Blood Pressure and Risk of Death from External Causes among Men Screened for the Multiple Risk Factor Intervention Trial

Paul D. Terry¹, Jerome L. Abramson¹, and James D. Neaton² for the MRFIT Research Group

¹ Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA.
² Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN.

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A few epidemiologic studies have shown an increased risk of death from external causes among men with hypertension. Previous studies were limited by small numbers of events, however, and none assessed the association of blood pressure with specific types of “accidental” death. The authors examined data obtained from baseline interviews and 25 years of mortality follow-up (1973–1999) for 347,978 men screened for the US Multiple Risk Factor Intervention Trial. Proportional hazards regression analyses were used to quantify associations of blood pressure with all external causes of death and individual causes. There were 3,910 deaths from external causes, including 2,313 unintentional injuries, 1,248 suicides, and 349 homicides. Compared with those for men whose blood pressure status was “normal” according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the multivariate-adjusted hazard ratios and 95% confidence intervals for death from external causes among men with prehypertension, stage 1 hypertension, and stage 2 hypertension were 0.91 (95% confidence interval: 0.83, 1.00), 1.06 (95% CI: 0.96, 1.16), and 1.44 (95% CI: 1.28, 1.62), respectively. Men with stage 2 hypertension had multivariate-adjusted hazard ratios of 1.90 for falls (95% CI: 1.32, 2.74), 1.45 for motor vehicle injuries (95% CI: 1.14, 1.85), 1.33 for other “accidents” (95% CI: 1.06, 1.66), 1.40 for suicide (95% CI: 1.13, 1.73), and 1.35 for homicide (95% CI: 0.92, 1.97). For men, hypertension may signal an increased risk of death from external causes.

accidental falls; accidents; epidemiologic studies; hypertension; mortality

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; MRFIT, Multiple Risk Factor Intervention Trial; SBP, systolic blood pressure.

Three epidemiologic studies have shown an increased risk of death from external causes among men with hypertension. Blood pressure was positively associated with death from combined external causes in a recent cohort study of middle-aged Lithuanian men, after adjustment for alcohol consumption, smoking, serum cholesterol level, and education (1). A positive association between blood pressure and risk of death from combined external causes also was shown in a cohort study of men in Italy, after adjustment for smoking and cholesterol level (2). A cohort study in Finland showed a positive association between blood pressure and death from combined external causes among men, but not women, after adjustment for smoking, alcohol consumption, cholesterol level, and education (3). In contrast, a smaller cohort study in Finland reported only that there was no significant association between any of the cardiovascular risk factors examined, including blood pressure, and risk of “violent (non-illness)” death (4).

Thus, an association between blood pressure and risk of death from external causes among men has been shown in...
some, but not all studies to date. However, all of these studies were limited by small sample sizes and relatively few deaths from external causes, the latter ranging from 83 to 236. Furthermore, none of these studies examined the association of blood pressure with specific types of “accidental” death, which may have distinct etiologies. Therefore, we used 25 years of mortality follow-up data from the large cohort of men screened for the Multiple Risk Factor Intervention Trial (MRFIT) to examine the association between blood pressure and risk of death from external causes, overall and by type.

MATERIALS AND METHODS

Men screened for MRFIT in 1973–1975 at 22 clinical centers in 18 cities across the continental United States provided their name, address, Social Security number, and date of birth (5, 6). They were asked to identify their race/ethnicity (White, Black, Oriental, Spanish American, American Indian, or other) and to indicate whether they were taking medicine for diabetes, whether they had ever been hospitalized for 2 weeks or more for a heart attack, and how many cigarettes per day they were smoking. Their blood pressure was taken three times with a standard mercury sphygmomanometer; we used the average of the second and third readings. A nonfasting blood sample was drawn, and serum total cholesterol was measured. These data were used to select men at high risk for coronary heart disease who might be eligible for the clinical trial. Details concerning screening procedures and the trial have been published elsewhere (7). Data on race/ethnicity-specific median household incomes for most zip (postal) code areas were available from the 1980 US Census. Data on the 347,978 screened men, aged 35–57 years, who had not been previously hospitalized for a heart attack and for whom complete screening data were available formed the basis of our study. The association of blood pressure with cardiovascular disease mortality has been described in detail for this cohort (8).

We used the participants’ names, dates of birth, and Social Security numbers to obtain mortality data from the Social Security Administration and National Death Index through December 31, 1999. For those who died before 1991, we obtained death certificates from states of residence, and underlying causes of death were coded according to the International Classification of Diseases, Ninth Revision (ICD-9) (9). Among those who died in 1991 or later, we obtained the date and primary cause of death (using either ICD-9 or the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)) via the National Death Index Plus Service.

Means and standard deviations (or percentages, when appropriate) were tabulated for the following individual risk factors according to cause of death: age, serum cholesterol, systolic blood pressure (SBP), diastolic blood pressure (DBP), presence and stage of hypertension (10), cigarette smoking status (smoker/nonsmoker), number of cigarettes smoked per day (among smokers), use of medicine for diabetes, and median household income on the basis of zip code of residence. Proportional hazards regression analyses (11) were used to quantify associations of blood pressure with all external causes of death (injuries, suicides, and homicides) and individual causes. In this paper, hazard ratios and 95 percent confidence intervals are cited.

Hypertension risk categories were based on the classifications outlined by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (12). Accordingly, participants were placed in one of the following categories: normal = <120 mmHg SBP and <80 mmHg DBP; prehypertension = 120–139 mmHg SBP or 80–89 mmHg DBP; stage 1 hypertension = 140–159 mmHg SBP or 90–99 mmHg DBP; and stage 2 hypertension = ≥160 mmHg SBP or ≥100 mmHg DBP. In addition, blood pressure was considered a continuous variable in regression analyses.

Death from external causes was the outcome considered (ICD-9 codes E800–E899 and ICD-10 codes V01–Y98). These deaths were further categorized as “accidental” deaths (all external deaths not due to suicide or homicide), motor vehicle injuries (ICD-9 codes E810–E829 and ICD-10 codes V01–V89), falls (ICD-9 codes E880–E888 and ICD-10 codes W00–W19), suicides (ICD-9 codes E950–E959 and ICD-10 codes X60–X84), homicides (ICD-9 codes 960–E969 and ICD-10 codes X85–Y09), and death from other injuries (deaths from external causes not included in the aforementioned categories, i.e., other “accidental” deaths) (9).

Regression analyses included as covariates age, race/ethnicity (Black vs. non-Black), income, serum cholesterol level, number of cigarettes smoked per day, and use of medication for diabetes. Assessments of interaction between blood pressure and other predictors were based on likelihood ratio tests comparing models with and without product terms representing the variables of interest. A similar approach was used to determine whether there was a quadratic association of SBP and DBP with mortality. All analyses were conducted by using SAS 8.2 software (SAS Institute, Inc., Cary, North Carolina). All p values were obtained from two-sided tests.

RESULTS

The average duration of follow-up (date of screening through December 31, 1999) of all 347,978 men in the cohort was 25 years or until death (a total of 7,932,315 person-years with death censoring). During follow-up, there were 3,910 deaths from external causes (2,313 injuries, 1,248 suicides, and 349 homicides). Mean baseline blood pressure levels and percentage hypertensive were greater for men who died from injuries, overall and for the common causes considered. For reference, characteristics of cardiovascular disease deaths and all deaths are also shown (table 1). For each cause considered, SBP and DBP were significantly higher (p < 0.0001) than levels for 25-year survivors. Men who died from cardiovascular disease had higher blood pressure levels than men who died from injuries (table 1). Men who died of external causes were also more likely than survivors to be of Black race/ethnicity, smoke cigarettes at baseline, use medicine for diabetes, and have a slightly lower median income.
Hypertension status was associated with risk of death from external causes (tables 2 and 3). Compared with those for participants whose blood pressure was “normal” according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the multivariate-adjusted hazard ratios and 95 percent confidence intervals for prehypertension, stage 1 hypertension, and stage 2 hypertension were 0.91 (95 percent confidence interval (CI): 0.83, 1.00), 1.06 (95 percent CI: 0.96, 1.16), and 1.44 (95 percent CI: 1.28, 1.62), respectively (the corresponding unadjusted hazard ratios were 0.93, 1.13, and 1.61). When hypertension status was examined according to major subcategories of deaths from external causes, multivariate-adjusted hazard ratios for men with stage 2 hypertension were 1.90 for falls (95 percent CI: 1.32, 2.74), 1.45 for motor vehicle injuries (95 percent CI: 1.14, 1.85), and 1.33 for falls. Prehypertension and stage 1 hypertension were associated with an elevated risk of death from cardiovascular disease (CVD) (1.14 and 1.33, respectively), but the difference was not statistically significant.

### TABLE 1. Baseline characteristics of men screened for the Multiple Risk Factor Intervention Trial according to cause of death, United States, 1973–1999

<table>
<thead>
<tr>
<th></th>
<th>All external causes</th>
<th>All “accidental” deaths</th>
<th>Motor vehicle deaths</th>
<th>Falls</th>
<th>Other injuries</th>
<th>Suicides</th>
<th>Homicides</th>
<th>CVD* deaths</th>
<th>All deaths</th>
<th>25-year survivors</th>
<th>All men</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP* (mean mmHg)</td>
<td>131.6</td>
<td>132.0</td>
<td>130.6</td>
<td>134.7</td>
<td>132.3</td>
<td>130.6</td>
<td>131.9</td>
<td>138.1</td>
<td>135.0</td>
<td>128.4</td>
<td>130.0</td>
</tr>
<tr>
<td>DBP* (mean mmHg)</td>
<td>84.7</td>
<td>84.8</td>
<td>84.5</td>
<td>85.3</td>
<td>84.8</td>
<td>84.4</td>
<td>85.4</td>
<td>87.8</td>
<td>86.0</td>
<td>83.0</td>
<td>83.7</td>
</tr>
<tr>
<td>SBP ≥140 or DBP ≥90 (%)</td>
<td>39.9</td>
<td>41.2</td>
<td>39.7</td>
<td>43.8</td>
<td>41.7</td>
<td>37.1</td>
<td>41.0</td>
<td>53.9</td>
<td>46.3</td>
<td>31.4</td>
<td>35.1</td>
</tr>
<tr>
<td>Age at screening (mean years)</td>
<td>46.6</td>
<td>47.0</td>
<td>46.1</td>
<td>48.9</td>
<td>47.1</td>
<td>46.3</td>
<td>45.3</td>
<td>49.3</td>
<td>49.0</td>
<td>44.9</td>
<td>45.9</td>
</tr>
<tr>
<td>Age at death (mean years)</td>
<td>59.9</td>
<td>60.6</td>
<td>59.0</td>
<td>65.2</td>
<td>60.2</td>
<td>59.7</td>
<td>55.8</td>
<td>65.2</td>
<td>65.2</td>
<td>NA*</td>
<td>NA</td>
</tr>
<tr>
<td>Cholesterol level (mean mg/dl)</td>
<td>214.3</td>
<td>215.7</td>
<td>213.4</td>
<td>215.4</td>
<td>218.2</td>
<td>213.7</td>
<td>206.8</td>
<td>225.6</td>
<td>219.2</td>
<td>212.4</td>
<td>214.1</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>44.6</td>
<td>41.9</td>
<td>40.5</td>
<td>38.9</td>
<td>44.5</td>
<td>47.4</td>
<td>52.4</td>
<td>48.2</td>
<td>49.8</td>
<td>32.0</td>
<td>36.4</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>2.6</td>
<td>2.9</td>
<td>1.8</td>
<td>2.9</td>
<td>3.9</td>
<td>2.0</td>
<td>2.9</td>
<td>4.7</td>
<td>3.6</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Black race/ethnicity (%)</td>
<td>9.5</td>
<td>9.0</td>
<td>9.9</td>
<td>4.4</td>
<td>10.1</td>
<td>3.7</td>
<td>33.2</td>
<td>8.1</td>
<td>8.4</td>
<td>5.8</td>
<td>6.5</td>
</tr>
<tr>
<td>Zip (postal) code median income ($)</td>
<td>19,327</td>
<td>19,395</td>
<td>19,235</td>
<td>19,769</td>
<td>19,483</td>
<td>19,683</td>
<td>16,525</td>
<td>19,437</td>
<td>19,874</td>
<td>20,480</td>
<td>20,260</td>
</tr>
<tr>
<td>No. of screenes</td>
<td>3,910</td>
<td>2,313</td>
<td>947</td>
<td>409</td>
<td>957</td>
<td>1,248</td>
<td>349</td>
<td>34,456</td>
<td>85,079</td>
<td>262,899</td>
<td>347,978</td>
</tr>
</tbody>
</table>

* CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; NA, not applicable.

### TABLE 2. External causes of death by JNC 7† blood pressure classification, United States, 1973–1999: age-adjusted rates per 10,000 person-years and Cox regression coefficients for SBP‡;

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>JNC 7 blood pressure classification</th>
<th>SBP coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Prehypertension</td>
</tr>
<tr>
<td></td>
<td>No. of deaths</td>
<td>Rate</td>
</tr>
<tr>
<td>All external causes</td>
<td>703</td>
<td>4.95</td>
</tr>
<tr>
<td>All “accidents”</td>
<td>413</td>
<td>2.95</td>
</tr>
<tr>
<td>Motor vehicle injuries</td>
<td>165</td>
<td>1.14</td>
</tr>
<tr>
<td>Falls</td>
<td>63</td>
<td>0.48</td>
</tr>
<tr>
<td>Other injuries</td>
<td>185</td>
<td>1.33</td>
</tr>
<tr>
<td>Suicides</td>
<td>229</td>
<td>1.57</td>
</tr>
<tr>
<td>Homicides</td>
<td>61</td>
<td>0.42</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>3,112</td>
<td>23.85</td>
</tr>
</tbody>
</table>

* p < 0.05; **p < 0.01.
† JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; SBP, systolic blood pressure.
‡ Model also includes covariates corresponding to age, race/ethnicity, income, serum cholesterol level, number of cigarettes smoked per day, and use of medication for diabetes.
Detection, Evaluation, and Treatment of High Blood Pressure according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

...increased risk of death from falls. A one standard deviation higher DBP (10.5 mmHg) was associated with an 18.6 percent increased risk; a one standard deviation higher SBP (15.9 mmHg) was associated with a 28.6 percent increased risk. Associations were stronger for SBP than for DBP. For example, a one standard deviation higher SBP was associated with a 17.1 percent increased risk. For death from falls, for which the strongest association was found, a 10-mmHg higher SBP was associated with a 17.1 percent increased risk.

For death from falls, for which the strongest association was found, a 10-mmHg higher SBP was associated with a 17.1 percent increased risk. For death from falls, for which the strongest association was found, a 10-mmHg higher SBP was associated with a 17.1 percent increased risk.

**TABLE 3. External causes of death by JNC 7† blood pressure classification, United States, 1973–1999: hazard ratios and 95% confidence intervals‡**

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Total no. of deaths</th>
<th>Normal (referent)</th>
<th>Prehypertension</th>
<th>Stage 1 hypertension</th>
<th>Stage 2 hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR† 95% CI</td>
<td>HR† 95% CI</td>
<td>HR† 95% CI</td>
</tr>
<tr>
<td>All external causes</td>
<td>3,910</td>
<td>1.00</td>
<td>0.91* 0.83, 1.00</td>
<td>1.06 0.96, 1.16</td>
<td>1.44** 1.28, 1.62</td>
</tr>
<tr>
<td>All “accidents”</td>
<td>2,313</td>
<td>1.00</td>
<td>0.88* 0.79, 0.99</td>
<td>1.07 0.94, 1.21</td>
<td>1.46** 1.26, 1.70</td>
</tr>
<tr>
<td>Motor vehicle injuries</td>
<td>947</td>
<td>1.00</td>
<td>0.96 0.80, 1.15</td>
<td>1.13 0.93, 1.38</td>
<td>1.45** 1.14, 1.85</td>
</tr>
<tr>
<td>Falls</td>
<td>409</td>
<td>1.00</td>
<td>1.06 0.79, 1.41</td>
<td>1.35 0.99, 1.84</td>
<td>1.90** 1.32, 2.74</td>
</tr>
<tr>
<td>Other injuries</td>
<td>957</td>
<td>1.00</td>
<td>0.76** 0.63, 0.90</td>
<td>0.92 0.76, 1.12</td>
<td>1.33* 1.06, 1.66</td>
</tr>
<tr>
<td>Suicides</td>
<td>1,248</td>
<td>1.00</td>
<td>0.96 0.82, 1.12</td>
<td>1.04 0.88, 1.24</td>
<td>1.40** 1.13, 1.73</td>
</tr>
<tr>
<td>Homicides</td>
<td>349</td>
<td>1.00</td>
<td>0.91 0.67, 1.22</td>
<td>0.99 0.71, 1.38</td>
<td>1.35 0.92, 1.97</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>34,456</td>
<td>1.00</td>
<td>1.48** 1.42, 1.54</td>
<td>2.29** 2.20, 2.38</td>
<td>3.59** 3.44, 3.75</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01.
† JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; HR, hazard ratio; CI, confidence interval.
‡ Model includes covariates corresponding to age, race/ethnicity, income, serum cholesterol level, number of cigarettes smoked per day, and use of medication for diabetes.

...external causes not classified as suicide or homicide was examined further. For these 2,313 deaths, assessment of risk of “accidental” deaths in 10-mmHg categories of SBP and DBP showed increased risk for participants whose SBP levels were 150 mmHg or higher or whose DBP levels were 100 mmHg or higher (figure 1). A significant quadratic relation between blood pressure, particularly DBP, and risk of “accidental” death was evident (p = 0.009 for SBP and p < 0.0001 for DBP). Estimated nadirs for SBP and DBP were 100 mmHg and 73 mmHg. The multivariate-adjusted hazard ratio for men whose SBP levels were 180 mmHg or higher compared with those whose SBP levels were less than 110 mmHg was 1.90 (95 percent CI: 1.33, 2.72).

**DISCUSSION**

Using 25 years of mortality follow-up data for the men screened for MRFIT, we found that those with stage 2...
FIGURE 1. Hazard ratios and 95% confidence intervals for deaths from injuries due to “accidents” according to systolic blood pressure (A) and diastolic blood pressure (B) levels in the US Multiple Risk Factor Intervention Trial, 1973–1999. Excluded are suicides and homicides (International Classification of Diseases, Ninth Revision codes E800–E999, excluding E950–E969; International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes S00–Z99, excluding X60–Y09). Hazard ratios were adjusted for age, race/ethnicity, income, serum cholesterol level, number of cigarettes smoked per day, and use of medication for diabetes.
hypertension according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure had approximately a 40–50 percent higher risk of death from external causes than men with normal blood pressure. The positive association with hypertension was also evident for specific categories of “accidental” deaths when examined separately, particularly falls. Overall, the association was weaker for homicides than for “accidental” deaths or suicides and was not statistically significant.

Our findings are consistent with those from three follow-up studies (discussed above) that examined the association between blood pressure and risk of death from external causes among men (1–3). One of these studies assessed the association among men and women separately, showing a positive association between SBP and risk of death from external causes among the men but not among a smaller group of women (3); the association remains virtually unexplored in women. In contrast, a smaller study reported no significant association between blood pressure and death from combined external causes (4). Another cohort study showed a weak association between low SBP and risk of suicide but did not examine associations with hypertension or other external causes of death (13).

We consider several possible explanations for the association we observed between hypertension and risk of death from external causes, and there may be others. One possibility is that the association is due to confounding. Potentially confounding factors include low socioeconomic status, heavy alcohol consumption, sleep apnea, and psychologic distress (e.g., hostility); these factors have been associated with the development of high blood pressure in men (14–16) and with a higher risk of injury-related death in men (17–20). Our estimates were adjusted for race/ethnicity and US Census-based median income, which helps argue against confounding by socioeconomic status, and adjustment for cigarette smoking may have partially controlled for the effects of alcohol, if such effects were present. Nonetheless, residual confounding by these factors, or confounding by other factors, is possible.

Another possible explanation is that hypertension leads to cerebrovascular damage and consequent cognitive or functional decline, which then increases the risk of death from external causes. Hypertension-related pathologic changes in the brain and its vasculature include vascular remodeling, impaired cerebral autoregulation, cerebral microbleeds, white matter lesions, unrecognized lacunar infarcts, and Alzheimer’s-like changes such as amyloid angiopathy and cerebral atrophy (21–23). These changes, particularly white matter lesions, have been associated with declines in frontal lobe integrity and executive function (22, 24, 25), declines in attention and reaction time (26, 27), reduced lower extremity mobility and balance (28, 29), and, perhaps as a consequence, motor vehicle accidents (26) and falls (30).

Hypertension itself has been associated with declines in various measures of cognitive and physiologic function in large prospective cohort studies (31–34). White matter lesions have also been associated with symptoms of depression (35), increased risk of which has also been associated with hypertension in prospective cohort studies (36). Depression is a known risk factor for suicide (37), but data on “accidental” (38) and homicide deaths among sufferers are scarce.

As to the small increase we found in risk of death from external causes among men with very low SBP or DBP, a prospective cohort study in Finland reported an increased risk of suicide and a smaller, statistically insignificant, increased risk of death from combined external causes among persons with low SBP compared with all others (13). Hypertension has been associated with various physiologic and psychologic symptoms (39), and several studies have noted a J-shaped curve between blood pressure and decline in cognitive function (32, 40, 41). There has also been concern that hypertension may increase risk of morbidity because of its association with fatigue (42).

The strengths of our study include large sample size, completeness of follow-up, and availability of data on a large number of deaths from external causes. These features enabled us to examine associations within subcategories of blood pressure with reasonable statistical power and to examine the associations with specific categories of external death separately. To our knowledge, no other study has assessed this association with a large enough sample size and number of events during follow-up to address the association between hypertension and external causes of death with sufficient precision.

Our study has three potential limitations. First, we did not have information on certain potentially confounding factors in our data, including alcohol consumption. Alcohol consumption has been associated both with blood pressure (16) and risk of death from external causes (18). For example, among 226,781 men participating in an American Cancer Society cohort study (18), increased risk of death from external causes was observed for those who consumed four or more drinks per day (approximately 14 percent of all men in that cohort) compared with abstainers, but not for men who drank less. The relative risk of death from external causes for heavy drinkers in that study was 1.3 (95 percent CI: 1.1, 1.6). Thus, we cannot discount confounding by alcohol consumption in our data, although adjustment for this variable did not alter the positive associations with blood pressure in two previous studies of external death (1, 3).

Second, we did not have information on use of antihypertensive medications, some of which, such as certain α-blockers, have been associated with postural hypotension (43, 44), particularly at first dose. Therefore, we cannot exclude the possibility that antihypertensive medicine–induced postural hypotension may be an intermediate step in the causal pathway between hypertension and death from external causes in some persons. In the Treatment of Mild Hypertension Study, differences among various treatment and placebo groups in the percentages reporting faintness, dizziness, and lightheadedness when standing up were modest (44). Furthermore, postural hypotension has generally not been shown to be an important predictor of nonvascular causes of mortality (45), suggesting that it would not be a major causal mechanism. As discussed above, there are plausible underlying mechanisms that do not depend on antihypertensive medicine use, namely, hypertension-related pathologic changes in the brain and its vasculature.
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Conflict of interest: none declared.

REFERENCES


