Systolic Blood Pressure and Mortality After Stroke
Too Low, No Go?

Michelle P. Lin, MD, MPH; Bruce Ovbiagele, MD, MSc, MAS; Daniela Markovic, MS; Amytis Towfighi, MD

Background and Purpose—Recent studies suggest a J-shaped association between systolic blood pressure (SBP) and cardiovascular events. The optimal SBP target after stroke remains unknown. We assessed the link between SBP and mortality after stroke.

Methods—We included adults (≥20 years) with self-reported stroke who participated in the National Health and Nutrition Examination Surveys 1998 to 2004, with mortality assessment in 2006. Baseline SBP was categorized as low to normal (<120 mm Hg), normal (120–140 mm Hg), and high (≥140 mm Hg). Independent relationships between baseline SBP and all-cause and vascular mortality were assessed using Cox proportional hazards.

Results—Of 31,126 adult participants, 455 had self-reported stroke and baseline BP readings: 19% had low to normal, 31% had normal, and 50% had high SBP. Two years after assessment, the low to normal SBP group tended to have the highest cumulative all-cause mortality (11.5%), compared with mortality rates of 8.5% and 7.5% in the normal and high SBP groups, respectively. Similar patterns were seen with vascular mortality. After adjusting for covariates, compared with the high SBP group, the low to normal group had higher all-cause mortality (adjusted hazard ratio, 1.96; 95% confidence interval, 1.13–3.93; P=0.007) and trended toward higher vascular mortality (adjusted hazard ratio, 2.08; 95% confidence interval, 0.93–4.68; P=0.075). Compared with the normal BP group, the risk of all-cause and vascular mortality trended higher in low to normal BP group but did not achieve statistical significance.

Conclusions—After stroke, compared with SBP in the high range, low to normal SBP is associated with poorer mortality outcomes. (Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.115.008821.)

Key Words: blood pressure ■ hypertension ■ mortality ■ Nutrition Surveys ■ secondary prevention ■ stroke
Beyond the acute stroke setting, 2 post hoc analyses of randomized controlled trials implied that there may be a J-shaped relationship between BP and recurrent vascular events within 2 years of an index stroke; poor outcomes were observed in both extremes of BPs.12,13 Both studies found that the association was more pronounced in the first 6 months after stroke. Most recently, an observational community-based study involving 483 participants with stroke and 10-year follow-up reported a 61% increased risk of combined vascular outcome (stroke, acute myocardial infarction, and death) among those with SBP ≤120 mm Hg compared with reference group of SBP 131 to 141 mm Hg.14

In this study, we used a nationally representative sample of US adults (≥20 years) who participated in the National Health and Nutrition Examination Surveys (NHANESs) III (1998–2004) with self-reported history of stroke to explore the effect of baseline SBP (during a single outpatient NHANES evaluation) on all-cause and vascular mortality, assessed in 2006.

**Methods**

**Study Population**

NHANESs are a series of cross-sectional, national, stratified, multi-stage probability surveys constituting representative samples of the civilian, noninstitutionalized US population. The surveys and examinations are conducted by the National Center for Health Statistics. Each survey participant completed a household interview and underwent a physical examination. Detailed descriptions of the plan and operation of each survey have been published.13 The study received approval from the National Center for Health Statistics Research.
Table 2. Survey-Weighted Incidence of All-Cause Mortality by SBP Category and Follow-Up Time

<table>
<thead>
<tr>
<th>Table 2. Survey-Weighted Incidence of All-Cause Mortality by SBP Category and Follow-Up Time</th>
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<tbody>
<tr>
<td>All-Cause Mortality</td>
</tr>
<tr>
<td>Time, y</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
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<td>3</td>
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</table>

SBP indicates systolic blood pressure.

Primary Outcome: Mortality

To calculate all-cause and vascular mortality rates, we used data from the NHANES III Linked Mortality File, in which NHANES III–eligible participants were matched, using a probabilistic matching algorithm, to the National Death Index through December 31, 2006, to determine their mortality status. The International Classification of Diseases Tenth Revision, codes I00–I99, were used to identify deaths from diseases of the vascular system. Participants not matched with a death record were considered alive through the entire follow-up period. A detailed description of the methodology is described elsewhere.16

BP Measurements

BP was obtained in accordance with the NHANES procedure manual.17 Briefly, after the patient had rested quietly in a seated position for 5 minutes, the maximum inflation level was determined, and 3 consecutive BP readings were obtained. If a BP measurement was interrupted or incomplete, a fourth attempt was made. Mean SBP of the measurements was used in the analyses.17

Statistical Analyses

Subjects were categorized by prespecified groups according to their mean of 3 SBP readings obtained at the NHANES visit: low to normal (<120 mm Hg), normal (120–140 mm Hg), and high (≥140 mm Hg). The SBP groups were chosen to reflect levels mentioned in guideline recommendations,3,4 for consistency with other studies,12,13,18,19 and practical considerations in routine clinical settings. Baseline sociodemographic and clinical characteristics were assessed by SBP group. The primary outcome was all-cause mortality and the secondary outcome was vascular mortality. Cumulative incidence curves of all-cause mortality were computed by SBP group using the Kaplan–Meier method and weighted appropriately. Cumulative incidence curves of vascular mortality were computed similarly after adjusting for the competing risk of nonvascular mortality. Models were fitted using SBP as categorical and continuous variables. To account for nonlinearity, a linear and a quadratic SBP term were included in the models.

To examine the association between SBP and all-cause and vascular mortality rates after stroke, univariate and multivariate analyses were performed using Cox regression models after adjusting for the survey design variables (ie, variables extracted from the NHANES surveys). For vascular mortality, the Cox model was expanded to a competing risk Cox model to adjust for the competing risk of nonvascular-related mortality. Covariates included in the multivariate model included age, sex/race/ethnicity, income:poverty ratio, hypertension, total serum cholesterol > 200 mg/dL, coronary artery disease, angina, congestive heart failure, body mass index, use of antihypertensive medication(s), and smoking.

Predictor analysis included in the final multivariate Cox regression models was performed using the backward stepwise procedure. We selected the final variables based on P<0.15 or hazard ratio (HR) >1.4 as the retention criterion. A slightly more liberal criterion for variable selection was used as not to miss any important confounders and risk biasing the results by omitting an important confounder. Covariates included in the final models for all-cause mortality and cardiovascular

Table 3. Survey-Weighted Incidence of Vascular Mortality by SBP Category and Follow-Up Time

<table>
<thead>
<tr>
<th>Table 3. Survey-Weighted Incidence of Vascular Mortality by SBP Category and Follow-Up Time</th>
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<tbody>
<tr>
<td>Vascular Mortality</td>
</tr>
<tr>
<td>Time, y</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>3</td>
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</tbody>
</table>

SBP indicates systolic blood pressure.
mortality were age, poverty:income ratio, diabetes mellitus, coronary artery disease, and smoking. Furthermore, the final Cox models also allowed for potential interactions of each SBP category with time (nonproportional hazards) by including the appropriate interaction terms into the models. Specifically, we tested for interactions of each SBP category with (1) log of time and (2) time categorized as <2, 2 to 4, and >4 years. The latter analysis did not impose any functional form (such as linearity) on the relationship between SBP category and the time variable in predicting mortality. The above interactions with time were evaluated at $P < 0.15$ as the level of significance using the $\chi^2$ test under the above Cox regression models. Finally, to evaluate the goodness of fit of the final regression model, we used methods by Hosmer and Lemeshaw adapted for time to event data.20

We excluded 45 participants from the analyses because of missing SBP data. This comprised 9% of the initial sample. To assess the potential influence of missing data on the results, we compared covariates between people with and without missing data to determine whether the distributions were comparable in the 2 groups. In addition, missing values for the covariates were imputed using the Markov Chain Monte Carlo method of imputation for the purpose of the multivariable analyses.21

Results

A total of 31,126 adults participated in NHANES III (1988–1994). Five hundred ninety reported history of stroke, of whom 135 were excluded for missing SBP data, nonpositive survey weights, or missing follow-up data. The final cohort consisted of 455 subjects: 88 (19%) had low to normal SBP, 141 (31%) had normal SBP, and 226 (50%) had high SBP. Compared with individuals with low to normal SBP, individuals with high SBP were older; more likely to be women, black, and poor; to have a history of hypertension, diabetes mellitus, and
hypercholesterolemia; and to use antihypertensive medications. They were less likely to be obese or to smoke (Table 1).

Mortality assessment was at a mean follow-up of 4.1 years (2.6–5.7 years). At 2 years, patients in the low to normal SBP group tended to have higher cumulative all-cause mortality (11.5%) compared with those with normal SBP (8.5%) and high SBP (7.6%; Tables 2 and 3; Figure I in the online-only Data Supplement). The pattern for vascular mortality was similar: 5.0% in the low to normal SBP group, 4.5% in the normal SBP group, and 4.1% in the high SBP group. This association reversed with time from baseline evaluation. At 6 years, individuals with high baseline SBP tended to have the highest cumulative all-cause mortality (36.5%), compared with 30.0% and 19.6% in normal and low to normal SBP groups. A similar pattern was evident for cardiovascular mortality, with mortality rates of 20.2% for high baseline SBP, 12.2% for normal baseline SBP, and 9.1% for low to normal baseline SBP (Tables 2 and 3; Figure I in the online-only Data Supplement).

We also assessed the SBP–mortality relationship using SBP as a continuous variable, and similarly found a significant correlation with all-cause mortality ($\text{P}=0.009$ for the linear term, $\text{P}=0.027$ for the quadratic term). There was a J-shaped relationship between SBP and all-cause mortality after adjusting for covariates (Figure [A]). Both low SBP and high SBP (approximately $>180$ mm Hg) were associated with greater risk of mortality compared with SBP in the normal or moderately high range (Figure [A]). Similar patterns were seen with cardiovascular mortality but were not as robust ($\text{P}=0.12$ for the linear, $\text{P}=0.11$ for the quadratic term). The J-shaped relationship between SBP and 5-year risk of cardiovascular mortality was similarly demonstrated using the quadratic model (Figure [B]).

In unadjusted analyses, there were no significant differences in the all-cause (low versus normal): HR, 0.86; 95% confidence interval [CI], 0.46–1.59; high versus normal: HR, 1.05; 95% CI, 0.66–1.67) or vascular (low versus normal: HR, 0.74; 95% CI, 0.30–1.85; high versus normal: HR, 1.28; 95% CI, 0.61–2.69) mortality rates across SBP groups averaging over follow-up time (Table 4). None of the interactions of SBP category with time were significant at $\text{P}<0.15$.

After adjustment for covariates, compared with the high SBP group, individuals with low to normal SBP had higher all-cause mortality (adjusted hazard ratio [AHR], 1.96; 95% CI, 1.13–3.39) and vascular mortality (AHR, 2.08; 95% CI, 0.93–4.68; Table 4). Compared with individuals with normal SBP, those with low to normal SBP had higher all-cause mortality (adjusted hazard ratio [AHR], 1.96; 95% CI, 1.13–3.39) and vascular mortality (AHR, 2.08; 95% CI, 0.93–4.68; Table 4). Compared with individuals with normal SBP, those with low to normal SBP had higher all-cause mortality (adjusted hazard ratio [AHR], 1.96; 95% CI, 1.13–3.39) and vascular mortality (AHR, 2.08; 95% CI, 0.93–4.68; Table 4).
and vascular mortality but neither of these associations were significant (AHR, 1.43; 95% CI, 0.82–2.50 and AHR, 1.71; 95% CI, 0.75–3.90). Individuals with high baseline SBP had lower all-cause and vascular mortality compared with those with normal SBP (AHR, 0.73; 95% CI, 0.45–1.18 and AHR, 0.82; 95% CI, 0.41–1.62), but these associations were not significant. To test the predictive accuracy of the final model, we applied that goodness-of-fit test to compare the predicted versus observed 5-year probabilities of all-cause mortality by decile and found that P=0.11 demonstrating good agreement (Table I in the online-only Data Supplement).

Assessment of the covariates revealed that older age, poverty, and diabetes mellitus were associated with higher all-cause mortality and older age, poverty, and coronary artery disease were associated with higher vascular mortality (Table 5). The AHR of aging per year was 1.06 (95% CI, 1.03–1.09) for all-cause mortality and 1.10 (95% CI, 1.06–1.13) for vascular mortality. Individuals with income:poverty ratio >400% had 60% lower all-cause mortality (AHR, 0.40; 95% CI, 0.18–0.90) and 86% lower vascular mortality (AHR, 0.14; 95% CI, 0.03–0.72) compared with those with a ratio <125%.

Diabetes mellitus was associated with higher all-cause mortality (AHR, 1.77; 95% CI, 1.01–3.08), but not vascular mortality (AHR, 1.43; 95% CI, 0.55–3.73). Coronary artery disease was associated with higher vascular mortality (AHR, 2.16; 95% CI, 1.08–4.32), but not all-cause mortality (AHR, 1.55; 95% CI, 0.84–2.85; Table 5). Current smokers tended to have higher all-cause and vascular mortality than their counterparts who did not smoke, but this association was not significant beyond chance (Table 5). Comparison of covariates between people with and without missing SBP data revealed a similar distribution of covariates. Furthermore, results using Markov Chain Monte Carlo imputation and additional sensitivity analyses closely agreed with results using complete cases on the covariates.

**Discussion**

In this community-based study of participants from the NHANES 1998 to 2004, we found that among individuals with a self-reported history of stroke, those with baseline SBP in the low to normal range had higher all-cause mortality and trended toward higher vascular mortality than individuals with normal SBP and high SBP, after adjusting for major sociodemographic and vascular risk factors during a mean follow-up of 4.1 years (2.6–5.7 years).

Our results support emerging data suggesting that there may indeed be a threshold beyond which further harm occurs with BP lowering. Two recent post hoc analyses of randomized controlled trials of secondary stroke prevention revealed that risk of recurrent stroke was higher in those with SBP <120 compared with those with SBP 120 to 140 mm Hg. A systematic review and meta-analysis of 11 published randomized controlled trials revealed that achieving SBP <130 mm Hg seemed to provide additional stroke protection only among people with risk factors but no established cardiovascular disease. Those with established cardiovascular disease at entry did not experience stroke risk reduction with tight BP control. BP control was associated with hypotension (relative risk, 3.43; 95% CI, 2.46–4.79) and occurrence of adverse events (relative risk, 1.18; 95% CI, 1.11–1.25).

Our study has several strengths: we used a large sample of individuals in the United States, with rigorous, validated methods for BP measurements, and information on a variety of comorbidities. This study also has several limitations. First, because stroke was assessed by self-report, we lacked information on stroke type, duration since stroke, stroke severity, and functional status; these factors, which may have had an effect on mortality, were not controlled for. Second, although BP was measured at the time of the NHANES examination, there were no subsequent BP measurements (because NHANES is a cross-sectional survey/examination). Third, NHANES only captures noninstitutionalized individuals and those who can comprehend and respond to surveys, resulting in a possible bias toward a healthier population. Fourth, missing data could introduce unaccounted selection bias; however, missing data analyses suggested that covariates were similar in the groups with versus without BP data and the Markov Chain Monte Carlo imputation demonstrated close agreement with study results. Fifth, patients with low to normal BP were younger, hence may have had a different stroke risk profile than older patients. This may have introduced confounding even after adjustment for age.

BP goals after stroke remain uncertain, given the limited data on outcomes. Forthcoming trials, including Secondary Stroke Prevention by Uniting Community and Chronic Care Model Teams Early to End Disparities (SUCCEED), Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED), Efficacy and Nitric Oxide in Stroke (ENOS) and Optimal Blood Pressure and Cholesterol Targets for Preventing Recurrent Stroke in Hypertensives (ESH–CHL–SHOT) may help further elucidate BP goals and the timing to achieve target BP. Meanwhile, new secondary stroke prevention guidelines support a target BP of <140/90 mm Hg and suggest individual tailoring of BP therapy combined with lifestyle modifications. Probability of success will likely increase if interventions are culturally tailored and take into account race/ethnic, sex-specific, educational, and socioeconomic factors.

**Disclosures**

None.

**References**

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Data Supplement (unedited) at:
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SUPPLEMENTAL MATERIAL
Supplemental Figure I. Cumulative incidence of (A) all-cause death, (B) vascular death by SBP group for persons with self-reported history of stroke, NHANES 1999-2004.
### Supplemental Table I. Goodness of fit test using predicted vs. observed 5 year probabilities of all-cause mortality by decile in the final model, P=0.11

<table>
<thead>
<tr>
<th>Predicted risk in decile</th>
<th>model predicted risk</th>
<th>observed risk*</th>
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<tbody>
<tr>
<td>1</td>
<td>73.6%</td>
<td>73.2%</td>
</tr>
<tr>
<td>2</td>
<td>55.9%</td>
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</tr>
<tr>
<td>3</td>
<td>47.7%</td>
<td>41.4%</td>
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<tr>
<td>4</td>
<td>40.5%</td>
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<td>8.3%</td>
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<tr>
<td>9</td>
<td>13.1%</td>
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<tr>
<td>10</td>
<td>5.8%</td>
<td>6.6%</td>
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</table>

* based on Kaplan-Meier observed risk
수축기 혈압과 뇌졸중 후 사망률

 너무 낮게는 가지 말아야 하나?

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(Stroke. 2015;46:1307-1313.)

Key Words: blood pressure ■ hypertension ■ mortality ■ Nutrition Surveys ■ secondary prevention ■ stroke

배경과 목적

최근의 연구들은 수축기 혈압과 심혈관 사건 사이에 J형 곡선의 연관성을 제시한다. 뇌졸중 후 수축기 혈압의 적절한 몰표치는 아직 알려지지 않았다. 연구자들은 수측기 혈압과 뇌졸중 후 사망률 사이의 연관성을 평가하였다.

방법

본 연구는 National Health and Nutrition Examination Surveys (1998–2004)와 2006년 사망률 조사에서 뇌졸중을 자가 보고한 20세 이상의 성인을 분석하였다. 기저 수축기 혈압은 저-정상(<120 mmHg), 정상(120–140 mmHg), 고(≥140 mmHg)로 분류되었다. 기저 수축기 혈압과 총 사망률, 혈관성 사망률의 독립적인 연관성을 콕스비례위험(Cox proportional hazards)을 사용하여 분석하였다.

결과

3126명의 성인참가자들 중 455명이 뇌졸중 자가보고를 하였다. 기저 혈압 판독에서 19%는 저-정상 수축기 혈압, 31%는 정상 수축기 혈압, 50%는 고 수측기 혈압을 보였다. 평가 후 2년 후에 저-정상 수축기 혈압군은 11.5%의 누적 총 사망률을 보였는데 정상 수축기 혈압군 8.5%와 고 수측기 혈압군 7.5% 사망률과 비교할 때 가장 높은 수치였다. 비슷한 양상을 혈관성 사망률에서도 나타났다. 공변량으로 보정하였을 때 저-정상 수축기 혈압군은 고 수측기 혈압군과 비교할 때 총 사망률은 유의한 증기를 보였고(보정 HR, 1.96; 95% CI, 1.13–3.39; P=0.017), 혈관성 사망률은 증가 경향성을 보였다(보정 HR, 2.08; 95% CI, 0.93–4.68; P=0.075). 정상혈압군과 비교할 때 저-정상혈압군에서 총 사망률과 혈관성 사망률이 높아지는 경향성을 보였으나 통계학적 유의성은 없었다.

결론

뇌졸중 후 정상 및 낮은 범주의 수축기 혈압은 높은 범주의 수축기 혈압비교할 때 더 불량한 사망률 결과를 보인다.

Table 4. Crude and Adjusted Hazard Ratios of All-Cause Mortality or Vascular Mortality by SBP

<table>
<thead>
<tr>
<th>SBP Group</th>
<th>All-Cause Mortality (n=130 Events)</th>
<th>Vascular Mortality (n=61 Events)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>Ref</td>
<td>0.86 (0.46–1.65)</td>
</tr>
<tr>
<td>SBP &gt; 140 mmHg</td>
<td>2.83 (1.00–7.97)</td>
<td>0.051</td>
</tr>
<tr>
<td>SBP &lt; 120 mmHg</td>
<td>1.43 (0.83–2.50)</td>
<td>0.208</td>
</tr>
<tr>
<td>SBP 120–139 mmHg</td>
<td>0.73 (0.45–1.16)</td>
<td>0.194</td>
</tr>
</tbody>
</table>

* Adjusting for age, sex, race, income, poverty income ratio, hypertension, total serum cholesterol >200 mg/dL, coronary artery disease, angina, congestive heart failure, body mass index, use of antihypertensive medication(s), smoking.