Mortality associated with diastolic hypertension and isolated systolic hypertension among men screened for the Multiple Risk Factor Intervention Trial

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ABSTRACT The large cohort of white men (317,871) 35 to 57 years old at initial screening for possible enrollment into the Multiple Risk Factor Intervention Trial (MRFIT) was examined with regard to initial blood pressure levels and subsequent coronary heart disease (CHD), stroke, and all-cause mortality. The overall prevalence of isolated systolic hypertension (ISH), defined as systolic blood pressure (SBP) greater than or equal to 160 mm Hg and diastolic blood pressure (DBP) less than 90 mm Hg, was 0.67% among white men screened for MRFIT and increased with age (0.31% among 35- to 39-year-olds to 1.7% among 55- to 57-year-olds). The 6 year CHD and all-cause mortality rates in men over 50 were highest in those with ISH compared with both subjects with diastolic hypertension and those with normal pressure. The relative risk of death from stroke in those with ISH, compared with that in those with SBP less than 160 mm Hg and those with DBP less than 90 mm Hg, was 3.0 (95% confidence interval 1.3 to 6.8). In addition, at any level of DBP, the level of SBP appeared to be the major determinant of all-cause and CHD mortality. The determinants of ISH in individuals under 60 years of age as well as their possible efficacy of its treatment should be evaluated further.


THE RISKS of stroke and coronary heart disease (CHD) are directly related to both the levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP).1 The argument concerning the relative importance of SBP and DBP is not new. In 1972 Page and Sidd2 wrote that "it seems evident that systolic hypertension merits more concerted study, and it does not deserve the current cavalier attitude with which it is regarded." More recently Fisher3 recommended that routine measurements of DBP be abandoned entirely and that patients be advised to keep their SBP at 130 mm Hg or less. This current controversy prompted us to examine subsequent coronary, stroke, and all-cause mortality in relationship to the levels of SBP and DBP in the large sample of white men screened for the Multiple Risk Factor Intervention Trial (MRFIT). MRFIT was a randomized clinical trial that involved screening and intervention for primary prevention of CHD in high-risk men 35 to 57 years old at baseline; its results have been reported.4 This article deals only with the follow-up of the white men screened for determination of their eligibility to participate in the trial. Their blood pressures by age group are listed in the Appendix.

In the elderly, pure isolated systolic hypertension (ISH) is associated with increased risks of morbidity and mortality, including a risk of stroke,5-7 but few studies have evaluated pure ISH in individuals less than 60 years of age. The 361,662 men screened for MRFIT offered the opportunity to measure subsequent mortality with respect to the presence of ISH in a relatively young population.

Mean arterial pressure (MAP) has also been studied as a risk factor for CHD and stroke. The MAP, which mathematically approximates 2/3 DBP + 1/3 SBP, could perhaps reflect more accurately the effect of changes in peripheral resistance accompanying hypertension as well as the afterload effect. The area under the aortic
pressure curve has been described as the tension-time
index and has been shown to correlate well with myo-
cardial oxygen demands. Theoretically, the incidence
of CHD might correlate better with some measure that
incorporates such considerations. The large sample of
men screened for MRFIT allowed for estimation of
mortality risks based on these considerations.

Methods

Study protocol. During the initial screening process for entry
into the study, blood pressures were taken with a mercury sphyg-
momanometer by use of a standard protocol. Blood pressure
was measured three times with the participant in the seated
position, and the mean of the last two readings was used as the
baseline blood pressure for this analysis. For the purposes of the
present study, men screened for MRFIT were retrospectively
classified by their baseline blood pressures.

Definitions. In the current analysis, normotension is defined
as SBP less than 140 mm Hg and fifth-phase DBP less than 90
mm Hg. Isolated systolic hypertension (ISH) is defined as SBP
greater than or equal to 160 mm Hg and fifth-phase DBP less
than 90 mm Hg, which is consistent with the Joint National
Committee’s definitions as well as the current Systolic Hyper-
tension in the Elderly Program (SHEP) entry criteria. Border-
line ISH is defined as SBP between 140 and 159 mm Hg and
fifth-phase DBP less than 90 mm Hg. The group with diastolic
hypertension includes all those with DBP greater than 90 mm
Hg, irrespective of SBP level. Since diastolic hypertension takes
precedence in the classification scheme, it should be noted that
in the analyses the diastolic hypertension group may include not
only those with normal SBP, but also those with SBP greater than
or equal to 160 mm Hg.

Statistical analysis. Analyses were restricted to the 317,871
white men in whom both SBP and DBP were recorded. There
were only 177 black men with ISH, 10 of whom had died by the
time of the 6-year follow-up, and therefore analyses were limited
to the white men only. Blood pressures were analyzed with regard
to all-cause mortality, CHD mortality as defined by the ninth
revision of the International Classification of Diseases (ICD)
codes 410-414, and stroke (ICD code 430-438). Death ascen-
tainment was accomplished through Social Security Adminis-
tration tracing procedures. Mortality rates were calculated for
6 years of follow-up; however, data from an extended period (up
to August 1982, for an average of 7.5 years of follow-up) were
included for regression analysis of stroke mortality. This allowed
for longer person-years of follow-up for this relatively uncom-
mon event in this younger white population. Use of the Social
Security Administration tracing procedures, although not as
complete as the National Death Index files, did not appear to
contribute to bias in death ascertainment in the overall sample
as of the 1981 follow-up when compared with known deaths
ascertained through MRFIT tracing procedures.

Age-specific prevalence and mortality rates, unless otherwise
specified, are presented for five age groups: 35 to 39, 40 to 44,
45 to 49, 50 to 54, and 55 to 57 years. Linear trends in mortality
with age and blood pressure level for both ISH and diastolic
hypertension were assessed with a procedure described by
Fleiss. Relative risks associated with ISH and diastolic hyper-
tension adjusted for age, serum cholesterol, and cigarettes per
day were calculated by proportional-hazards regression. Simi-
larly, regression coefficients for SBP, DBP, and MAP for the end
points of stroke, CHD, and all-cause mortality were estimated
with Cox’s model. Population-attributable risks were calculated
as described elsewhere.

Results

SBP and DBP were highly correlated for the white
MRFIT men in initial evaluation (correlation coefficient = .692). The prevalence of ISH, borderline ISH and ISH together, and diastolic hypertension rose with age (table 1; p < .001 for linear trend). There were 2142
white men with ISH, a prevalence of 0.67%. The prevalence of diastolic hypertension was much greater than that of ISH, with an overall prevalence of 26.6% compared with 7.9% for both ISH and borderline ISH together.

The combined influences of SBP and DBP on CHD and
all-cause mortality are shown in figures 1 and 2, in which initial blood pressures are grouped into cat-
egories of SBP and subcategories of DBP. The age-
adjusted all-cause and CHD 6-year mortality rates by
level of SBP and DBP for white MRFIT men 35 to 57
years old at initial screening were similar within each
grouping of SBP, independent of whether the DBP was
less than 80 mm Hg or greater than 100 mm Hg. The
mortality rates rose with each successive level of SBP
increment. At the highest level of SBP (figure 2), there
was an increase in CHD mortality when DBP was
greater than or equal to 80 mm Hg. At lower levels of
SBP (less than 160 mm Hg), mortality rates for both
all-cause and CHD mortality were similar within each
SBP grouping when DBP was less than 100 mm Hg.

Table 2 shows all-cause and CHD age-adjusted mor-
tality rates per 1000 white men with DBP less than 80
mm Hg. This analysis was restricted to white men with
DBP less than 80 mm Hg to reduce the misclassification
bias due to possible borderline diastolic hypertension.
Again, both all-cause and CHD mortality rates rose with
each successive SBP level (p < .001 for linear trend).

### TABLE 1
Prevalence of ISH and diastolic hypertension by age for white male
MRFIT screenees (rate per 1000)

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>ISH (SBP ≥160 mm Hg and DBP &lt;90 mm Hg)</th>
<th>Borderline ISH and ISH (SBP ≥140 mm Hg and DBP &lt;90 mm Hg)</th>
<th>Diastolic hypertension (DBP ≥90 mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of men screened</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>35–39</td>
<td>64,323</td>
<td>200</td>
<td>0.31</td>
</tr>
<tr>
<td>40–44</td>
<td>68,689</td>
<td>239</td>
<td>0.35</td>
</tr>
<tr>
<td>45–49</td>
<td>75,199</td>
<td>366</td>
<td>0.49</td>
</tr>
<tr>
<td>50–54</td>
<td>75,446</td>
<td>755</td>
<td>0.10</td>
</tr>
<tr>
<td>55–57</td>
<td>75,538</td>
<td>582</td>
<td>1.70</td>
</tr>
<tr>
<td>Total</td>
<td>317,871</td>
<td>2,142</td>
<td>0.67</td>
</tr>
</tbody>
</table>

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There were 131 total deaths among white men with ISH who were screened. The 6 year all-cause and CHD age-specific mortality rates per 1000 white men by blood pressure category are shown in Table 3. Results are categorized in groups of less than 50, 50 to 54, and 55 to 57 years of age. Numbers of deaths in men under age 50 precluded further stratification. For both total mortality and CHD mortality for the combined 50 to 57 years age groups, death rates for individuals with ISH were approximately 1.5 times those for individuals with diastolic hypertension. The adjusted relative risk (ISH/diastolic hypertension) for CHD was 1.53 ($p < .001$) and the adjusted relative risk for all-cause mortality was 1.54 ($p < .001$). The adjusted relative risk associated with ISH compared with the combined borderline ISH and normotensive group was 2.65 ($p < .001$) for CHD and 2.20 ($p < .001$) for all-cause mortality, respectively. All-cause death rates in the less than 50 year age group were also substantially elevated for subjects with ISH compared with those for subjects with diastolic hypertension.

FIGURE 1. Age-adjusted 6 year mortality by level of SBP and DBP for white MRFIT screenees (age 35 to 57 at initial screening).

FIGURE 2. Age-adjusted 6 year CHD mortality by level of SBP and DBP for white MRFIT screenees (age 35 to 57 at initial screening).
TABLE 2
All-Cause and CHD age-adjusted mortality by SBP level per 1000 white male MRFIT screenees with DBP less than 80 mm Hg (6 year follow-up)

<table>
<thead>
<tr>
<th>SBP Level (mm Hg)</th>
<th>No. of men screened</th>
<th>CHD mortality</th>
<th>No. CHD deaths</th>
<th>All-cause mortality</th>
<th>No. all-cause deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>58,617</td>
<td>4.3</td>
<td>227</td>
<td>15.5</td>
<td>836</td>
</tr>
<tr>
<td>120–139</td>
<td>45,099</td>
<td>5.3</td>
<td>231</td>
<td>18.8</td>
<td>825</td>
</tr>
<tr>
<td>140–159</td>
<td>4,641</td>
<td>9.7</td>
<td>59</td>
<td>27.8</td>
<td>154</td>
</tr>
<tr>
<td>160+</td>
<td>486</td>
<td>11.7</td>
<td>10</td>
<td>45.7</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>108,843</td>
<td></td>
<td>527</td>
<td></td>
<td>1,844</td>
</tr>
</tbody>
</table>

with diastolic hypertension and the combined borderline ISH and normotensive group, although these results must be interpreted with caution since there were only 25 all-cause deaths and only five CHD deaths among individuals with ISH in this lowest age range.

Although the men screened for MRFIT represented a relatively young population, there were 194 stroke deaths among the white men after 6 years of follow-up. There were only three stroke deaths in the ISH group compared with 102 deaths in the diastolic hypertension group, and the adjusted relative risk for death from stroke in the ISH compared with the borderline ISH and normotensive combined group was 2.0 (95% confidence limit 0.6 to 6.4) after adjustment for age, serum cholesterol, cigarettes per day, and presence of diabetes. The relative risk for death from stroke in the diastolic hypertension group was 2.8 (95% confidence limit 2.1 to 3.8). When the follow-up period was extended to an average of 7.5 years, however, there were 261 stroke deaths in the white population, six of which were in the ISH group. The adjusted relative risk of death from stroke in the ISH group was 3.0 (95% confidence limit 1.3 to 6.8) compared with the normotensive and borderline ISH combined group.

For the MRFIT men, stroke, CHD, and all-cause age-adjusted mortality rates increased as MAP increased (figure 3; p < .001 for linear trend for each end point). Figures 4 and 5, however, show the relative importance of SBP vs MAP for risk of all-cause and CHD mortality. These data are limited to the SBP 120 to 159 mm Hg range due to the limited numbers in the other strata that met both the SBP and quintile of MAP criteria. As can be seen in figure 4, all-cause mortality appears to be more a function of SBP. For the CHD

TABLE 3
All-cause and CHD 6 year age-specific mortality per 1000 white male MRFIT screenees

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>ISH (SBP ≥160 mm Hg, DBP &lt;90 mm Hg)</th>
<th>Diastolic hypertension (SBP ≥90 mm Hg)</th>
<th>Borderline ISH and normotension (SBP &lt;160 mm Hg, DBP &lt;90 mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause</td>
<td>n Rate</td>
<td>n Rate</td>
<td>n Rate</td>
</tr>
<tr>
<td>&lt;50</td>
<td>25 31.1</td>
<td>983 19.2</td>
<td>1822 11.7</td>
</tr>
<tr>
<td>50–54</td>
<td>47 62.3</td>
<td>869 38.0</td>
<td>1396 26.9</td>
</tr>
<tr>
<td>55–57</td>
<td>59 101.4</td>
<td>539 52.0</td>
<td>947 40.7</td>
</tr>
<tr>
<td>CHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>5 6.2</td>
<td>382 7.5</td>
<td>528 3.4</td>
</tr>
<tr>
<td>50–54</td>
<td>25 33.1</td>
<td>353 15.5</td>
<td>455 8.8</td>
</tr>
<tr>
<td>55–57</td>
<td>29 49.8</td>
<td>214 20.6</td>
<td>314 13.5</td>
</tr>
</tbody>
</table>

n = number of deaths.

FIGURE 3. Age-adjusted stroke, CHD, and all-cause mortality for white MRFIT screenees by MAP (6 year follow-up).
mortality rates, however, MAP does appear to be a contributing factor in the SBP range 120 to 139 mm Hg (figure 5). As demonstrated by comparison of mortality rates within the same MAP but different SBP strata, both SBP and MAP are associated with an increased CHD mortality.

SBP, DBP, and MAP are in actuality continuous variables. Therefore, regression coefficients corresponding to each measured variable were estimated in addition to corresponding risks associated with the usual definitions of hypertension. Regression coefficients were calculated for CHD, stroke, and all-cause mortality. Included in each of these models were age, cigarettes per day, and serum cholesterol levels, as well as the specific blood pressure measurement. Table 4 gives the estimated regression coefficients and the relative risks associated with a 1 SD increase in SBP, DBP, and MAP. Relative risks were similar for each mea-

**FIGURE 4.** Age-adjusted all-cause 6 year mortality by level of SBP and MAP for white MRFIT screenees (age 35 to 57 at initial screening).

**FIGURE 5.** Age-adjusted 6 year CHD mortality by level of SBP and MAP for white MRFIT screenees (age 35 to 57 at initial screening).
TABLE 4
Regression coefficients and relative risk for stroke, CHD, and all-cause mortality by blood pressure for white male MRFIT screenees (6 year follow-up)

<table>
<thead>
<tr>
<th></th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>MAP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>SE</td>
<td>RR</td>
</tr>
<tr>
<td>Stroke</td>
<td>.0331</td>
<td>.0030</td>
<td>1.68</td>
</tr>
<tr>
<td>CHD</td>
<td>.0209</td>
<td>.0011</td>
<td>1.39</td>
</tr>
<tr>
<td>Total</td>
<td>.0153</td>
<td>.0007</td>
<td>1.27</td>
</tr>
</tbody>
</table>

*Estimated in the presence of age, cigarettes per day, and serum cholesterol concentration.

*Relative risk of death per 1 SD change: SBP = 15.7 mm Hg; DBP = 10.4 mm Hg; MAP = 11.2 mm Hg.

measurement (SBP, DBP, and MAP) for each end point. Regression coefficients were larger for stroke than for CHD.

Population-attributable risks by blood pressure status were also calculated for CHD, stroke, and all-cause mortality for SBP greater than or equal to 140 mm Hg, SBP greater than or equal to 160 mm Hg, DBP greater than or equal to 90 mm Hg, and DBP greater than or equal to 100 mm Hg (table 5). Risks were greatest in all three disease categories for SBP greater than or equal to 140 mm Hg than for any of the other three blood pressure levels. Therefore, there is little evidence that measurement of DBP is a better predictor of clinical events than SBP or MAP in this population.

Discussion

The prevalence and prognostic significance of isolated systolic hypertension in the elderly have been well-documented from previous community studies. Isolated systolic hypertension has also been studied in 158,906 people 30 to 69 years old who were initially screened for the Hypertension Detection and Follow-up Program (HDFP). Prevalence of ISH in the HDFP population was slightly higher than in the present MRFIT study, but conclusions are similar. Not only did those elderly people screened who had ISH have higher death rates at 8 years of follow-up than did those who had SBP less than 160 mm Hg, but this was also true in the younger age groups (except the 30 to 49 age group on antihypertensive drugs, in which numbers of deaths were very small).

Sixty years ago Paulin described essential hypertension as "a condition in which the patient has a persistent elevation of the systolic, and usually the diastolic, blood pressure for which there is no demonstrable cause." With time that definition has evolved to that of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, which in May 1984 stated that "the initial goal of antihypertensive therapy is to achieve and maintain DBPs at lower than 90 mm Hg if feasible. A reasonable further goal is the lowest DBP consistent with safety and tolerance." No treatment goal was defined for evaluation of SBP.

One wonders how the definition of Paulin describing hypertension primarily in terms of SBP evolved into the current definition emphasizing DBP. Table 6 outlines many of the major studies done on the relative contributions of SBP and DBP to cardiovascular morbidity and mortality. It appears from many of the longitudinal studies that SBP may actually be a better predictor of mortality than DBP, although many methodologic problems are inherent in some of these studies, especially the earlier ones in which the blood pressure measurement technique was not standardized, or fourth rather than fifth phase Korotkoff sounds were measured. Hense et al. recently concluded that fifth phase DBP is more reliable than fourth phase both for clinical and epidemiologic purposes.

It is also curious that the Veterans Administration study, the first randomized double-blind clinical trial of antihypertensive drug therapy, used DBP as the treatment criterion despite the few earlier studies indicating that SBP may be more predictive of subsequent morbid events. Clinicians at this time believed that DBP more closely reflected morbid hypertensive sequelae. Furthermore, it was thought that the use of DBP rather than SBP as the treatment variable would minimize the
<table>
<thead>
<tr>
<th>Study</th>
<th>Population and size</th>
<th>Study design</th>
<th>Duration of study</th>
<th>End points</th>
<th>Results and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Build and blood pressure, 1959(^{21, 22})</td>
<td>3,900,000 insured persons initially 15–69 years old</td>
<td>Retrospective (pooled data of 26 insurance companies)</td>
<td>1–19 years follow-up</td>
<td>All-cause mortality</td>
<td>There was a greater rise in mortality with increasing levels of SBP than with DBP. No standardization of BP measurement technique.</td>
</tr>
<tr>
<td>Morris et al., 1966(^{23})</td>
<td>687 male London busmen</td>
<td>Historical cohort</td>
<td>5 years follow-up</td>
<td>Incidence of CHD, including death</td>
<td>SBP was a better predictor of CHD than casual DBP. Study showed benefit of treatment when BP was greater than 164/104 mm Hg in men.</td>
</tr>
<tr>
<td>Veterans Administration, 1967 and 1970(^{24, 25})</td>
<td>143 male patients, DBP 115–129 mm Hg(^{24})</td>
<td>Randomized, double-blind, clinical trial</td>
<td>Average of 15.7 months for placebo and 20.7 months for active(^{24})</td>
<td>Cardiac, CNS, and renal complications and death</td>
<td></td>
</tr>
<tr>
<td>Framingham, 1974(^{1})</td>
<td>5209 men and women 30–62 years old</td>
<td>Prospective</td>
<td>18 years follow-up</td>
<td>CHD, stroke, CHF, intermittent claudication incidence; cardiovascular and all-cause mortality</td>
<td>There was a greater impact of SBP than DBP (by size of regression coefficients) on end points of hypertensive disease. Early phases of study not standardized.(^{26}) Gradient for risk of stroke was stronger for increases in SBP than for DBP. Risk of CHD was more strongly associated with SBP than DBP, MAP, or pulse pressure in 39–49 year olds. In 50–59 year olds, SBP, DBP, and MAP had similar predictive strengths (multiple logistic regression model).</td>
</tr>
<tr>
<td>Chicago Stroke Study, 1974(^{27})</td>
<td>2772 men and women 65–74 years old</td>
<td>Prospective</td>
<td>3 years follow-up</td>
<td>Stroke incidence and mortality</td>
<td></td>
</tr>
<tr>
<td>Western Collaborative Group, 1976(^{28})</td>
<td>3154 men 39–59 years old</td>
<td>Prospective</td>
<td>8.5 years follow-up</td>
<td>Clinical and silent CHD events and CHD mortality</td>
<td></td>
</tr>
<tr>
<td>Manitoba Study, 1978(^{29, 30})</td>
<td>3983 WWII Canadian pilots, most between 25–34 years at entry</td>
<td>Historical cohort</td>
<td>26 years follow-up</td>
<td>Cerebrovascular and CHD incidence and mortality</td>
<td>Cerebrovascular: SBP was a better predictor than DBP. CHD: DBP was more important in men less than 45 years old. SBP was a better predictor in men greater than 45 years old. BP measurement technique not standardized.(^{31})</td>
</tr>
<tr>
<td>DHSS Hypertension Care Computing Project, 1979(^{32})</td>
<td>2587 treated hypertensive patients; tertiary and primary care settings</td>
<td>Prospective</td>
<td>Average of 4 years follow-up</td>
<td>Cardiovascular, renal, and all-cause mortality</td>
<td>SBP was a better predictor of survival than DBP.</td>
</tr>
<tr>
<td>Evans County, Georgia, 1980(^{33})</td>
<td>1904 persons (biphasic) 40–69 years of age</td>
<td>Historical cohort</td>
<td>10 years follow-up</td>
<td>All-cause mortality</td>
<td>SBP had the highest population-attributable fraction in the entire population of all CHD risk</td>
</tr>
</tbody>
</table>
### TABLE 6 (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Population and size</th>
<th>Study design</th>
<th>Duration of study</th>
<th>End points</th>
<th>Results and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyer et al., 1982&lt;sup&gt;24&lt;/sup&gt;</td>
<td>58,035 men and women from four Chicago studies</td>
<td>Pooled data from cross-sectional and prospective studies</td>
<td>5–17 years follow-up for cross-sectional and prospective studies combined</td>
<td>ECG abnormalities; cardiovascular, stroke, all-cause mortality</td>
<td>Cross-sectional studies suggested that ISH may be related to prevalence of ECG abnormalities. Prospective studies: ISH not an independent risk factor for cardiovascular and all-cause mortality. SBP was more important than DBP in the logistic model.</td>
</tr>
<tr>
<td>Miall, 1982&lt;sup&gt;25&lt;/sup&gt;</td>
<td>2680 people in Wales</td>
<td>Prospective</td>
<td>17 years follow-up</td>
<td>Stroke, cardiovascular and all-cause mortality</td>
<td>For both men and women greater than or equal to 65 years old, chi-square values relating death to SBP were higher than values for DBP. Fourth-phase DBP was measured. SBP was a powerful predictor of future occurrence of CHD; DBP showed little relationship with CHD incidence.</td>
</tr>
<tr>
<td>Italian Research Group, 1982&lt;sup&gt;26&lt;/sup&gt;</td>
<td>1712 Italian men initially 40–59 years old</td>
<td>Prospective</td>
<td>20 years follow-up</td>
<td>CHD incidence and total mortality</td>
<td>SBP was more strongly related to all-cause, CHD, and cardiovascular mortality than DBP; DBP was more strongly related to stroke than was SBP. Baseline SBP was significantly associated with end points; there was no association with DBP.</td>
</tr>
<tr>
<td>Honolulu Heart Program, 1983&lt;sup&gt;27&lt;/sup&gt;</td>
<td>7610 Japanese men initially 45–68 years old and living in Hawaii</td>
<td>Prospective</td>
<td>10 years follow-up</td>
<td>All-cause, CHD, other cardiovascular, and stroke mortality</td>
<td>SBP was more strongly related to all-cause, CHD, and cardiovascular mortality than DBP; DBP was more strongly related to stroke than was SBP. Baseline SBP was significantly associated with end points; there was no association with DBP.</td>
</tr>
<tr>
<td>Australian National BP Study, 1984&lt;sup&gt;28&lt;/sup&gt;</td>
<td>3427 men and women 30–69 years old with DBP 95–109 and SBP less than 200 mm Hg&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Randomized double-blind clinical trial (current analysis: retrospective classification by baseline BP)</td>
<td>Average of 4 years follow-up</td>
<td>All-cause and cardiovascular mortality; stroke, CHD, and severe hypertensive sequelae incidence</td>
<td>Baseline SBP was predictive of all-cause mortality (twofold increase in age-adjusted mortality from lowest to highest SBP group). Baseline DBP had little effect on mortality.</td>
</tr>
<tr>
<td>Hypertension Detection and Follow-up Program, 1986&lt;sup&gt;21&lt;/sup&gt;</td>
<td>10,940 men and women 30–69 years old with DBP ≥90 mm Hg&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Randomized clinical trial (current analysis: retrospective classification by baseline BP)</td>
<td>5 years follow-up</td>
<td>All-cause mortality</td>
<td>Cardiovascular morbidity and mortality were related to randomization SBP, but not DBP, by both intention-to-treat and on-treatment analysis.</td>
</tr>
<tr>
<td>European Working Party on High Blood Pressure in the Elderly, 1986&lt;sup&gt;31&lt;/sup&gt;</td>
<td>840 men and women 60 years old or more with BP 160–239/90–119 mm Hg</td>
<td>Randomized double-blind clinical trial (current analysis: retrospective classification by baseline BP)</td>
<td>Average of 4.63 years for placebo and 4.69 years for active&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Cardiovascular mortality and morbidity (stroke, papille-dema, retinal hemorrhages and exudates, severe CHF)</td>
<td>Cardiovascular morbidity and mortality were related to randomization SBP, but not DBP, by both intention-to-treat and on-treatment analysis.</td>
</tr>
</tbody>
</table>

BP = blood pressure; CNS = central nervous system; CHF = congestive heart failure; ECG = electrocardiographic.
age-related increase in SBP during the final data analysis. It appears that subsequent randomized clinical trials used DBP almost exclusively as the treatment criterion based on the Veterans Administration experience. Researchers from the Evans County, GA, study have suggested that findings of clinical trials that used DBP as the basis for intervention be reanalyzed to determine whether benefit was due to SBP rather than DBP reduction.33

A small percentage of the men originally screened was subsequently enrolled in the MRFIT (12,866 of 361,662 total screened). Information obtained at the initial examination is limited to the presence of other cardiovascular risk factors (blood pressure level, smoking, serum cholesterol, presence of known diabetes, and history of heart disease). Body weight, diet history, use of antihypertensive medications, and other disease history were not obtained at first screen evaluation. Final analysis is based on International Classification of Disease codes from death certificate data without clinical or pathologic verification. Nevertheless, given the limitations of the study design, the large sample size does provide a basis for examination of the role of diastolic hypertension as compared with ISH in all-cause, stroke, and CHD mortality. In white men with ISH the relative risk for death from stroke was 3.0 (95% confidence limit 1.3 to 6.8) relative to borderline ISH and normotensive combined groups, after adjusting for age, serum cholesterol, cigarettes per day, and presence of diabetes (average follow-up of 7.5 years). Although these data regarding stroke mortality are statistically significant, they must be interpreted with caution due to the small number of stroke deaths in the ISH category (six deaths) and the possibility of incomplete death ascertainment during the lengthened (average 7.5 years) follow-up period. The results also suggest strongly that ISH is a risk factor for subsequent all-cause and CHD mortality. The 6 year all-cause and CHD mortality rates in white men 50 to 57 years old were higher in those with ISH than in either the diastolic hypertension or the combined borderline ISH and normotensive group. Death rates for ISH in the less than 50 years old group are difficult to interpret due to the smaller number of deaths. Systolic hypertension may therefore be more significant than diastolic hypertension in the general population considering the absence of elderly individuals from this cohort. Population-attributable risks, as presented in table 5, support this hypothesis. These data suggest that SBP is as good, if not a better, predictor than DBP of major end points across the range of blood pressure measurements, even in a middle-aged population.

The implications of these findings suggest the need for reevaluation of the definition of hypertension as currently recommended based primarily on DBP. The recommendation of Fisher that we abandon the use of DBP may seem radical, but is perhaps correct.

The lower prevalence of systolic hypertension as compared with diastolic hypertension (table 1) is strictly an artifact due to an arbitrary definition of the level of blood pressure used to establish the criteria. The risk of disease (CHD, stroke, and total mortality) increased with the level of either SBP or DBP. The determinants of an elevated SBP in individuals under 60 years of age in the absence of increased DBP should be carefully investigated. Whether ISH should be treated in the absence of diastolic hypertension in older individuals is now being evaluated by the Systolic Hypertension in the Elderly Program.47 While awaiting the final recommendations of this double-blind clinical trial, the Working Group on Hypertension in the Elderly has tentatively recommended cautiously lowering elevated SBP to the 140 to 160 mm Hg range.48 ISH should be considered an important risk factor for all-cause, stroke, and CHD mortality among middle-aged white men, and the treatment of ISH in individuals less than 60 years of age may require further evaluation as well.

Participating centers

The principal investigators and senior staff of the clinical, coordinating and support centers, the NHLBI, and members of the MRFIT Policy Advisory Board and Mortality Review Committee are as follows:


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*Perry HM: Personal communication.
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Table: Blood pressure levels by age group for 317,871 white MRFIT screenees

<table>
<thead>
<tr>
<th>Age group (yr)</th>
<th>DBP (mm Hg)</th>
<th>SBP (mm Hg)</th>
<th>MAP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>35–39</td>
<td>81.5</td>
<td>126.4</td>
<td>96.5</td>
</tr>
<tr>
<td>40–44</td>
<td>83.0</td>
<td>127.6</td>
<td>97.9</td>
</tr>
<tr>
<td>45–49</td>
<td>84.1</td>
<td>129.8</td>
<td>99.3</td>
</tr>
<tr>
<td>50–54</td>
<td>84.6</td>
<td>132.6</td>
<td>100.6</td>
</tr>
<tr>
<td>55–57</td>
<td>84.5</td>
<td>135.1</td>
<td>101.4</td>
</tr>
<tr>
<td>Total</td>
<td>83.5</td>
<td>129.8</td>
<td>99.0</td>
</tr>
</tbody>
</table>

References

12. Wentworth DN, Neaton JD, Rasmussen WL: An evaluation of the Social Security Administration Master Beneficiary Record file and...
the National Death Index in the ascertainment of vital status. Am J Public Health 73: 1270, 1983
20. Paulin IE: Ultimate results of essential hypertension. JAMA 87: 925, 1926
25. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension II: results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA 213: 1143, 1970
27. Shekelle RB, Ostfeld AM, Klawans HL: Hypertension and risk of stroke in an elderly population. Stroke 5: 71, 1974
36. Italian Research Group of the Seven Countries Study: Incidence and prediction of coronary heart disease in two Italian rural populations followed-up for 20 years. Acta Cardiol 37: 129, 1982
40. Five-year findings of the Hypertension Detection and Follow-up Program: I. Reduction in mortality of persons with high blood pressure, including mild hypertension. JAMA 242: 2562, 1979
44. Hense HW, Stieber J, Chambless L: Factors associated with measured differences between fourth and fifth phase diastolic blood pressure. Int J Epidemiol 15: 513, 1986
47. Wittenberg CK: Systolic hypertension therapy trial begins. JAMA 253: 1700, 1985
Mortality associated with diastolic hypertension and isolated systolic hypertension among men screened for the Multiple Risk Factor Intervention Trial.

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