressure measurements indicating hypertension increased as a function of age, whereas diastolic blood-pressure measurements indicating hypertension peaked in the fifth decade of life (Fig. 2).

RELATIONSHIP BETWEEN BLOOD PRESSURE AND CARDIOVASCULAR OUTCOMES

Quantiles of increasing systolic blood pressure were associated with an increased risk of an adverse outcome (Fig. 3A and 3B). A J-curve relationship was seen between the diastolic blood pressure and the composite outcome, with a high risk of myocardial infarction, ischemic stroke, or hemorrhagic stroke in both the lowest and highest deciles for diastolic blood pressure (Fig. 3C).

Figure 1. Relationship between Systolic and Diastolic Blood Pressures and Distribution of Blood-Pressure Measurements.

A scatter plot shows the relation between systolic and diastolic blood pressures (Panel A). Dashed lines indicate thresholds of 140 mm Hg for systolic blood pressure and 90 mm Hg for diastolic blood pressure, and solid lines indicate thresholds of 130 mm Hg and 80 mm Hg, respectively. For plotting purposes, a sample of 250,000 measurements was randomly selected. For the full data set (36,784,850 measurements), the regression coefficient between the z-score–standardized systolic and diastolic blood pressures was 0.54 (R^2=0.29). Panel B shows analyses according to hypertension threshold. The percentages of measurements in various categories are shown; percentages may not total 100 because of rounding. In the analysis that used thresholds of 140 mm Hg for systolic blood pressure and 90 mm Hg for diastolic blood pressure (left side), 18.9% of the measurements showed a systolic blood pressure of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, or both. In the analysis that used thresholds of 130 mm Hg for systolic blood pressure and 80 mm Hg for diastolic blood pressure (right side), 43.5% of the measurements showed a systolic blood pressure of at least 130 mm Hg, a diastolic blood pressure of at least 80 mm Hg, or both.



Age and other covariates appeared to explain at least part of this relationship (Fig. 3D). In Cox regression models comparing participants in the lowest quartile of diastolic blood pressure with those in the middle two quartiles, the unadjusted hazard ratio for the composite outcome was 1.44 (95% confidence interval [CI], 1.41 to 1.48; P<0.001), whereas after adjustment for all covariates, the hazard ratio was 0.90 (95% CI, 0.88 to 0.92; P<0.001). With adjustment for the above covariates but without control for age, the analysis showed that lower diastolic blood pressure was associated with adverse outcomes (hazard ratio, 1.15; 95% CI, 1.13 to 1.18; P<0.001). Stratification of the adjusted models according to race or ethnic group or to sex showed similar results across subgroups (Figs. S6 and S7 in the Supplementary Appendix).

In multivariable Cox regression analysis of the composite outcome, the burden of systolic hypertension (≥140 mm Hg) was associated with the composite outcome (hazard ratio per unit increase in z score, 1.18; 95% CI, 1.17 to 1.18; P<0.001). In the same model, the burden of diastolic hypertension (≥90 mm Hg) was also independently associated with the composite outcome (hazard ratio per unit increase in z score, 1.06; 95% CI, 1.06 to 1.07; P<0.001). Stratification of these models according to race or ethnic group or to sex showed similar results across these categories. Similar results were obtained with the use of the lower threshold of 130/80 mm Hg or higher (for systolic blood pressure of ≥130: hazard ratio per unit increase in z score, 1.18; 95% CI, 1.17 to 1.19; P<0.001; for diastolic blood pressure of ≥80 mm Hg: hazard ratio, 1.08; 95% CI, 1.06 to 1.09; P<0.001). When we used blood pressures from only the baseline period, similar results were seen for both hypertension thresholds.

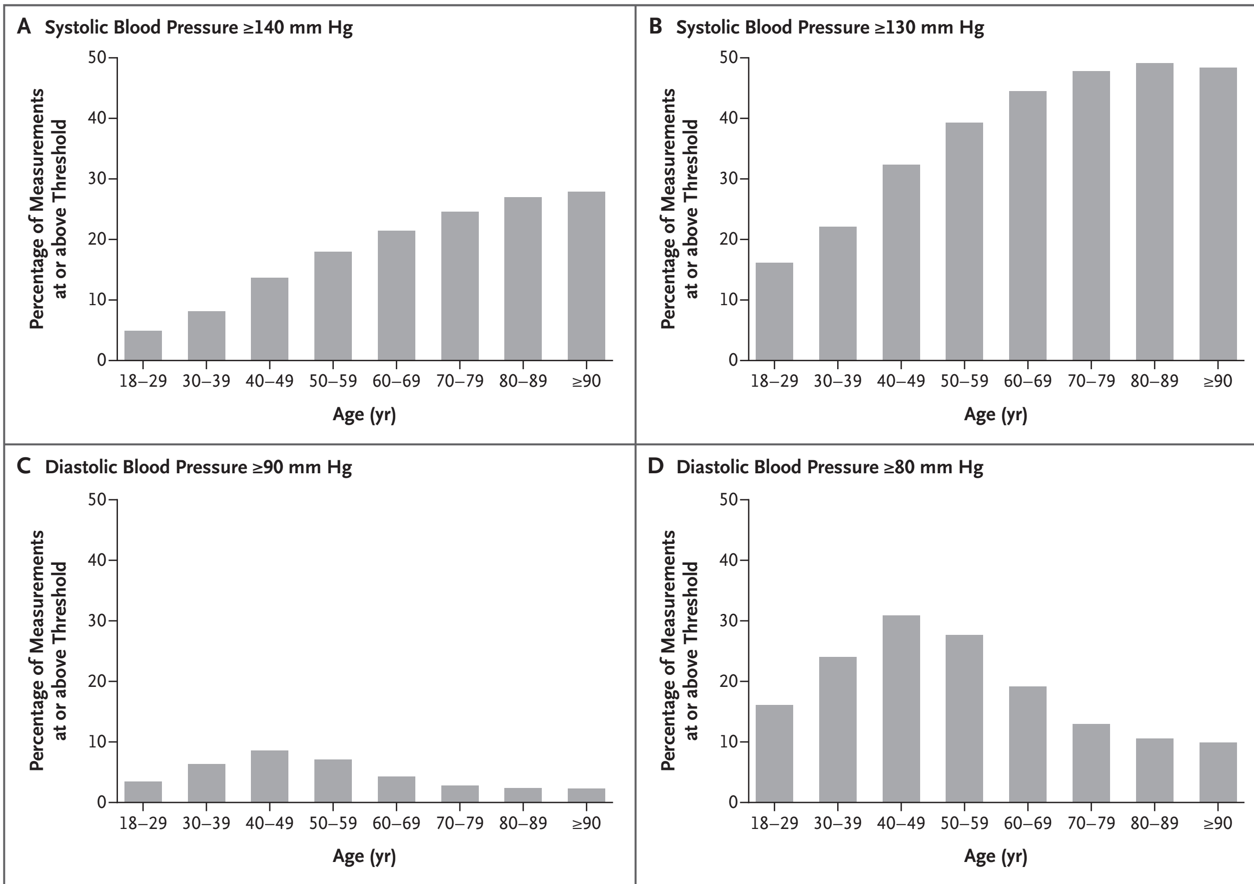


Figure 2. Relationship between Age and Blood-Pressure Elevation in Individual Measurements.
Shown is the distribution of blood pressures as a function of age, at the level of individual blood-pressure measurements, according to thresholds for systolic and diastolic blood pressures.

Details are provided in Figure S8 and Tables S1 through S3 in the Supplementary Appendix.

We also constructed models in which continuous blood pressures were used without the introduction of thresholds. Among participants for whom the mean systolic or diastolic blood pressure was above the 75th percentile (avoiding potential nonordinal effects at the low-to-normal range of blood pressures), both systolic blood pressure (hazard ratio per unit increase in z score, 1.40; 95% CI, 1.38 to 1.43; P<0.001) and diastolic blood pressure (hazard ratio per unit increase in z score, 1.22; 95% CI, 1.20 to 1.24; P<0.001) predicted outcomes independently (Fig. S8 in the Supplementary Appendix). Similar results were obtained with these predictors for the full cohort (for systolic blood pressure: hazard ratio per unit increase in z score, 1.20; 95% CI, 1.18 to 1.21; P<0.001; for diastolic blood pressure: hazard ratio per unit increase in z score, 1.16; 95% CI, 1.15 to 1.18; P<0.001).

Similar relationships between systolic and diastolic hypertension and adverse outcomes were seen in models stratified according to either baseline cardiovascular disease or ACC–AHA risk estimation.[5] These relationships also did not differ when we compared participants taking antihypertensive medications throughout the observation period with participants who were not taking antihypertensive medications at any point. Control for the number of blood-pressure measurements also did not alter the relationship between blood pressures and cardiovascular outcomes. The overall pattern of a greater effect of systolic blood pressure on outcomes was observed across age groups, with lower hazard ratios for both systolic and diastolic hypertension burden observed at older ages. Details are pro-

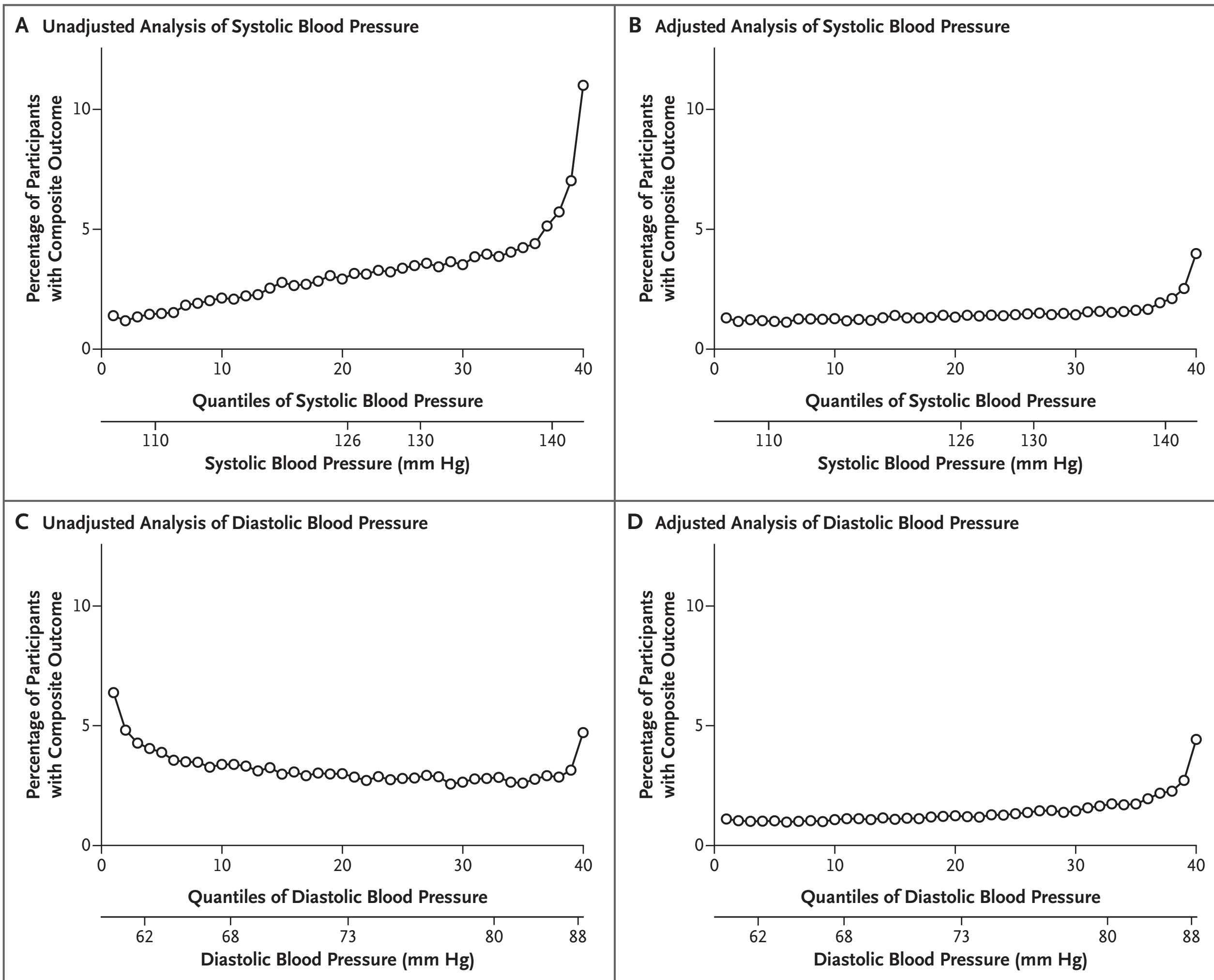


Figure 3. Relationship between Outcomes and Systolic and Diastolic Blood Pressures.

In all panels, approximate positions of systolic or diastolic (as appropriate) blood-pressure levels of interest are indicated along the x axis. Panel A shows the unadjusted percentage of participants with myocardial infarction, ischemic stroke, or hemorrhagic stroke (the composite outcome) according to 40 quantiles of systolic blood pressure. Panel B shows the adjusted percentage of participants with the composite outcome according to 40 quantiles of systolic pressure, controlling for age, race or ethnic group, and coexisting conditions, from model estimation of multivariable logistic regression with covariates held at means (area under the receiver-operating-characteristic [ROC] curve for this model, 0.821; pseudo $R^2 = 0.158$). Panel C shows the unadjusted percentage of participants with the composite outcome according to 40 quantiles of diastolic blood pressure. Panel D shows the adjusted percentage of participants with the composite outcome according to 40 quantiles of diastolic pressure, controlling for age, race or ethnic group, and coexisting conditions (area under the ROC curve for this model, 0.821; pseudo $R^2 = 0.157$).

vided in Figure S9 and Tables S4 through S7 in the Supplementary Appendix.

At both thresholds, the burden of isolated diastolic hypertension was also associated with the composite outcome among participants who did not have a burden of systolic hypertension. In study participants with an average systolic blood pressure below 140 mm Hg, a diastolic hypertension burden of at least 90 mm Hg predicted a composite outcome event (hazard ratio per unit increase in z score, 1.66; 95% CI, 1.53 to 1.79; P<0.001), and in participants with an average systolic blood pressure below 130 mm Hg, a diastolic hypertension burden of at least 80 mm Hg also predicted a composite outcome event (hazard ratio per unit increase in z score, 1.52; 95% CI, 1.03 to 2.23; P=0.03).

Systolic hypertension had a greater effect at lower diastolic blood pressures. Systolic hypertension of at least 140 mm Hg had a greater effect on adverse outcomes among participants in the lowest quartile of diastolic blood pressure (hazard ratio per unit increase in z score, 1.21; 95% CI, 1.20 to 1.23; P<0.001) than it did among participants in the highest quartile of diastolic blood pressure (hazard ratio per unit increase in z score, 1.16; 95% CI, 1.15 to 1.17; P<0.001). Similar results were obtained with regard to systolic hypertension of at least 130 mm Hg (hazard ratio per unit increase in z score, 1.25; 95% CI, 1.23 to 1.27; P<0.001; vs. 1.11; 95% CI, 1.09 to 1.12; P<0.001) (Fig. S10 in the Supplementary Appendix).

We used a logistic-regression model to estimate the risk of myocardial infarction, ischemic stroke, or hemorrhagic stroke across a range of systolic and diastolic blood pressures (Fig. 4). Participants with a weighted average systolic blood pressure of approximately 160 mm Hg (z score, +3) had a predicted risk of a composite outcome event at 8 years of 4.8%, whereas those with a systolic blood pressure of approximately 136 mm Hg (z score, +1) had a predicted risk of 1.9%. Participants with a diastolic blood pressure of approximately 96 mm Hg (z score, +3) had a predicted risk of the composite outcome of 3.6%, whereas those with a diastolic blood pressure of approximately 81 mm Hg (z score, +1) had a predicted risk of 1.9%.

DISCUSSION

We found that systolic and diastolic hypertension independently predicted adverse outcomes, despite a greater effect of systolic hypertension. We observed that the relationship between systolic blood pressure, diastolic blood pressure, and adverse cardiovascular outcomes was not altered by choice of threshold (≥140/90 mm Hg vs. ≥130/80 mm Hg) — a finding that supports recent guideline changes that tightened blood-pressure targets for high-risk patients.[6]

The J-curve relationship between diastolic blood pressure and adverse cardiovascular outcomes[7-10] appeared to be particularly important in the context of the lower blood-pressure targets that were included in the 2017 hypertension guidelines,[6] which were influenced by the Systolic Blood Pressure Intervention Trial (SPRINT).[17] We found that the J curve was explained at least in part by the relationship to age and other covariates; in addition, we found that systolic hypertension had a greater effect in the group of participants with lower diastolic blood pressures, an observation that had been previously reported to explain the J curve.[18] It should be noted that our general outpatient cohort had a low prevalence of coronary artery disease, and a direct J-curve relationship may be of greater importance in patients with active coronary artery disease or in those with conditions involving end-organ microcirculatory abnormalities.[9,10]

Hypertension guidelines include both systolic and diastolic blood-pressure targets.[1,2,19-21] Despite this, it has been argued, on the basis of data from the Framingham Heart Study,[2] that treatment for hypertension could improve with measurement of only systolic blood pressure.[3] Our results show that this would be inappropriate: although systolic blood pressure indeed had a greater effect, systolic and diastolic blood pressures each independently influenced cardiovascular outcomes, and therefore diastolic blood pressure ought not to be ignored.

Our study has certain limitations. Data were

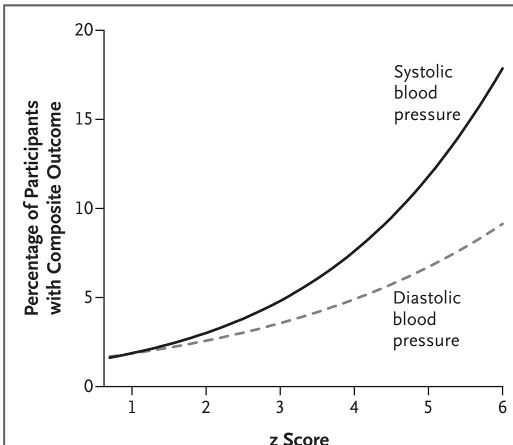


Figure 4. Multivariable Modeling of Adverse Cardiovascular Outcomes.

Shown is a model estimation of the relationship between systolic blood pressure (solid line) and diastolic blood pressure (dashed line) z scores and the risk of the composite outcome among participants above the 75th percentile for systolic blood pressure (>133 mm Hg) or diastolic blood pressure (>78 mm Hg). The analysis was conducted with the use of multivariable logistic regression with control for age, sex, race or ethnic group, and coexisting conditions (area under the ROC curve for this model, 0.795; pseudo R^2 = 0.144).

obtained retrospectively from prospectively populated clinical databases. Blood-pressure values were obtained in routine clinical practice by the automated oscillometric method. Although this method aligns with the majority of clinical blood-pressure measurements that are obtained in typical practice, it may not align as well with the averaged auscultatory method that is applied in some research studies. Although we included data on antihypertensive treatment, we did not include data on measures such as diet modification. Death was used for censoring purposes, but it was not part of the primary outcome. We controlled for hypercholesterolemia as part of the medical history, but we did not include measured cholesterol values. Finally, our results from a large, multiethnic, and generally healthy population, across a wide range of ages, may not apply to specific subpopulations.

Our study also has certain strengths. We analyzed blood pressures from routine clinical practice using standardized oscillometric blood-pressure measurement, at a near population-level scale.[22] Automated oscillometric measurements obtained by medical assistants may have minimized the risk of "white-coat hypertension" (i.e., blood pressure elevated in the clinical setting but normal elsewhere) in our cohort.[23] Because our data came from a comprehensive electronic medical record,[13,14] rather than a billing and administrative database, we used rigorously identified covariates and outcomes. We included every routine outpatient blood-pressure reading for every participant in the cohort, which allowed for a granular estimate of hypertension burden.

In conclusion, both systolic and diastolic hypertension contribute significantly to cardiovascular risk, regardless of the threshold used for hypertension (≥140/90 mm Hg or ≥130/80 mm Hg).

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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