Does Low Diastolic Blood Pressure Contribute to the Risk of Recurrent Hypertensive Cardiovascular Disease Events?
The Framingham Heart Study


Abstract—Whether low diastolic blood pressure (DBP) is a risk factor for recurrent cardiovascular disease (CVD) events in persons with isolated systolic hypertension is controversial. We studied 791 individuals (mean age 75 years, 47% female, mean follow-up time: 8±6 years) with DBP <70 (n=225) versus 70 to 89 mm Hg (n=566) after initial CVD events in the original and offspring cohorts of the Framingham Heart Study. Recurrent CVD events occurred in 153 (68%) participants with lower DBP and 271 (48%) with higher DBP (P<0.0001). Risk of recurrent CVD events in risk factor-adjusted Cox regression was higher in those with DBP <70 mm Hg versus DBP 70 to 89 mm Hg in both treated (hazard ratio, 5.1 [95% confidence interval: 3.8–6.9] P<0.0001) and untreated individuals (hazard ratio, 11.7 [95% confidence interval: 6.5–21.1] P<0.0001; treatment interaction: P=0.71). Individually, coronary heart disease, heart failure, and stroke recurrent events were more likely with DBP <70 mm Hg versus 70 to 89 mm Hg (P<0.0001). To examine for an effect of wide pulse pressure on excess risk associated with low DBP, we defined 4 binary groupings of pulse pressure (≥68 versus <68 mm Hg) and DBP (<70 versus 70–89 mm Hg). CVD incidence rates were higher only in the group with pulse pressure ≥68 and DBP <70 mm Hg (76% versus 46%–54%; P<0.001). Persons with isolated systolic hypertension and prior CVD events have increased risk for recurrent CVD events in the presence of DBP <70 mm Hg versus DBP 70 to 89 mm Hg, whether treated or untreated, supporting wide pulse pressure as an important risk modifier for the adverse effect of low DBP. *(Hypertension. 2015;65:00-00. DOI: 10.1161/HYPERTENSIONAHA.114.04581)*

Key Words: blood pressure ■ cardiovascular disease ■ epidemiology

For >30 years, there has been controversy regarding the clinical significance of low diastolic blood pressure (DBP) in patients treated for hypertension because it relates to increased cardiovascular disease (CVD) risk in general and to coronary heart disease (CHD) risk in particular. This has not been studied in those with pre-existing CVD, a population with greater risk than those without initial events. Therefore, in the present study, we limited our investigation to persons who survived an initial CVD event—CHD, heart failure (HF), or stroke. We divided these persons into 2 groups: (1) those with isolated systolic hypertension (ISH; systolic blood pressure [SBP] ≥140 and DBP <90 mm Hg) with DBP 70 to 89 mm Hg, in the presence or absence of antihypertensive treatment; these persons are at higher risk because of widened pulse pressure and increased arterial stiffness; and (2) persons with ISH with a low mean arterial pressure that is associated with a low DBP, ie, <70 mm Hg in the absence or presence of antihypertensive treatment; we hypothesized that group 2 persons would be at even higher risk than group 1.

We addressed the following questions in the present investigation: First, is there increased risk for recurrent CVD events in individuals with a DBP of <70 mm Hg versus those with a DBP 70 to 89 mm Hg in those with ISH, regardless of the presence or absence of antihypertensive treatment? Second, is there increased risk for individual CVD components examined separately (CHD, HF, or stroke events) in the presence versus absence of antihypertensive treatment in individuals with a DBP of <70 mm Hg versus a DBP 70 to 89 mm Hg? Third, can we judge the relative importance of wide pulse pressure versus low DBP in predicting CVD events?

Methods

Overview

The Framingham Heart Study began in 1948 enrolling 5209 men and women, 30 to 62 years of age who underwent repeated examinations biennially. In 1971, 5124 men and women who were children or the spouses of children of the original Framingham Heart Study were examined. The Framingham Heart Study and its offspring began in 1971 enrolling 5195 men and women, 6 to 82 years of age who were children of the original Framingham Heart Study participants.
enrolled in the Framingham Offspring cohort. The offsporing cohort underwent repeated examinations every 4 years. A detailed description of this study design, the method for assessing BP, and the method of classifying CVD end points have been published elsewhere. Initial and recurrent CVD events consisted of CHD (myocardial infarctions, coronary insufficiency, or sudden cardiac death), HF, or stroke. Inclusion criteria included postprimary CVD event survivors with the presence of ISH, with or without receiving antihypertensive treatment. Exclusion criteria were the absence of a study visit within 5-year postinitial CVD event.

Study Sample
As shown in the flow diagram (Figure 1), inclusion criteria resulted in 791 participants who survived their initial CVD event, appeared for ≥1 postprimary CVD event visit within 5 year of their initial event, and had evidence of ISH. There were an additional 130 initial CVD event survivors that were excluded from the analysis: 121 had insufficient risk factor covariates for Cox regression modeling and 19 had their first visits beyond the 5-years postprimary CVD exclusion criterion. Of the initial 791 event survivors with postprimary event visits, 367 were without recurrent CVD events and therefore were censored: 72 with DBP <70 mm Hg and 295 with DBP 70 to 89 mm Hg. Of the 424 subjects with recurrent CVD events, 153 had DBP <70 mm Hg and 271 had DBP 70 to 89 mm Hg. We began the study with the second biannual examination (1950) and extended it through 2005. Because of the long duration of the study, we tested for secular trend by adjusting for consecutive decades of occurrence of index primary events (<1960s, 1960–1969, 1970–1979, ≥1980).

Assessment of Risk Factors and Cardiovascular Events
Current cigarette smoking was defined as regularly smoking cigarettes at any time during the prior year. Body mass index was calculated as body weight (in kilograms) divided by the square of height (in meters). A fasting blood glucose level of ≥7.0 mmol/L (126 mg/dl) in the offspring cohort, a nonfasting glucose of ≥11.0 mmol/L (200 mg/dl); in the original cohort, or the use of hypoglycemic medications (in both cohorts) defined diabetes mellitus and serum cholesterol (high-density lipoprotein cholesterol was not included because it was not available for baseline visits before 1970). Hypertensive treatment refers to any medication(s) prescribed specifically for hypertension at the examination after the primary CVD event and before the recurrent CVD event; in the absence of this information, the participant was defined as not receiving antihypertensive therapy.

Data Analysis
At the first available visit after the initial event, comparisons were made between participants with DBP <70 versus DBP 70 to 89 mm Hg (Table 1). In addition, the 826 individuals who had secondary events without visits between their initial and recurrent events did not qualify for Cox regression analysis; nevertheless, we compared characteristics of these 826 with 424 persons with visits and recurrent events. Comparisons between various groups utilized χ² for categorical analysis and paired t-tests for continuous data.

Cox regression models were performed calculating hazard ratios (HRs) and 95% confidence intervals (CIs) (1) unadjusted, (2) adjusted for age and sex, and (3) adjusted additionally for body mass index, total cholesterol, smoking, and diabetes mellitus to test the relation of DBP <70 mm Hg versus DBP 70 to 89 mm Hg for recurrent CVD event risk (CHD, HF, and stroke events) examined together and separately as individual events in models for (1) combined antihypertensive treated and untreated, (2) antihypertensive treated, and (3) untreated individuals. All models were stratified by quintiles of time from the date of the primary CVD event to the first postexamination visit (cut points for quintiles in days were <165, 166–317, 318–471, 472–650, and 651–1806). Last, interaction terms were added to test for homogeneity of the DBP effect by treatment status.

To judge the potential modifying effect of wide pulse pressure on excess risk associated with low DBP, we defined 4 groups from binary groupings of median pulse pressure (268 verses <68 mm Hg) and categorical DBP (<70 versus 70–89 mm Hg), followed by Cox modeling with those in the lowest pulse pressure DBP group defined as reference category.

Results
Comparison Between Participants With DBP <70 mm Hg Versus Those With DBP 70 to 89 mm Hg
The participants with DBP <70 mm Hg were older by almost a decade at the time of their recurrent event (P<0.01; Table 1). Not unexpectedly, there was a higher incidence of diabetes mellitus in older participants with DBP <70 mm Hg as compared to those with DBP 70 to 89 mm Hg. The mean blood pressures at the last available clinic visit in participants treated with antihypertensive medication before the recurrent CVD events (not shown in Table 1) were 146/64 mm Hg in those with DBP <70 mm Hg and 153/85 mm Hg in those with DBP 70 to 89 mm Hg (P<0.01).

Comparison Between Individuals With Visits Versus Without Visits Between Events
Participants without visits between initial and recurrent events were older by 5.2 years than those in visits between events (P<0.01). The most striking difference in those without visits between events was the close temporal relation between initial and recurrent CVD events: 47% of treated and 42% of untreated recurrent CVD events occurred within 1 week of the initial CVD events (P<0.01); 64% of the treated and 56% of untreated subjects occurred within 1 month of the initial events (P<0.01). The mean follow-up time to recurrent events was 1.9 years in those without visits between events and 7.9 years in those with ≥1 visits between events (P<0.01). The proportion of the 3 types of recurrent CVD events (CHD, HF, and stroke) did not differ between those with and without postprimary visits. However, CVD deaths were significantly more common in people without postprimary CVD event visits (40%
untreated, 32% treated) in comparison with those with visits between events (12% untreated, 10% treated; \( P < 0.01 \)).

**Bivariate Analysis**

Of 791 hypertensive participants (mean age 75 years, female 47%), who survived their initial CVD event, 225 (28%) had DBP <70 mmHg and 566 (72%) had DBP 70 to 89 mmHg, of which 153 of 225 (68%) and 271 of 566 (48%), respectively, experienced CVD events \( (P < 0.0001) \). The mean follow-up time between the initial and recurrent events was 8.0±6 years.

**Cox Proportional Hazard Regression Modeling**

There was an increased risk of recurrent CVD events in risk factor-adjusted Cox regression models with DBP <70 mmHg versus DBP 70 to 89 mmHg in combined treated and untreated persons (HR, 5.9 [95% CI, 4.6–7.5] \( P < 0.0001 \)) after adjusting for age, sex, body mass index, total cholesterol, smoking, and diabetic status (Tables 2–4; Figure 2). Adjustment for SBP as a continuous variable in the regression model enhanced the HR slightly (HR, 6.2 [95% CI: 4.8–8.1] \( P < 0.0001 \)). The mean follow-up time between the initial and recurrent events was 8.0±6 years.

**Wide Pulse Pressure Modifies the Effect of Low DBP on CVD Risk**

For the 791 postinitial CVD event survivors, the combination of pulse pressure \( \geq 68 \) together with DBP <70 mmHg had the highest incidence of subjects who developed CVD events (Figure 3). In Cox regression, with the lowest pulse pressure—DBP grouping as the reference category, the adjusted HR for DBP <70 mmHg and pulse pressure \( \geq 68 \) mmHg was 2.40 (95% CI: 1.6–3.7) \( P < 0.0001 \), consistent with the hypothesis that increased CVD risk was associated with DBP <70 mmHg only when combined with a pulse pressure of \( \geq 68 \) mmHg.

**Discussion**

In a previous Framingham report, \( ^{14} \) we showed that middle-aged and older individuals with ISH in the absence of prior CVD events (CHD, HF, or stroke) and without antihypertensive treatment were at greater CVD risk in the presence of DBP <70 versus DBP 70 to 89 mmHg; these conclusions were confirmed by the Monica, Risk, Genetics, Archiving, and Monograph (MORGAM) Project study. \( ^{15} \) Our present investigation is the first community-based study to show that both treated and untreated individuals with ISH and DBP <70 mmHg were at greater risk for recurrent CVD events than those with DBP 70 to 89 mmHg. Second, similar findings were present when examining single CVD end points of CHD, HF, or stroke. Third, CVD event rates were highest in the group with widened pulse pressure and DBP <70 mmHg compared with those with low pulse pressure and low DBP, whether treated or untreated, supporting wide pulse pressure as an important risk modifier of the adverse effect from low DBP.
Frequency and CVD Risk of DBP <70 mm Hg in Persons With ISH

We have previously shown in US adults that DBP <70 mm Hg is present in 30% of untreated persons with ISH (versus 35% in treated). There was a 3-fold greater prevalence of CVD events from the highest to the lowest DBP strata in untreated ISH. Furthermore, advanced age, female sex, and diabetes mellitus, but not treatment status, were associated with low DBP. Similarly, Ungar et al. showed that low ambulatory DBP was associated with greater all-cause mortality in older patients with ISH after adjusting for antihypertensive treatment and other covariates. The Framingham Heart Study showed that a DBP of <70 mm Hg versus DBP 70 to 89 mm Hg in the absence of antihypertensive therapy could add a risk equivalent of ≈20 mm Hg of increase in SBP—in other words, a potential risk-equivalent shift from prehypertension to stage 1 systolic hypertension or from stage 1 to stage 2 systolic hypertension. Moreover, as shown by Wang et al., antihypertensive therapy will maximize the decrease in SBP and minimize the reduction in DBP in direct proportion to age-related widening of pulse pressure. Therefore, not only is DBP <70 mm Hg common and associated with increased CVD risk in untreated elderly persons with ISH but also antihypertensive therapy has only a minimal effect in further lowering of DBP compared with the lowering of SBP.

Antihypertensive Treatment as a Cause of Recurrent CHD Events

Because post hoc analyses of intervention trials are fraught with bias and confounding, they cannot answer whether antihypertensive treatment induces CHD events in the presence of a low DBP. DBP declines with age, female sex, diabetes mellitus, chronic kidney disease, HF, incident cancer, and

<table>
<thead>
<tr>
<th>Total CVD</th>
<th>χ²</th>
<th>P Value</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>DBP &lt;70 vs 70–89 mm Hg</td>
<td>238.4</td>
<td>&lt;0.0001</td>
<td>5.9</td>
</tr>
<tr>
<td>Age- and sex-adjusted</td>
<td>DBP &lt;70 vs 70–89 mm Hg</td>
<td>190.8</td>
<td>&lt;0.0001</td>
<td>5.7</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>7.5</td>
<td>0.0063</td>
<td>0.7</td>
<td>0.6–0.9</td>
</tr>
<tr>
<td>Fully adjusted*</td>
<td>DBP &lt;70 vs 70–89 mm Hg</td>
<td>189.6</td>
<td>&lt;0.0001</td>
<td>5.9</td>
</tr>
<tr>
<td>Age (per SD)</td>
<td>9.1</td>
<td>0.0026</td>
<td>1.2</td>
<td>1.1–1.4</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>10.8</td>
<td>0.001</td>
<td>0.7</td>
<td>0.6–0.9</td>
</tr>
<tr>
<td>BMI (per SD)</td>
<td>0.016</td>
<td>0.898</td>
<td>0.99</td>
<td>0.9–1.1</td>
</tr>
<tr>
<td>Total cholesterol (per SD)</td>
<td>10.0</td>
<td>0.0016</td>
<td>1.2</td>
<td>1.1–1.3</td>
</tr>
<tr>
<td>Smoking (current vs other)</td>
<td>0.8</td>
<td>0.3701</td>
<td>1.1</td>
<td>0.9–1.4</td>
</tr>
<tr>
<td>Diabetes mellitus (yes vs no)</td>
<td>14.1</td>
<td>0.0002</td>
<td>1.7</td>
<td>1.3–2.2</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; and HR, hazard ratio.

*Adjusted for age per SD, sex (male vs female), BMI (per SD), total cholesterol (per SD), smoking (yes vs no), and diabetes mellitus (yes vs no).
wider pulse pressure. If such patients experience CHD events in intervention trials, it is not necessarily that antihypertensive treatment caused the event, but rather that a low baseline DBP (and increased pulse pressure) predicted their future event. In a previous Framingham investigation, Kannel et al.22 noted that CHD events in persons with low DBP were mainly in those with increased SBP, suggesting that ISH with increased pulse pressure may have been responsible, rather than the presence of antihypertensive treatment. Importantly, excessive treatment was not likely the cause of the low DBP because a lower frequency of treatment was related to a lower DBP.23 Furthermore, antihypertensive therapy in an elderly person with ISH preferentially decreases SBP over DBP,18,20 lowers pulse pressure, decreases arterial stiffness, and therefore theoretically may improve the coronary oxygen supply/demand ratio of the left ventricle—thereby providing protection from ischemia. The Framingham Heart Study results22 have been confirmed by the Cardiovascular Research Using Linked Bespoke Studies and Electronic Health Records (CALIBER) program (Linked Bespoke studies and the Electronic health Records of 1.25 million patients), which showed an absence of DBP J-curve except when accompanied by SBP $\geq 140$ mm Hg.23

Taken together, the findings in this study suggest that antihypertensive treatment was not related to recurrent CHD events. First, the increase in CVD risk with DBP $<70$ mm Hg versus DBP $70$ to $89$ mm Hg was equally distributed in treated and untreated persons. Second, the increased CVD risk in association with DBP $<70$ mm Hg versus DBP $\geq 70$ mm Hg was equally distributed in treated and untreated persons. Second, the increased CVD risk in association with DBP $<70$ mm Hg versus DBP $\geq 70$ mm Hg was equally distributed in treated and untreated persons.

Figure 2. Fully adjusted hazard ratios (HRs) for total and individual cardiovascular disease (CVD) events (coronary heart disease [CHD], heart failure [HF], and stroke), respectively, occurring in subjects with diastolic blood pressure (DBP) $<70$ mm Hg versus DBP $70$ to $89$ mm Hg in (1) treated and untreated, (2) treated, and (3) untreated groups, respectively (all HRs $P<0.0001$). The y-axis refers to the comparison between DBP $<70$ mm Hg vs DBP $70$ to $89$ mm Hg.

Table 4. Cox Regressions for Combined CVD Events: Untreated Only

<table>
<thead>
<tr>
<th>Total CVD</th>
<th>$\chi^2$</th>
<th>P Value</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP $&lt;70$ vs 70–89 mm Hg</td>
<td>73.8</td>
<td>$&lt;0.0001$</td>
<td>9.2</td>
<td>5.5–15.2</td>
</tr>
<tr>
<td>Age- and sex-adjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP $&lt;70$ vs 70–89 mm Hg</td>
<td>70.3</td>
<td>$&lt;0.0001$</td>
<td>12.0</td>
<td>6.7–21.5</td>
</tr>
<tr>
<td>Age (per *SD)</td>
<td>3.2</td>
<td>0.0742</td>
<td>0.9</td>
<td>0.9–1.0</td>
</tr>
<tr>
<td>Sex</td>
<td>0.7</td>
<td>0.4033</td>
<td>0.8</td>
<td>0.6–1.2</td>
</tr>
<tr>
<td>Fully adjusted*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP $&lt;70$ vs 70–89 mm Hg</td>
<td>67.0</td>
<td>$&lt;0.0001$</td>
<td>11.7</td>
<td>6.5–21.0</td>
</tr>
<tr>
<td>Age (per SD)</td>
<td>1.6</td>
<td>0.2063</td>
<td>0.9</td>
<td>0.7–1.1</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>1.4</td>
<td>0.2332</td>
<td>0.8</td>
<td>0.5–1.2</td>
</tr>
<tr>
<td>BMI (per SD)</td>
<td>3.0</td>
<td>0.0823</td>
<td>0.8</td>
<td>0.7–1.0</td>
</tr>
<tr>
<td>Total cholesterol (per SD)</td>
<td>1.7</td>
<td>0.1981</td>
<td>1.1</td>
<td>0.9–1.3</td>
</tr>
<tr>
<td>Smoking (yes vs no)</td>
<td>0.7</td>
<td>0.3967</td>
<td>1.2</td>
<td>0.8–1.8</td>
</tr>
<tr>
<td>Diabetes mellitus (yes vs no)</td>
<td>3.9</td>
<td>0.0492</td>
<td>1.7</td>
<td>1.0–2.9</td>
</tr>
</tbody>
</table>

$n=791$ for all Cox models; strata (quintiles) were determined using time between primary event and first postprimary event visit. BMI indicates body mass index; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; and HR, hazard ratio.

*Adjusted for age per SD, sex (male vs female), BMI (per SD), total cholesterol (per SD), smoking (yes vs no), and diabetes mellitus (yes vs no).
Significance of Subjects With Recurrent CVD Events Without Return Visits

Of the 826 individuals who did not have visits between their initial and recurrent CVD events, there was a striking difference in clinical course compared with the 424 who did attend ≥1 office visits. The highest event rate occurred in individuals with DBP <70 mm Hg and pulse pressures of ≥68 mm Hg that predicted CVD events significantly. \( P<0.0001 \) across the 4 DBP×pulse pressure groupings; \( \chi^2=32.6 \). No other binary paring of pulse pressure and DBP showed significant prediction of CVD events.

Causes of Increased Recurrent CVD Events in Association With Low DBP

Aging plays an important role as an effect modifier in influencing the presence or absence of DBP in predicting CVD risk.\(^2\) From age 60 years onward, there is a shift in favor of pulse pressure over SBP as a predictor of CVD risk; thus, DBP now displays a J-curve of CVD risk in older people with ISH.\(^2\) Traditionally, increased pulse pressure as a marker of large artery stiffness has been shown to be an independent CVD risk factor.\(^3\)–\(^5\) After 60 years of age, the fall in DBP and rapid widening of pulse pressure become surrogate markers of arterial stiffness. Furthermore, we postulate that the increase in CVD risk is in part related to a pernicious combination of faulty microvascular function resulting from increased elastic artery stiffness in combination with low diastolic perfusion pressure. Interestingly, our Cox regression analyses showed that low DBP is a much greater contributor to risk than age, sex, body mass index, total cholesterol, smoking, or diabetes, attesting to the singular importance of the combination of wide pulse pressure and low DBP to recurrent CVD risk in persons with initial CVD events.

The J-curve controversy has been recently summarized in 2 articles entitled Aggressive Blood Pressure Lowering is Dangerous: The J-Curve: con side\(^2\) of the argument versus the pro side\(^2\) of the argument. However, neither of the authors considered a low DBP in association with ISH as predisposing to J-curve CVD events.

Strengths and Limitations

The strengths of our investigation include a wide time interval of data collection in initial CVD event survivors and the standardized measurements from the well-characterized Framingham Heart Study. However, in this observational study, we could not control for who received antihypertensive treatment before or after the initial event, nor the type or amount of treatment. Furthermore, although our medication variable specified an antihypertensive indication, these may have been prescribed for both antihypertensive and other cardiovascular indications. Last, we do not have information on physical functioning nor the possible presence of significant orthostatic hypotension. Nevertheless, the results of our Cox regression models with nonsignificant treatment interactions are strong evidence against a treatment-induced effect of low DBP on CVD events. Finally, of the 826 subjects without return visits after their initial CVD events who did not qualify for our main analysis, we can only speculate that many of these individuals had a likelihood of reverse causation with a high mortality rate within a short time after their primary CVD event.

Many factors interact to lower DBP and influence CHD risk, so only an intervention trial including subjects with low DBP, randomized to various active treatment levels of SBP-lowering, can establish whether high-baseline CVD risk can be modified by treatment. Furthermore, the optimal therapeutic reduction in SBP and DBP in the older patient with ISH that maximizes benefit is a separate question from the safety of lowering high SBP in the presence of low DBP.
Perspective
This is the first community-based study to show that persons with an initial CVD event and persistent isolated systolic hypertension in combination of DBP <70 mm Hg versus DBP 70–89 mmHg had increased risk for recurrent CVD events. These findings support wide pulse pressure in combination with low DBP as important risk factors, largely independent of antihypertensive treatment status. Whether specific risk factor modifications might be considered to address this possible excess risk in such individuals may be the subject of future investigations.

Disclosures
None.

References

What Is New?
• Increased recurrent cardiovascular disease risk in persons with isolated systolic hypertension, whether treated or untreated, was related to wide pulse pressure as a risk modifier for the adverse effect of a low diastolic blood pressure <70 mm Hg.

What Is Relevant?
• We postulate that increased cardiovascular disease risk is related to the pernicious effects of faulty microvascular function resulting from increased elastic artery stiffness in combination with low diastolic perfusion pressure.

Novelty and Significance

What Is Relevant?
• We postulate that increased cardiovascular disease risk is related to the pernicious effects of faulty microvascular function resulting from increased elastic artery stiffness in combination with low diastolic perfusion pressure.

Summary
Persons with an initial cardiovascular disease event and persistent isolated systolic hypertension, who subsequently have diastolic blood pressure <70 mm Hg versus diastolic blood pressure 70 to 89 mm Hg, have increased risk for a recurrent cardiovascular disease event, supporting wide pulse pressure in combination with low diastolic blood pressure as important risk factors independent of treatment status.
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Data Supplement (unedited) at:
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The Framingham Heart Study


Abstract

Objective: To determine whether low diastolic blood pressure (DBP) is associated with an increased risk of recurrent cardiovascular disease (CVD) events in patients with hypertension.

Background: Previous studies have shown an inverse relationship between DBP and the risk of CVD events. However, the relationship between low DBP and CVD events in patients with hypertension is less clear.

Methods: We used data from the Framingham Heart Study to examine the relationship between DBP and the risk of CVD events in patients with hypertension. We defined low DBP as less than 70 mmHg and high DBP as 70 to 89 mmHg.

Results: Of the 5,215 patients with hypertension, 2,741 had low DBP and 2,474 had high DBP. During an average follow-up of 12 years, there were 711 CVD events (41% of the low DBP group vs. 49% of the high DBP group). Low DBP was associated with a significantly lower risk of CVD events (hazard ratio 0.69, 95% confidence interval 0.57 to 0.84).

Conclusion: Low DBP is associated with a lower risk of CVD events in patients with hypertension. These findings suggest that lowering DBP may be an important strategy for reducing the risk of CVD events in this population.

Key words: hypertension, low DBP, cardiovascular disease.
方法

概述
弗雷明汉心脏研究始于1948年，纳入5209例男性和女性。年龄为30～62岁，两年复查一次[4-10]。1971年，弗雷明汉心脏研究原始队列的孩子或配偶被纳入弗雷明汉后代队列，包括5124例女性和男性[11]。后代队列每年一次接受反复检查。根据研究已详细描述了本研究的设计、血压的评估方法和CVD终点的分类等[12,13]。首次和复发性CVD事件包括CHD(心梗、冠状动脉功能不全或心源性猝死)、心衰或卒中。纳入标准包括ISH患者经历首次CVD事件后的幸存者，接受或未接受降压治疗，排除标准为首次CVD事件后5年未接受随访。

研究对象
如研究流程图所示(图1)，79例患者符合纳入标准。这些患者包括历首次CVD事件后的幸存者，且在首次CVD事件后5年内接受1次以上的CVD事件随访，证实为ISH。此外，在发生首次CVD事件后存活的130例患者在分析时被排除：121例患者在Cox回归建模时没有足够的危险因素(危险因素包括生命史、临床病史、药物治疗史、家族史等)，19例患者的随访时间超过(首次CVD事件后)年这一排除标准。在79例经历首次CVD事件后存活且接受CVD事件随访的患者中，367例未发生CVD事件复发，72例DBP<70 mmHg，295例DBP为70～89 mmHg，在242例发生CVD事件复发的患者中，153例DBP<70 mmHg，271例DBP为70～89 mmHg。本研究在1950年进行第二次检查(每年两次)时开始，至2005年结束。由于本研究持续时间较长，我们通过校正每连续十年首次事件的发生率(<1960, 1960～1969, 1970～1979和≥1980)来检验长期趋势。

危险因素和心血管事件的评估
目前吸烟的定义为在前一年内任何时候规律吸烟，体重指数计算为体重(kg)除以身高(m)的平方。糖尿病的定义为空腹血糖水平≥11.0 mmol/L(200 mg/dL)。非空腹血糖水平≥11.0 mmol/L(200 mg/dL)。高密度脂蛋白胆固醇，因为1970年之前没有该指标的基线访视数据未纳入分析。高血压治疗是指在发生首次CVD事件后以及CVD事件复发之前这段时间服用专门的高血压治疗药物。在无此信息的情况下，将受试者定义为未接受降压治疗。

数据分析
先比较了在首次CVD事件后的第一次随访时，DBP<70 mmHg和DBP为70～89 mmHg的患者(表1)特征。另外，在首次CVD事件后至CVD复发期间，共826例受试者出现CVD复发但未接受随访，因此不符合Cox回归分析的要求，不过我们比较了这826例患者与424例发生CVD事件复发且接受随访的患者特征，组间比较采用卡方检验分析分类变量，采用F检验分析连续变量。

通过Cox回归模型计算危险比(hazard ratio, HR)和95%可信区间(confidence interval, CI)，包括：(1)校正的；(2)校正年龄和性别；(3)进一步校正体重指数、总胆固醇、吸烟和糖尿病，以检验DBP<70 mmHg和DBP为70～89 mmHg与CVD事件复发风险(CHD，心衰和卒中事件)的关系，在下述患者中进行CVD事件的总体分析或单个分析：(1)接受治疗和未接受降压治疗的患者；(2)接受降压治疗的患者；(3)未接受降压治疗的患者。所有模型均依据首次CVD事件发生的时间至之后首次随访时间的五分位数进行分层(五分位数的界值为<165, 166～317, 318～471, 472～650和651～1806天)。最后，在模型中加入相互作用的变量，以检验不同治疗状态下DBP效应的同质性。

为了判断高脉压对低DBP相关额外风险的潜在影响，我们根据中位脉压水平(≥68 vs<68 mmHg)和DBP分类(≥70 mmHg vs 70～89 mmHg)两分法将患者分为4组，之后用最低脉压和DBP组作为参考组进行Cox建模。

图1 本流程图描述了经历首次高血压性心血管事件后的幸存者中，接受≥1次随访且符合研究入选标准的791例患者。
* 其他130例有CVD事件复发和接受了诊室随访的患者被排除在分析之外；121例患者的协变量数据缺失，19例患者的首次随访时间超过了首次CVD事件后5年达到排除标准。DBP：舒张压。
表1. 比较首次心血管事件后接受诊查随访时患者的特征

<table>
<thead>
<tr>
<th></th>
<th>DBP 70–89 mm Hg</th>
<th>DBP &lt;70mm Hg</th>
<th>总数</th>
</tr>
</thead>
<tbody>
<tr>
<td>患者数</td>
<td>566</td>
<td>225</td>
<td>791*</td>
</tr>
<tr>
<td>男性例数 (%)</td>
<td>596 (59%) †</td>
<td>92 (41%)</td>
<td>424 (53%)</td>
</tr>
<tr>
<td>发生初始事件时的平均年龄 (岁)</td>
<td>66.2 ‡</td>
<td>74.6</td>
<td>68.6</td>
</tr>
<tr>
<td>发生初始事件后的首次SBP水平 (mm Hg)</td>
<td>150.1</td>
<td>144.5</td>
<td>148.3</td>
</tr>
<tr>
<td>发生初始事件后的首次DBP水平 (mm Hg)</td>
<td>84.9</td>
<td>67.4</td>
<td>79.9</td>
</tr>
<tr>
<td>发生初始事件后的首次脉压水平 (mm Hg)</td>
<td>65.2</td>
<td>77.1</td>
<td>68.6</td>
</tr>
<tr>
<td>BMI</td>
<td>27.5</td>
<td>27.3</td>
<td>27.4</td>
</tr>
<tr>
<td>总胆固醇 (mg/dL)</td>
<td>235.2</td>
<td>223.1</td>
<td>231.8</td>
</tr>
<tr>
<td>吸烟 (%)</td>
<td>215 (38%)</td>
<td>51 (23%)</td>
<td>266 (34%)</td>
</tr>
<tr>
<td>糖尿病 (%)</td>
<td>66 (12%)</td>
<td>43 (19%)</td>
<td>109 (14%)</td>
</tr>
<tr>
<td>初始和复发事件的平均间隔 (年)</td>
<td>7.7</td>
<td>8.4</td>
<td>7.9</td>
</tr>
<tr>
<td>初始CHD (%)</td>
<td>267 (47%)</td>
<td>84 (37%)</td>
<td>351 (44%)</td>
</tr>
<tr>
<td>初始心衰 (%)</td>
<td>76 (13%)</td>
<td>47 (21%)</td>
<td>123 (16%)</td>
</tr>
<tr>
<td>初始卒中 (%)</td>
<td>223 (39%)</td>
<td>94 (42%)</td>
<td>317 (40%)</td>
</tr>
<tr>
<td>复发性CHD (%)</td>
<td>135 (24%)</td>
<td>49 (22%)</td>
<td>184 (23%)</td>
</tr>
<tr>
<td>复发性心衰 (%)</td>
<td>107 (19%)</td>
<td>58 (26%)</td>
<td>165 (21%)</td>
</tr>
<tr>
<td>复发性卒中 (%)</td>
<td>122 (22%)</td>
<td>46 (20%)</td>
<td>168 (21%)</td>
</tr>
<tr>
<td>复发性CVD (%)</td>
<td>271 (48%)</td>
<td>153 (68%)</td>
<td>424 (54%)</td>
</tr>
<tr>
<td>死亡率 (%)</td>
<td>65 (12%)</td>
<td>16 (7%)</td>
<td>81 (10%)</td>
</tr>
</tbody>
</table>

BMI：体重指数；BP：血压；CVD：心血管疾病；CHD：冠心病；DBP：舒张压；SBP：收缩压。
*根据首次CVD事件后最终复查后的首次血压水平的分组。
†P<0.01；‡P<0.05；DBP 70–89 mm Hg vs DBP<70 mm Hg。

结果

比较DBP<70 mmHg和70–89 mmHg的患者

DBP<70 mmHg的患者CVD事件复发时的年龄几乎比70–89 mmHg的患者大10岁(P<0.01, 表1)。不出所料，年龄更大的DBP<70 mmHg的患者相比DBP为70–89 mmHg的患者糖尿病发生率更高，CVD事件复发前接受了降压治疗的患者在末次临床随访时DBP<70 mmHg和DBP为70–89 mmHg的患者平均血压分别为146/64 mmHg和153/85 mmHg(P<0.01)。

比较事件期间接受和未接受随访的患者

在CVD事件首次发生至复发期间，未接受随访相比接受随访的患者年龄大5.2 岁 (P<0.01)。最为明显的差异是首次和复发CVD事件之间的时间关系，在两次事件期间未接受随访的患者，47%接受降压治疗的患者和42%接受降压治疗的患者在首次CVD事件后1周内出现CVD事件复发 (P<0.01)；64%接受降压治疗的患者和56%未接受降压治疗的患者在首次CVD事件后1个月内出现CVD事件复发 (P<0.01)。两次事件之间未接受随访患者的至事件复发的平均随访时间为1.9年，接受1次以上随访的患者时间为7.9年 (P<0.01)。三种类型的复发性CVD事件 (CHD、心衰和卒中) 的比例在首次事件后接受和未接受随访的患者之间无差异。不过，首次CVD事件后未接受随访的患者CVD死亡 (40%未接受降压治疗者，32%接受降压治疗者) 较接受随访的患者 (12%未接受降压治疗者，10%接受降压治疗者) 明显更多 (P<0.01)。

双变量分析

在791例发生首次CVD事件后存活的高血压患者中 (平均年龄75岁，女性占47%)，225例 (28%) DBP<70 mmHg，566例 (72%) DBP为70–89 mmHg，其中分别有68% (153/225) 和48% (271/566) 的患者发生CVD事件复发 (P<0.0001)。首次和复发CVD事件之间的平均随访时间为8.0±6年。

Cox比例风险回归模型

校正危险因素 (年龄、性别、体重指数、总胆固醇、吸烟和糖尿病情况) 的Cox回归模型分析显示，所有接受和未接受降压治疗的患者中，DBP<70 mmHg相比DBP为70–89 mmHg的患者CVD事件的复发风险显著增加 (HR=5.9，95% CI: 4.6–7.5; P<0.0001，表2–4和图2)。在回归模型中将SBP以连续变量进行校正使得危险比轻度增加 (HR=6.2，95% CI: 4.8–8.1，P<0.0001)。另外，低DBP所引起的CVD风险增加既见于接受降压治疗的患者 (HR=5.1，95% CI: 3.8–6.9，P<0.0001)，也见于未接受降压治疗的患者 (HR=11.7，95% CI: 6.5–21.1，P<0.0001) (治疗的相互作用: P=0.71)。另外，在接受和未接受降压治疗组中DBP<70 mmHg与单个CVD事件如CHD、心衰和卒中的风险增加相关 (图2)。所有低DBP与降压治疗相互作用均无显著统计学意义。Cox模型调整对长期趋势的检验未降低DBP<70 mmHg患者相比DBP为70–89 mmHg患者风险增加的HR；实际上，HR还轻度增加 (HR=6.8，95% CI: 5.2–8.8，P<0.0001)。
高脉压改变低DBP对CVD风险的影响

对于791例经历首次CVD事件后的幸存者，脉压≥68 mmHg和DBP<70 mmHg的患者CVD发病率最高（图3）。在将脉压最低的DBP组作为参照的Cox回归分析中，DBP<70 mmHg和脉压≥68 mmHg的校正HR为2.40（95% CI: 1.6–3.7，P<0.0001），表明DBP<70 mmHg仅在脉压同时≥68 mmHg时才增加CVD风险的假说。

**讨论**

在既往对弗雷明汉研究的报道中[34]，我们发现对于既往没有发生CVD事件（CHD、心衰或卒中）和未接受降压治疗的中老年ISH患者，其中DBP<70 mmHg相比DBP为70–89 mmHg患者的CVD风险更高。这些研究结果得到了莫尼卡风险、遗传学、存档与专论（Monica, Risk, Genetics, Archiving, and Monograph, MORGAM）项目研究的证实[35]。本研究是首个基于社区的研究，结果说明接受和未接受降压治疗的DBP<70 mmHg的ISH患者相比DBP为70–89 mmHg的ISH患者CVD事件复发风险增加。其次，当观察单个CVD终点，包括CHD、心衰或卒中时，得出了相似的结果。第三，在高脉压且DBP<70 mmHg的患者中CVD事件发生率最高，无论是否接受降压治疗，高脉压都是低DBP导致不良效应风险的重要调节因子。

**表3 总体CVD事件的Cox回归分析，接受治疗的患者**

<table>
<thead>
<tr>
<th>总体CVD</th>
<th>χ²</th>
<th>P值</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>未校正</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP&lt;70 vs 70–89 mmHg</td>
<td>155.9</td>
<td>&lt;0.0001</td>
<td>5.3</td>
<td>4.1–6.9</td>
</tr>
<tr>
<td>校正了年龄和性别</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP&lt;70 vs 70–89 mmHg</td>
<td>121.4</td>
<td>&lt;0.0001</td>
<td>4.9</td>
<td>3.7–6.5</td>
</tr>
<tr>
<td>年龄（每个标准差）</td>
<td>10.4</td>
<td>0.0012</td>
<td>1.0</td>
<td>1.0–1.0</td>
</tr>
<tr>
<td>性别（男性 vs 女性）</td>
<td>5.5</td>
<td>0.0188</td>
<td>0.7</td>
<td>0.6–1.0</td>
</tr>
<tr>
<td>全部校正后*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP&lt;70 vs 70–89 mmHg</td>
<td>122.3</td>
<td>&lt;0.0001</td>
<td>5.1</td>
<td>3.8–6.9</td>
</tr>
<tr>
<td>年龄（每个标准差）</td>
<td>16.4</td>
<td>&lt;0.0001</td>
<td>1.4</td>
<td>1.2–1.7</td>
</tr>
<tr>
<td>性别（男性 vs 女性）</td>
<td>9.5</td>
<td>0.0021</td>
<td>0.7</td>
<td>0.5–0.9</td>
</tr>
<tr>
<td>BMI (每个SD)</td>
<td>0.4</td>
<td>0.5071</td>
<td>1.0</td>
<td>0.9–1.2</td>
</tr>
<tr>
<td>总胆固醇（每个标准差）</td>
<td>10.4</td>
<td>0.0013</td>
<td>1.3</td>
<td>1.1–1.4</td>
</tr>
<tr>
<td>吸烟（目前吸烟 vs 其他）</td>
<td>0.02</td>
<td>0.8762</td>
<td>0.9</td>
<td>0.7–1.3</td>
</tr>
<tr>
<td>糖尿病（是 vs 否）</td>
<td>10.1</td>
<td>0.0015</td>
<td>1.7</td>
<td>1.2–2.3</td>
</tr>
</tbody>
</table>

BMI: 体重指数；CI: 可信区间；CVD: 心血管疾病；DBP: 舒张压；HR: 危险比。

*校正了年龄（每个标准差）、性别（男性 vs 女性）、BMI（每个标准差）、总胆固醇（每个标准差）、吸烟（是或否）和糖尿病（是或否）。

ISH患者中DBP<70 mmHg的比例及其CVD风险

我们的既往研究发现，美国30%未接受治疗的成年ISH患者DBP<70 mmHg（在治疗患者中的比例为35%）。在未治疗的ISH患者，DBP<70%中位数比最低组的CVD患病率为高3倍。另外，高龄、女性和糖尿病与低DBP相关，而非治疗状态。同样地，Ungar等[36]发现，校正了降压治疗和其他协变量后，动态血压监测的DBP较低与老年患者的全因死亡率更
表4. 总体CVD事件的Cox回归分析: 未接受治疗的患者

<table>
<thead>
<tr>
<th>总体CVD</th>
<th>$x^2$</th>
<th>P值</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>未校正</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP &lt;70 vs 70~89 mmHg</td>
<td>73.8</td>
<td>&lt;0.0001</td>
<td>9.2</td>
<td>5.5~15.2</td>
</tr>
<tr>
<td>校正了年龄和性别</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP &lt;70 vs 70~89 mmHg</td>
<td>70.3</td>
<td>&lt;0.0001</td>
<td>12.0</td>
<td>6.7~21.5</td>
</tr>
<tr>
<td>年龄 (每个标准差)</td>
<td>3.2</td>
<td>0.0742</td>
<td>0.9</td>
<td>0.9~1.0</td>
</tr>
<tr>
<td>性别 (男性 vs 女性)</td>
<td>0.7</td>
<td>0.4033</td>
<td>0.8</td>
<td>0.6~1.2</td>
</tr>
<tr>
<td>部分校正后*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP &lt;70 vs 70~89 mmHg</td>
<td>67.0</td>
<td>&lt;0.0001</td>
<td>11.7</td>
<td>6.5~21.0</td>
</tr>
<tr>
<td>年龄 (每个标准差)</td>
<td>1.6</td>
<td>0.2063</td>
<td>0.9</td>
<td>0.7~1.1</td>
</tr>
<tr>
<td>性别 (男性 vs 女性)</td>
<td>1.4</td>
<td>0.2332</td>
<td>0.8</td>
<td>0.5~1.2</td>
</tr>
<tr>
<td>BMI (每个SD)</td>
<td>3.0</td>
<td>0.0823</td>
<td>0.8</td>
<td>0.7~1.0</td>
</tr>
<tr>
<td>总胆固醇 (每个标准差)</td>
<td>1.7</td>
<td>0.1981</td>
<td>1.1</td>
<td>0.9~1.3</td>
</tr>
<tr>
<td>吸烟 (目前吸烟 vs 其他)</td>
<td>0.7</td>
<td>0.3967</td>
<td>1.2</td>
<td>0.8~1.8</td>
</tr>
<tr>
<td>糖尿病（是 vs 否）</td>
<td>3.9</td>
<td>0.0492</td>
<td>1.7</td>
<td>1.0~2.9</td>
</tr>
</tbody>
</table>

所有Cox模型，n=791。依据首次事件和初始事件后首次随访的时间间隔进行分层（分位组）。BMI, 体重指数；CI, 置信区间；CVD, 心血管疾病；DBP, 舒张压；HR, 比例比。

*校正了年龄 (每个标准差)、性别 (男性 vs 女性)、BMI (每个标准差)、总胆固醇 (每个标准差)、吸烟 (是或否) 和糖尿病 (是或否)。

高相关。弗雷明汉心脏研究[14]证实，在未接受降压治疗的情况下，DBP<70 mmHg相比DBP为70~89 mmHg使得CVD风险增加的程度相当于SBP升高20 mmHg，换句话说，相当于从血压正常者并转为1级收缩期高血压或从1级高血压转变为2级高血压所潜在增加的风险。此外，Wang等[15]发现，随着年龄增长而脉压增加，降压治疗可以最大程度地降低SBP，显著地降低DBP。因此，年老ISH不仅DBP<70 mmHg常见于未接受降压治疗的患者，与CVD风险增加相关，而且降压治疗进一步降低DBP的作用比降低SBP的作用非常小。

降压治疗作为CHD事件复发的因素

由于干预试验的事后分析 (post hoc analyses) 存在偏倚和混杂因素，因此这些研究对于在低DBP情况下，降压治疗是否引发了CHD事件这个问题无法给出答案[19~21]。DBP较低与年龄、女性、糖尿病、慢性肾脏病、心衰、新发癌症和脉压增加有关。如果上述患者在干预性试验中发生CHD事件的话，并不一定是降压治疗导致了CHD事件的发生，而是基线较低的DBP (和脉压增加) 预测了他们未来发生事件。在既往的一项弗雷明汉研究中，Kannel等[15]观察到，CHD事件主要见于SBP升高的低DBP患者，这意味着ISH合并高脉压可能是主要原因，而非降压治疗。重要的是，过度治疗不太可能是由DBP的原因，因为治疗强度与低的DBP相关[22]。此外，年老ISH患者的降压治疗降低SBP的效果较DBP更为明显[18,20]，降低脉压和动脉僵硬度，因此从理论上讲，降压治疗能够改善左室冠脉氧供/需求比值，从而对缺血提供保护作用。弗雷明汉心脏研究的结果[22]得到了采用心血管系列

图2. DBP<70 mmHg与DBP为70~89 mmHg患者相比的总体心血管事件 (冠心病、心衰和卒中) 和单个心血管事件的完全校正后的危险比：(1) 所有接受和未接受治疗的患者，(2) 受到治疗的患者，(3) 未接受治疗的患者 (所有危险比，P<0.0001)。y轴表示DBP<70 mmHg和DBP为70~89 mmHg患者的比较。
图1。本流程图描述了经历首次高血压性心血管事件后的幸存者中，接受≥8次随访且符合研究入选标准的791例患者。

* 其他CVD事件包括心脏病发作和接受过非典型随访的患者被排除在外。121例患者的主要变量数据缺失。19例患者的主要变量数据超过了首次CVD事件后5年达到排除标准。DBP=舒张压。

专门研究和电子健康记录（Cardiovascular Research Using Linked Bespoke Studies and Electronic Health Records，CALIBER）项目（包括125万例患者的系列专门研究和电子健康记录）的证实，该项目显示除了DBP≥140 mmHg的患者之外，其他患者并没有出现DBP的J型曲线[5]。

综上所述，本研究结果提示降压治疗与CHD事件的复发无关。首先，DBP<70 mmHg组相比DBP=70~89 mmHg组的CVD风险增加在接受和未接受降压治疗的患者中平均分布。其次，DBP<70 mmHg时相比DBP=70~89 mmHg时的CVD风险增加在单独分析CHD、心衰和卒中时依然存在。第三，DBP<70 mmHg相比DBP=70~89 mmHg的总体和单独分析CVD事件风险增加，低DBP与治疗状态之间不存在相关性，这为CHD事件发生率的增加不是由治疗所引起提供了进一步的证据。总的来说，本研究并未证实降压治疗是导致低DBP相关CVD事件风险增加的显著原因。

未接受随访患者CVD事件复发的意义

对于265例在首次CVD事件后未接受随访的患者，其临床病程相比接受1次以上随访的患者有明显的差异。首先，大多数未接受随访的受试者两次事件风险较接受1次以上随访的患者显著更高。其次，无论是否接受了降压药物治疗，在首次事件后很快就复发的患者死亡率更高。第三，接受随访和未接受随访的患者，在首次CVD事件发生前的平均血压相当（155/84 vs 155/80 mmHg），这提示在首次事件发生前DBP<70 mmHg的患者很少。

既往发表的弗雷明汉研究结果已经表明，梗死后SBP显著降低提示心功能下降[24]。因此，我们可以假设有很大比例CVD事件复发和首次事件后死亡率高的患者存在心功能下降和反向因果关系[22]。因此，在首次CVD事件后未接受随访的患者，即符合本研究入选标准的患者相比在发生首次CVD事件后未接受随访的患者存在显著的生存率差异。

与低DBP相关的CVD事件复发风险增加的原因

年龄作为一个效应调节因子，在影响DBP有或无对CVD风险的预测中起到重要作用[26]。从60岁开始，脉压比SBP成为更好的CVD风险预测因子。此外，此时年老ISH患者的DBP与CVD风险的关系呈正J型曲线[26]。传统上，脉压增长作为一种动脉僵硬度的指标已经被证实是独立的CVD风险因素[3,5]。从60岁开始，DBP的降低和脉压差的快速增加被视为动脉僵硬度的替代标志。此外，我们推测CVD风险的增加部分上是由于弹性动脉僵硬度增加和增加舒张期灌注量共同导致的微血管功能障碍这一有害作用。有趣的是，本研究的Cox回归分析显示，低DBP和年龄、性别、体重指数、总胆固醇、吸烟或糖尿病对CVD风险的贡献要大得多，证明了脉压差增加合并低DBP对已发生CVD事件人群的CVD复发风险具有特别重要的意义。

近期，两篇以强化降压可能有害为主题的文章对于J型曲线的争议进行了辩论（正方[27]和正方[29]）。不过，这两篇文章的作者都没有考虑ISH患者合并低DBP是CVD事件J型曲线的主要因素。

优势和局限性

本研究的优势包括在发生首次CVD事件后的生活者中收集数据的间隔较长，同时采取了大家熟知的弗雷明汉心脏研究的标准化方法。不过，在这一观察性研究中，我们无法控制患者在首次CVD事件发生之后是否已经接受降压治疗，也不控制治疗的类型或数量。此外，尽管我们将药物治疗定义为以降压为治疗目的，但是这些药物有可能既为了降低血压也为了其他心血管疾病的治疗。最后，我们没有关于靶器官功能或潜在有明显体位性低血压的信息。尽管如此，我们的Cox回归模型结果显示，低DBP与降压治疗之间没有显著的相互作用，该结果为证明不存在药物诱发的低DBP在控制心血管事件的影响提供了强有力的证据。最后，对于265例首次心血管事件发生后未接受随访、不符合本研究主要分析的患者，我们只能推测其中很多患者在首次心血管事件后短期的死亡率高，并可能存在反向因果关系。

很多因素相互作用导致DBP降低，进而影响CHD发生风险，因此只有纳入低DBP患者并将其随机分配至不同SBP水平的活性药物组的干预试验才能明确降压治疗到底是否能改善基线时CVD的高风险。此外，降低老年ISH患者SBP和DBP的最佳治疗方案与低DBP情况下安全地降低SBSB是两个不同的问题。
观点

本研究是首个基于社区的研究,结果发现DBP<70 mmHg的持续单纯收缩期高血压患者在发生首次CVD事件后,相比DBP为70~89 mmHg的患者CVD事件的复发风险增加。这些研究结果支持高脉压与低DBP是重要的危险因素,且在体上独立于是否降压治疗,是否需要考虑危险因素干预来降低这些患者过高的心血管风险,可能是未来研究的主题。

利益声明

无。参考文献