Blood Pressure Change and Survival After Age 75


Higher diastolic pressure predicted better survival in men 75 years or older in two prior analyses in the Rancho Bernardo population. Diastolic change was implicated as a possible explanation. We studied this by assessing survival according to blood pressure change in 795 men and women aged 75 years and older at the time of a second measurement taken an average of 11 years after the first, who were then followed for 5 years. Sex-specific analyses compared participants with a diastolic decrease of 5 mm Hg or greater and participants with a systolic decrease of 10 mm Hg or greater with those whose blood pressure levels did not change or increased. In men, after adjustment for baseline pressure, a decrease in diastolic pressure of 5 mm Hg or greater was associated with higher all-cause mortality (relative risk, 2.33; 95% confidence interval, 1.39 to 3.91) and cardiovascular mortality (3.13, 1.47 to 6.66). The mortality risk was strongest in men who took antihypertensive medication and had a fall in diastolic pressure (1233, 2.73 to 55.72) compared with treated men whose pressures did not decrease. Among men with isolated systolic hypertension, those treated whose diastolic pressure remained stable had the best survival. A systolic fall in men and a decrease in either diastolic or systolic in women was not associated with poorer survival after adjustment for baseline pressure. We conclude that a fall in diastolic pressure of 5 mm Hg was associated with poor survival in men after age 75. This risk was strongest in men who took antihypertensive medication. (Hypertension. 1993;22:551-559.)

KEY WORDS • blood pressure • cardiovascular diseases • antihypertensive agents • survival • elderly

The US population aged 75 years or more has been projected to grow by 29% between the years 1989 and 2000. Little is known about the relations between traditional cardiovascular risk factors and survival at these ages, but a few studies have found surprising contrasts in survival associations in the very old compared with younger people. People age at different rates, and “elderly” populations having a lower age limit of 70 years or younger probably include two groups—those whose physiology remains similar to middle-aged adults and those who are biologically older. There are sex differences as well, at least with regard to cardiovascular aging, in which women seem to age more slowly than men.

Adequate numbers of the very old and attention to possible sex differences are prerequisites for the evaluation of potential contrasts in risk factor-survival associations in people of advanced age. Taken from this perspective, extrapolation of studies of “the elderly” to the very old may be complicated by the contributions of “younger” elderly whose physiology may more closely resemble that of middle-aged people and who often comprise most of the sample. Also, if interactions are present, adjustment for age, sex, or both may not provide accurate estimates of risk associations. Multivariate analyses may mask the true relation if there are opposing effects in two or more subgroups. This may explain the disparity in risk factor associations reported in the “elderly” using data from cohorts that have different age and sex distributions.

We have previously reported that men aged 75 years and older with higher diastolic blood pressure (DBP) had better survival rates than men at these ages with lower DBP. This relation was linear, and we found no threshold for DBP below which this effect disappeared. Results in women and younger men showed the conventional association, with poorer survival at higher blood pressures. These findings were consistent with results from another study in a different cohort. Analyzes to look for factors that could explain the phenomenon of poorer survival in men with lower DBP, including use of antihypertensive medication, history of hypertension, history of coronary disease, isolated systolic hypertension (ISH), blood lipids, blood glucose, smoking, obesity, and change in DBP (as a continuous variable), failed to provide an explanation. The Established Populations for Epidemiologic Studies of the Elderly (EPESE), which enrolled men and women aged 65 years and older in three communities, also reported this association between lower DBP and mortality through 5 years of follow-up in one of three cohorts (East Boston) but found that it disappeared after 2 years in the other two populations. The present analysis was designed to assess whether a clinically significant fall in either or both components of
TABLE 1. Number of Participants, Percent All-Cause and Cardiovascular Disease Mortality, and 11-Year Mean Blood Pressure Change According to Blood Pressure Change Category

<table>
<thead>
<tr>
<th>Change Category</th>
<th>SBP</th>
<th>DBP</th>
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<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>% Mortality</td>
</tr>
<tr>
<td>Decrease ≥10 mm Hg</td>
<td>96 (23.6)</td>
<td>34.4</td>
</tr>
<tr>
<td>Decrease 0 to 10 mm Hg</td>
<td>61 (15.0)</td>
<td>29.5</td>
</tr>
<tr>
<td>No change or increase</td>
<td>249 (61.3)</td>
<td>26.1</td>
</tr>
<tr>
<td>Total</td>
<td>406</td>
<td>28.6</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease; SBP, systolic blood pressure; and DBP, diastolic blood pressure. Number of participants for CVD mortality analyses (348 men and 359 women) was smaller than for all-cause mortality because subjects with noncardiac causes of death were excluded. Data are for men and women aged 75 years and older at the 1984-1987 visit.

blood pressure during an 11-year interval was associated with poorer survival in a subsequent 5-year follow-up period in men and women aged 75 years or older and to evaluate whether the use of antihypertensive medication influenced this risk.

Methods

Between 1972 and 1974 all adult residents of Rancho Bernardo, Calif, were invited to participate in a Lipid Research Clinic (LRC) Prevalence Study. Eighty-two percent of the target population 40 through 79 years of age (n=4382) participated. Blood pressure was obtained using a clinical protocol after the participant had been seated for at least 5 minutes. A subsequent visit (visit 2) was conducted an average of 6 months later in a 15% random sample of the original population. Visit 2 blood pressures were taken according to the Hypertension Detection and Follow-up Program (HDFFP) protocol. During 1984-1987, 2480 of the 3431 survivors members of the original cohort initially aged 40 through 79 years returned for another evaluation for chronic diseases.

The 388 women and 407 men who were at least 65 years old at the 1972-1974 visit (and thus were 75 years or older by 1984-1987) and who returned during 1984-1987 constituted the population for the present study. Of these participants, one man and three women were excluded for a missing blood pressure measurement. Blood pressure at the latter visit was measured using the HDFFP protocol. Interval blood pressure change was calculated by subtracting the blood pressure at the 1972-1987 visit from the 1984-1987 measurement. For many of these older subjects, the DBP change was a negative number owing to a trend for lower DBP with increasing age in the elderly. An additional population composed of all 895 men aged 50 through 69 years at the 1984-1987 visit was used as a younger comparison group for these analyses. All participants provided informed consent at each visit, and the study protocols were approved by the University of California, San Diego, Committee on Investigations Involving Human Subjects.

Clinically relevant categories for DBP change were defined as (1) no change or increase, (2) less than 5 mm Hg decrease, and (3) greater than or equal to 5 mm Hg decrease. Parallel groups for systolic blood pressure (SBP) were based on an interval change of 10 mm Hg. At the 1984-1987 visit, all currently used medications were recorded and validated by checking prescriptions or containers. ISH was defined as SBP greater than or equal to 160 mm Hg and DBP less than 90 mm Hg. Vital status was obtained yearly and was known for an average of 5 years beyond the 1984-1987 visit for all participants. Cardiovascular disease (CVD) deaths were those assigned ICD-9 codes 400 through 438 by a certified nosologist. Associations between risk factors and survival were tested using proportional hazards regression and Kaplan-Meier procedures. Analyses were performed using EPILOG PLUS statistical software (Epicenter Software, Pasadena, Calif). All P values are two-tailed.

Results

Mean SBP increased in both sexes (by 4.8 mm Hg in men and 11.7 mm Hg in women), and mean DBP decreased (by 6.0 mm Hg in both men and women). As shown in Table 1, less than a quarter of men and women had a fall in SBP of 10 mm Hg or greater, but more than half had a decrease in DBP of 5 mm Hg or greater over the average 11-year interval between the two measurements. Within the three change categories for each blood pressure measurement, the mean interval change in blood pressure was similar in men and women. During the 5-year follow-up period, 28.6% of men and 15.8% of women died; approximately 60% of these were CVD deaths (Table 1).

Table 2 shows age-adjusted relative risks from proportional hazards regression models for all-cause and CVD mortality for each sex. Results are shown for all people of each sex and are stratified on the use of
antihypertensive medication. In each model the reference group consists of people with the same exposure but who had no change or an increase in blood pressure. In all men, these analyses showed a significant excess risk associated with a decrease in DBP of at least 10 mm Hg for both all-cause mortality (age-adjusted relative risk [A-ARR], 2.13; 95% confidence interval [CI], 1.34 to 3.38) and CVD death (A-ARR, 2.93; 95% CI, 1.47 to 5.86). This relation was much stronger in men who took antihypertensive medications than in men who did not. Men who took antihypertensive drugs and had a drop in DBP of 5 mm Hg or greater were more than seven times more likely to die (A-ARR, 7.12; 95% CI, 1.70 to 29.90) than men who also took these drugs but did not experience a drop in DBP. These men also had an increased risk of CVD death but at a marginal level of statistical significance (A-ARR, 3.95; 95% CI, 0.90 to 17.31). A quadratic term for DBP change was not statistically significant in any model for all men or for the subgroups defined by medication use. In men, none of the hazard estimates for a decrease of at least 10 mm Hg in SBP were statistically significant in models for all-cause mortality. With stratification on use of antihypertensive medication, there was an association between a 10 mm Hg fall in SBP and CVD mortality that was limited to men who did not take antihypertensive medication. A similar association was not found for all-cause mortality.

In women, there was no association between a fall in DBP and mortality, nor was there any difference in these DBP associations according to use of antihypertensive medication. A relation between SBP change and mortality was seen in women: a drop of at least 10 mm Hg in SBP was associated with an increased risk of death from all causes (A-ARR, 2.28; 95% CI, 1.29 to 4.02) and CVD death (A-ARR, 2.83; 95% CI, 1.34 to 5.95). The risk of CVD death was greatest for women who did not use antihypertensive medications. Results for women were unchanged by the addition of estrogen use to the model.

To account for regression to the mean and/or severity of hypertension at baseline, we repeated these analyses with adjustment for baseline blood pressure. Results of these models are presented in Table 3. Accounting for baseline blood pressure reduced all associations between a drop in SBP and death in both sexes to levels that were not statistically significant. In women, DBP change remained unassociated with mortality after adjustment for baseline DBP. By contrast, in men, the risk associated with the use of antihypertensive drugs nearly doubled compared with models not adjusted for baseline DBP (A-ARR, 12.33; 95% CI, 2.73 to 55.72 for all-cause mortality, and A-ARR, 7.43; 95% CI, 1.51 to 36.58 for CVD death). Thus, after adjustment for regression to the mean and the initial severity of hypertension, only a fall in DBP in men remained a significant predictor of death. Subgroup analyses showed this effect to be concentrated in men who took antihypertensive medications. As in the more basic models, quadratic terms for DBP change in these multiply adjusted models were not significant. The Figure contrasts the relative risks of mortality, after adjustment for baseline DBP, in men who had an interval fall of at least 5 mm Hg in DBP compared with men who had no change or an increase in DBP. Point estimates are shown for all men and are stratified on the use of antihypertensive medications.

Analyses were repeated for the subset of 259 participants who had blood pressure measured by the standardized HDFP method at both visit 2 (approximately 6
months after visit 1, the primary 1972-1974 visit) and the 1984-1987 visit to see if variation in the blood pressure measurement due to the difference in method explained these findings. The correlation between DBP measured in men at visit 1 and visit 2 was .56. For SBP measurements in men, the correlation was .53. In women, the corresponding values were .39 and .42. All survival trends remained qualitatively identical when visit 2 data were used as the baseline instead of visit 1 data (results not shown).

To test whether this association was present in younger men, we repeated these analyses in the 895 men of this cohort aged 50 through 69 years at the later visit. Before adjustment for baseline blood pressure, there were marginal elevations in the risk associated with a decrease in DBP of 5 mm Hg or greater for all causes (A-ARR, 1.48; 95% CI, 0.98 to 2.25) and CVD mortality (A-ARR, 1.76; 95% CI, 0.95 to 3.30). A decrease in SBP of 10 mm Hg or greater was weakly associated with all-cause mortality (A-ARR, 1.36; 95% CI, 0.88 to 2.10) and more strongly related with CVD death (A-ARR, 1.87; 95% CI, 1.02 to 3.44). After adjustment for baseline blood pressure, none of these findings remained statistically significant. In models stratified on antihypertensive drug use at the recent visit, the only significant finding was for an increased risk of CVD death in men with an SBP drop who did not take antihypertensive drugs (A-ARR, 2.62; 95% CI, 1.08 to 6.34, with adjustment for baseline SBP, and A-ARR, 3.76; 95% CI, 1.73 to 8.20, without adjustment). Thus, patterns in these younger men differed from those observed in the oldest men, as did the patterns seen in the oldest women.

We next considered whether the duration of antihypertensive therapy influenced this association in men. Table 4 shows the number and percent (crude) mortality for men by DBP change category and antihypertensive medication use status at the two clinic visits. Among men who were on these drugs at both visits, those who had an interval drop in DBP of at least 5 mm Hg had

Table 3. Age-Adjusted Relative Risks From Proportional Hazards Regression by Sex for All Participants and Stratified by Use of Antihypertensive Medication at the Later Visit With Adjustment for Baseline Blood Pressure

<table>
<thead>
<tr>
<th>Model</th>
<th>All Men</th>
<th>Nonuser</th>
<th>User</th>
<th>All Women</th>
<th>Nonuser</th>
<th>User</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age+SBP change group</strong></td>
<td></td>
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<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-ARR (P)+SBP</td>
<td>1.27 (.36)</td>
<td>1.36 (.40)</td>
<td>1.00 (.99)</td>
<td>1.39 (.33)</td>
<td>1.81 (.40)</td>
<td>0.95 (.89)</td>
</tr>
<tr>
<td>95% CI+SBP</td>
<td>0.76-2.13</td>
<td>0.66-2.80</td>
<td>0.47-2.17</td>
<td>0.72-2.68</td>
<td>0.46-7.18</td>
<td>0.43-2.09</td>
</tr>
<tr>
<td>CVD Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-ARR (P)+SBP</td>
<td>1.37 (.37)</td>
<td>1.88 (.17)</td>
<td>0.76 (.61)</td>
<td>1.67 (.24)</td>
<td>3.03 (.19)</td>
<td>1.27 (.66)</td>
</tr>
<tr>
<td>95% CI+SBP</td>
<td>0.69-2.75</td>
<td>0.76-4.66</td>
<td>0.27-2.16</td>
<td>0.72-3.89</td>
<td>0.58-15.78</td>
<td>0.45-3.60</td>
</tr>
<tr>
<td><strong>Age+DBP change group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-ARR (P)+DBP</td>
<td>2.33 (.00)</td>
<td>1.89 (.05)</td>
<td>12.33 (.00)</td>
<td>0.87 (.67)</td>
<td>0.95 (.93)</td>
<td>0.71 (.42)</td>
</tr>
<tr>
<td>95% CI+DBP</td>
<td>1.39-3.91</td>
<td>0.99-3.60</td>
<td>2.73-55.72</td>
<td>0.46-1.63</td>
<td>0.33-2.72</td>
<td>0.31-1.64</td>
</tr>
<tr>
<td>CVD mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-ARR (P)+DBP</td>
<td>3.13 (.00)</td>
<td>2.41 (.06)</td>
<td>7.43 (.01)</td>
<td>0.79 (.59)</td>
<td>0.71 (.63)</td>
<td>0.74 (.59)</td>
</tr>
<tr>
<td>95% CI+DBP</td>
<td>1.47-6.66</td>
<td>0.97-5.96</td>
<td>1.51-36.58</td>
<td>0.34-1.86</td>
<td>0.17-2.91</td>
<td>0.24-2.22</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; A-ARR, age-adjusted relative risk; CI, confidence interval; CVD, cardiovascular disease; and DBP, diastolic blood pressure. Data are for SBP decrease of ≥10 mm Hg vs no change or increase or DBP decrease of ≥5 mm Hg vs no change or increase, men and women aged 75 years and older at the 1984-1987 visit.

*Results for women were unchanged by the addition of estrogen use to the model.

Bar graph shows relative risks for death, adjusted for age and baseline diastolic blood pressure (DBP) in all men and by use of antihypertensive medication for interval change in DBP of 5 mm Hg or greater vs no change or increase in DBP. CVD indicates cardiovascular disease.
Table 4. Antihypertensive Medication Use Pattern at Each Visit by Diastolic Blood Pressure Change Category and Crude Mortality

<table>
<thead>
<tr>
<th>DBP Change Category</th>
<th>n</th>
<th>% Mortality</th>
<th>n</th>
<th>% Mortality</th>
<th>n</th>
<th>% Mortality</th>
<th>n</th>
<th>% Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease ≥5 mm Hg</td>
<td>102</td>
<td>36.3</td>
<td>4</td>
<td>50.0</td>
<td>52</td>
<td>36.5</td>
<td>32</td>
<td>43.7</td>
</tr>
<tr>
<td>Decrease 1 to 5 mm Hg</td>
<td>20</td>
<td>20.0</td>
<td>1</td>
<td>100.0</td>
<td>12</td>
<td>25.0</td>
<td>8</td>
<td>37.5</td>
</tr>
<tr>
<td>No change or increase</td>
<td>81</td>
<td>21.0</td>
<td>2</td>
<td>50.0</td>
<td>16</td>
<td>12.5</td>
<td>13</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>203</td>
<td>28.6</td>
<td>7</td>
<td>57.1</td>
<td>80</td>
<td>30.0</td>
<td>53</td>
<td>32.1</td>
</tr>
</tbody>
</table>

DBP indicates diastolic blood pressure. Antihypertensive medication use pattern was unknown for 63 men, 14% of the decrease ≥5 mm Hg group, 18% of the decrease 1 to 5 mm Hg group, and 17% of the no change or increase group. Data are for men aged 75 years or older at the 1984-1987 visit.

For all-cause mortality before stratification on antihypertensive use was 2.16 (95% CI, 1.14 to 4.09); for users of antihypertensive medication, the A-ARR was 8.79 (95% CI, 1.75 to 44.00), whereas for men who did not take antihypertensive medications, the A-ARR was 1.98 (95% CI, 0.87 to 4.52). By contrast with DBP change and consistent with results for the entire follow-up period, an SBP decrease of 10 mm Hg or greater in the latter 2.5 years of follow-up was not significantly associated with death in any subgroup. Analyses limited to the first 3 years of the follow-up interval (not shown) likewise yielded identical trends.

Because most hypertension in the very old is ISH, we investigated these associations by ISH status. Antihypertensive treatment was weakly protective in men aged 75 years or more with ISH (A-ARR for all-cause mortality, 0.74; 95% CI, 0.31 to 1.77, and for CVD death, 0.65; 95% CI, 0.18 to 2.33). Because sequelae of ISH, treated or not, could potentially explain some of the observations regarding blood pressure change, categorical analyses were done separately for men with and without ISH. After adjustment for baseline DBP, the A-ARR associated with a drop in DBP of 5 mm Hg or greater for men without ISH was 1.79 (95% CI, 0.99 to 3.20) for all-cause mortality and 2.99 (95% CI, 1.23 to 7.26) for CVD death. For men with ISH, the corresponding A-ARR values were 6.98 (95% CI, 2.14 to 22.78) for all-cause mortality and 5.43 (95% CI, 1.25 to 23.62) for CVD mortality.

To assess how this change in DBP was reflected in survival of men treated and not treated for ISH, we further evaluated these associations in models stratified on both antihypertensive use at the later visit and ISH. These results are displayed in Table 5. Because 54 men with uncertain medication status were excluded, the point estimates for men with and without ISH given in the paragraph above do not reflect the middle of the two categories for each shown in Table 5. The crude rates and the multiply adjusted point estimates from these strata indicate that men who did not have ISH but who took antihypertensive medication and had a decrease in DBP of 5 mm Hg or greater had a substantially increased risk of death, although statistical power was compromised by small numbers, and confidence limits were wide (A-ARR, 13.71; 95% CI, 1.67 to 112.49 for all-cause mortality). Among men with ISH, the relative risk of death in those who took antihypertensive medication and had a decrease in DBP of 5 mm Hg or greater, compared with men with ISH who also took the greatest percent mortality. None of the men who were on treatment at both visits but maintained their DBP at or above the baseline level died. In men who started taking these drugs during the interval between clinical visits, those who experienced a fall in DBP of 5 mm Hg or greater had poorer survival than men with similar exposure whose DBP decreased less or increased. Men who did not take antihypertensive drugs at either visit but who had a drop in DBP of 5 mm Hg or greater also had poorer survival than men whose DBP levels were preserved or increased. We compared the mortality risk in men with a DBP fall of 5 mm Hg or greater in each of the four categories of antihypertensive use with the mortality risk in men who did not take antihypertensive medication at either visit and who had no change or an increase in DBP over the interval. Antihypertensive use at these two visits was coded as No/No, Yes/No, No/Yes, and Yes/Yes. Models were adjusted for age and baseline DBP. The A-ARR for the No/No pattern was 2.24 (95% CI, 1.19 to 4.19); for Yes/No, 3.97 (95% CI, 0.89 to 17.77); for No/Yes, 2.95 (95% CI, 1.30 to 6.68); and for Yes/Yes, 3.45 (95% CI, 1.47 to 8.08). The two classes of medication accounted for nearly all use were diuretics and β-blockers. Separate analyses limited to users of each class of medication showed identical effects for both, although the results in these subgroups were not statistically significant because of the small number of men in each category.

To test the possibility that falling DBP was simply a marker for poor global health status that was associated with early mortality, we repeated all the above models for men eliminating the 61 subjects who died in the first 2.5 years (the first half of the follow-up interval). Results based on the remaining 55 deaths, including those stratified on medication use, were strongly concordant with the estimates for the entire 5-year follow-up period. For all men aged 75 years or older at the 1984-1987 visit.
these drugs but had no change in DBP, was 8.80 (95% CI, 0.97 to 79.68). The relative risk was stronger, at 15.32 (95% CI, 2.04 to 115.22), in men with ISH who were not treated with medication but had a decrease in DBP of 5 mm Hg or greater compared with untreated men with ISH whose DBP did not fall.

Because treatment for ISH may reduce both components of blood pressure, we estimated the relative risks associated with a decrease in DBP of 5 mm Hg or greater in the ISH/medication categories with further adjustment for the interval change in SBP (Table 5). With this adjustment, the pattern related to treatment changed. The relative risk of death associated with a fall in DBP of 5 mm Hg or greater was higher in men who took antihypertensive drugs (A-ARR, 27.35; 95% CI, 2.10 to 356.31) than in men who did not (A-ARR, 17.60; 95% CI, 2.10 to 153.90). The coefficient for SBP change was negative (suggesting protection with lowered SBP) only in the models for men without ISH who did not take antihypertensive medication. It was positive in all other models and reached statistical significance only in the model for CVD mortality in men with ISH who took antihypertensive medication.

Because the combined effects of interval changes in DBP and SBP could be more important than either alone, we assessed survival in these men based on categories defined with both components of blood pressure using Kaplan-Meier survival procedures. For all men, when SBP did not change or increased, there was a linear trend for worse survival as DBP decreased ($\chi^2$ for trend, 6.39; $P=0.01$). Trends for DBP change within categories of SBP decrease from 0 to 10 mm Hg and greater than or equal to 10 mm Hg were not statistically significant. When DBP change categories were held constant to evaluate the effect of SBP change within each of those three levels, no SBP trends were significant. Among the 75 men who had the greatest decrease in both components of blood pressure (SBP decrease $\geq$10 mm Hg and DBP decrease $\geq$5 mm Hg), observed/expected mortality was very near unity (1.08). In contrast, among the 102 men who had no change or an increase in SBP but a decrease in DBP of greater than or equal to 5 mm Hg, there was a 38% excess in mortality (observed/expected rate, 1.38). Analyses restricted to men with ISH who took antihypertensive medication and who had stable or increased SBP showed a trend for poorer survival with decreasing DBP that was of borderline statistical significance ($n=25$, $\chi^2$ for trend, $P=0.06$). No other trends for survival by blood pressure change categories approached significance in men with ISH who took antihypertensive medication, in part because of small numbers in some cells. All of the nine men who took antihypertensive medication and had a decrease in SBP of 5 mm Hg or greater also had a decrease in DBP of 5 mm Hg or greater; three of them died.

**Discussion**

We have previously reported that lower DBP was associated with poorer survival in men aged 75 years and older regardless of its cause. The present study shows that a fall in DBP of 5 mm Hg or greater, particularly when associated with use of antihypertensive medication, represents one means of entering this high-risk group. Adjustment for baseline DBP further increased the risk estimate associated with antihypertensive use, making prior hypertension and regression to the mean unlikely explanations. Duration of use of antihypertensive drugs did not appear to affect the risk associated with this decrease in DBP, because the percentage mortality in men who were on therapy at both visits (32%) was similar to that of men who were taking medication only at the second visit (30%).

It could be argued that a fall in blood pressure was associated with increased mortality because it was a marker for declining health. However, we have previously reported that the association between lower DBP and mortality was not explained by deaths early in the follow-up period. Eliminating all deaths in the first half of the follow-up period in the present analysis likewise did not alter the trends observed. Also, the lack of a threshold for this effect, as shown in earlier reports of a
linear relation between higher DBP and survival in men aged 75 years or more\(^2,7\) argues against major circulatory failure as the explanation. Primary circulatory failure, rather than an effect limited to DBP change, also seems an unlikely explanation, because the observed/expected mortality for men with the largest decreases in both DBP and SBP was near unity, whereas the ratio for those with no change or an increase in SBP but a drop in DBP of 5 mm Hg or greater was elevated.

Further evidence against the hypothesis that this decrease in DBP simply represents a marker for poor health followed by early demise was provided by the striking similarity between the relative risks obtained using only the deaths in the second half of the follow-up interval and those from models that included all events. Indeed, perhaps the most compelling aspect of these data was that, regardless of the initial visit chosen (visit 1 or visit 2) and regardless of the follow-up interval studied (the first 3 years, the first 5 years, or the latter 2.5 years), the results were consistent, even to the subgroup level.

Associations between SBP change and mortality were found primarily in women and were much weaker. Adjustment for baseline SBP eliminated all relations between a drop in SBP and mortality. These results could be explained by the severity of hypertension at the first visit or by regression to the mean. Use of antihypertensive medications did not increase the risk of death in women.

Results in younger men were also different from those in men aged 75 years and older. In men aged 50 to 69 years, no associations remained between a fall in DBP of 5 mm Hg or greater and mortality after adjustment for baseline DBP. Also, there were no significant associations between antihypertensive medication use, a decrease in blood pressure, and mortality in younger men. A decrease in SBP of 10 mm Hg or greater was associated with increased mortality only in men 50 to 69 years old not taking antihypertensive medications.

The results in younger men and in women 75 years and older indicate that the associations reported here for a clinically significant decrease in DBP are relevant only to men aged 75 years and older. Based on the finding of better survival for women with higher blood pressure in the Finnish community study,\(^3\) one might speculate that similar effects may become evident in women at still older ages. The age distribution of women in our population does not allow us to assess that possibility at this time.

The finding that adjustment for baseline DBP strengthened the risk estimate for a DBP fall associated with use of antihypertensive medication reinforces the thesis that higher DBP is associated with better survival in these oldest men. Without adjustment, the protective effect associated with higher baseline DBP attenuates the risk estimate. When adjustment removed that protective effect, the risk estimate doubled. On the other hand, in younger men and in women, initial findings of a possible association between a drop in SBP and mortality were eliminated by adjustment for baseline SBP, suggesting that there is no true physiological relation. Rather, prior disease, regression to the mean, or both probably explained those unadjusted findings.

For men 75 years or older with and without ISH, a drop of at least 5 mm Hg in DBP was associated with poorer survival. Thus, ISH itself did not explain these findings. Stratification on the use of antihypertensive medication and ISH suggested that use of medication made an important contribution to this risk. The hazard was approximately 10 times greater in men without ISH who took medication and had a decrease in DBP of 5 mm Hg or greater compared with men without ISH who did not take medication but whose DBP also decreased the same amount. Few deaths occurred in the men with ISH who took medication and had no change or an increase in their DBP. After SBP reduction was accounted for in survival models for men with ISH, a drop in DBP associated with antihypertensive treatment carried a high risk of mortality. These results suggest that it may be safest to reduce the systolic component of ISH while preserving DBP in men after age 75.

The participants in this study were white and lived in a community of relatively high socioeconomic status with good access to health care. The prevalence of hypertension in these men aged 75 years and older was 34%, comparable to the 38% level in men aged 65 years and older in the Cardiovascular Health Study.\(^8\) Little has been published on community-dwelling populations with people in these oldest age ranges. It is possible that these associations might emerge earlier in less healthy men. On the other hand, their access to health care (more than 90% visited a doctor in the year before the study visit) could obscure a mortality difference in situations in which clinical management affects the outcome.

The Systolic Hypertension in the Elderly Program (SHEP) demonstrated a reduction in combined nonfatal and fatal CVD in a clinical trial that compared antihypertensive medication with placebo in men and women aged 60 years and older.\(^9\) Our finding that antihypertensive treatment was weakly associated with improved survival in men with ISH is consistent with those results, but our analyses suggest that treatment of ISH is associated with better survival in men after age 75 if DBP is preserved. In contrasting our results with SHEP it is important to recognize differences in the design of these studies. Participants in SHEP were highly selected; only approximately 1% of those screened entered the study, reflecting exclusion for existing disease, willingness to enter a clinical trial, and the presence of mild to moderate ISH. By contrast, the Rancho Bernardo Study is a community-based population sample. Also, although there was no age-sex interaction for treatment effect, SHEP reports to date have not looked at all-cause and CVD mortality by age- and sex-specific subgroups. An age threshold effect like that described here could be masked by a limited contribution of small numbers of SHEP men older than age 75 to the test for interaction. Thus, comparable results for men aged 75 years or more followed in SHEP are not presently available, and possible interaction by age and sex as observed in the Rancho Bernardo cohort cannot be evaluated.

The European Working Party on Hypertension in the Elderly (EWPH) found that antihypertensive treatment reduced CVD mortality in people aged 60 to 75 years, but treatment was associated with increased mortality in people aged 75 to 97 years.\(^10\) This crossover
in treatment effect at about age 75 is consistent with our findings in men. However, the EWPHE study included women as well, and their mortality experience contributed to the excess observed after age 75. In the present study we found no increased risk associated with treatment in women.

In the East Boston cohort of the EPESE study, men and women aged 65 years and older who had DBP less than 75 mm Hg had poorer survival at 2 years than those with higher blood pressures. Similar relations were seen in subgroups taking and not taking antihypertensive medication; but among those who took medication, moderate DBP (75 to 89 mm Hg) was associated with slightly better survival than high DBP (90 mm Hg or greater). These findings are concordant with our present report to the extent that lower DBP was associated with poorer survival in subjects both on and off blood pressure treatment. However, data on blood pressure change were not reported, so direct comparison with the present analyses cannot be made. In the other two EPESE populations, higher DBP was associated with poorer survival among those taking antihypertensive medications but not in participants who did not take these drugs. Results were not reported by age or sex. Given the differing effects by age and sex observed in the Rancho Bernardo population, it is possible that the inconsistencies in the three EPESE cohorts result from age and sex interactions.

A report from the Framingham study also found an association between low DBP and mortality in subjects aged 45 to 84 years and attributed this excess risk to preexisting myocardial infarction. We previously tested this hypothesis in the Rancho Bernardo population and found it did not explain the excess mortality in the oldest men with low DBP. The consistency of our results after early deaths were eliminated argues against this explanation for the results of the present analysis.

Aging of the cardiovascular system is associated with a number of well-documented changes, including increased peripheral vascular resistance and decreased ventricular and peripheral vascular compliance. The aging heart maintains cardiac output by increasing end-diastolic volume and by applying the Frank-Starling mechanism. β-Adrenergic modulation is also reduced. In the face of reduced DBP, these aging-related changes may limit the range of physiological adjustment available to maintain perfusion to vital organs, including the myocardium, which has little intrinsic autoregulatory capability. Thus, it is plausible that lower DBP in the aged cardiovascular system could be hazardous. This effect may be generalized across major organ systems, because the risk estimates in all men for CVD mortality were similar to those for all-cause mortality. For men on antihypertensive drugs, the risk estimates for CVD mortality were uniformly lower than for all-cause mortality, suggesting an increase in non-CVD causes of death.

The lack of an association in women represents another gender-related difference in CVD risk. Women tend to develop CVD later than men; that delay could also extend to physiological changes related to senescence. We currently lack adequate numbers of women substantially older than these men to test the possibility that women manifest this phenomenon later.

Poorer survival with excessive lowering of DBP in hypertensive individuals has been reported in several studies of younger cohorts in which a J-shaped curve between DBP and survival has been evident. In these populations, subjects at both the lower and upper ranges of DBP had increased mortality. It has been suggested that this J-shaped relation can explain the poorer survival with lower DBP in elderly hypertensive subjects. We looked for a J-shaped relation using a quadratic model but did not find it. However, we cannot exclude the possibility that the inverse association we detected represents the middle and left deflected portions of a "J" and that the lack of very high DBP values in our cohort obscured the ascending limb of a relation that shifted upward along a substantially elevated DBP. Alternatively, men with elevations of DBP in the range that could describe a "J" may have succumbed to complications of this condition before reaching the ages described here.

It is very likely that another physiological epoch characterized by normative function that differs from that in younger people begins at an age beyond what we have traditionally defined as elderly. The existence of similar differences at other stages in the life cycle is clearly established: young children are different from adolescents, who are different from adults. As with any biologic phenomenon, the age of onset varies. Sex differences, possibly related to rates of aging, are also important. Results from studies that include both younger elderly and the very old are probably influenced by these age and sex effects and will likely show the effects associated with the predominant age-sex group. Effect estimates from such studies could also be influenced and most likely would be weakened by these age and sex interactions. Most studies of the elderly reported to date are based on populations with mean ages nearer to 70 than 80 years, so they may not show effects consistent with analyses limited to the very old.

The finding, isolated to men, that a drop in DBP associated with use of antihypertensive medication was associated with increased mortality suggests that caution is warranted in the use of antihypertensive treatment in very old men. This study used observational data; further study of these associations using clinical trial data from antihypertensive studies in men, and perhaps women, aged 75 years and older is indicated. These results suggest that, in treating ISH in men aged 75 years and older, drugs and doses that reduce SBP while preserving DBP may be associated with better survival than treatments that reduce both components. These findings also raise the possibility that treatment of diastolic hypertension in men 75 years or older should be reserved for those with substantial, not moderate, elevations of DBP.

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