EDITORIAL

Comprehensive health care and noncardiovascular mortality: an unlikely explanation of the findings from the Hypertension Detection and Follow-up Program

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THE HYPERTENSION Detection and Follow-up Program (HDFP) showed a significant reduction in both cardiovascular and noncardiovascular death rates in patients receiving stepped care. Over the past three years, several reports have suggested that the results of treatment reported in the HDFP were due to comprehensive medical care of hypertensive patients in a stepped care treatment group rather than to a specific hypotensive effect of drug therapy. Also, the clinical significance of the 19% reduction in cardiovascular mortality in patients under stepped care in comparison with those receiving referred care is questionable, because noncardiovascular mortality was reduced by 14% in the former group.

In any hypertension intervention study in which the group on active therapy is seen more frequently than the control group, it is legitimate to ask whether the final benefits result from specific antihypertensive medication and effective blood pressure control or from general contact and comprehensive health care. Because of the implications for management of hypertensive patients it is deemed necessary to advance explanations for reduced noncardiovascular mortality among those that are successfully treated. A decrease in cardiovascular mortality might be expected to be responsible for an increase in mortality from cancer and other important causes of death over a long follow-up time because of competing risk. Therefore, if anything, the noncardiovascular mortality might have been expected to rise rather than fall in response to a decrease of cardiovascular mortality.

Evidence for effective control of “mild” hypertension in lowering noncardiovascular death rate. The number of noncardiovascular deaths by cause for the five years of the HDFP experience are summarized in table 1. In all except three categories, violent deaths and renal and infectious disease, there were fewer deaths in the total stepped care than in the referred care group. Stratum I patients (diastolic blood pressure 90 to 104 mm Hg) accounted for the majority of this difference. For those in strata II (diastolic blood pressure 105 to 114 mm Hg) and III (diastolic blood pressure ≥115 mm Hg) differences were small between stepped care and referred care groups with respect to numbers of both cardiovascular and noncardiovascular deaths.

The greatest reduction in all-cause mortality occurred in the subgroup of stratum I patients with baseline diastolic blood pressure levels of 90 to 94 mm Hg who were free of target organ damage (table 2). They had no evidence of coronary heart disease, stroke, electrocardiographic abnormalities, intermittent claudication, or elevated creatinine levels and were not on blood pressure medication at the initiation of the trial. At that time (1973 to 1974), many physicians would have considered this group to be “healthy” and their diastolic blood pressures would not have mandated any antihypertensive therapy. Yet after five years of HDFP protocol therapy, there was a reduction in deaths in the stepped care group of 34%. Mortality per 1000 from stroke, myocardial infarction, all cardiovascular diseases, and all noncardiovascular diseases in the stepped care group was 6.9, 3.2, 2.9, and 2.7, respectively, lower than in the referred care group. However, there was only a 7.9% reduction in mortality in the stratum I patients in the stepped care compared with the referred care group when target organ damage was present at baseline. This suggests that elevated blood pressure is most successfully treated before the development of target organ damage.

The percentage of patients with diastolic blood pressure of 90 to 104 mm Hg on drug treatment in the stepped care group was 75% at year 2 and remained at
that level over the next 3 years. In the referred care group only 54% of patients were on drug treatment at year 5. Actively treated patients in the stepped care group with the mildest hypertension (diastolic blood pressure of 90 to 94 mm Hg), by protocol, were under a strict medical treatment regimen with the goal of reducing diastolic blood pressure by 10 mm Hg or reaching 80 to 84 mm Hg. The reduction in pressure in this group was from 92 mm Hg at baseline to 82 mm Hg at year 5 in patients receiving stepped care, while in those receiving referred care it was reduced from 92 mm Hg at baseline to 87 mm Hg at year 5.

No comprehensive preventive medical care beyond blood pressure control was either given or necessary in the HDFP stepped care patients who were essentially "healthy" (those with diastolic blood pressure of 90 to 94 mm Hg and free of target organ damage; table 2). A small subgroup of patients with blood pressures in the same range at baseline but with manifestations of target organ damage and on antihypertensive drug therapy when enrolled in the study might have undergone some additional diagnostic tests and received other therapy. However, the resulting nonsignificant 7.9% lower all-cause mortality rate in the stepped care compared with the referred care group argues against any beneficial effect of a more comprehensive medical regimen after target organ damage has occurred (table 2).

**Level of comprehensive health care for stepped care patients.** A Department of Health and Human Services publication of working papers for an NHLBI conference on implications of the Hypertension Detection and Follow-up Program (No. 83-2116, 1982) presents the evidence for the close comparability between stepped and referred care in many respects, but not with regard to antihypertensive therapy. A "general medical care" effect on the outcome of 5 years of treatment in patients receiving stepped care should have been reflected in other than strictly hypertension-related findings, i.e., in greater smoking cessation, cholesterol reduction, and weight control. However, in none of these parameters was a preventive medical care effect detectable in the stepped care over the referred care group. Percentage of smokers decreased to 34% in both groups, cholesterol levels declined to 220 mg/dl in both, and average weights remained unchanged.

Employment and retirement rates were virtually identical (table 3) in the two groups and neither annual hospitalization rates nor disability days per year varied significantly. The slightly less likelihood of disability in patients receiving stepped care could have resulted from the lower incidence of the cardiovascular complications of hypertension in that group. This idea is supported by the reported frequency of various illnesses occurring in the past year. A higher incidence of gout at year 5 in the stepped care group was found and would be expected with the more intensive diuretic therapy these patients received. The lower incidence of myocardial infarction, previously unrecorded in hypertension research, was confirmed by a recent report of reduced incidence of fatal coronary heart disease, nonfatal myocardial infarcts, and angina pectoris in patients receiving stepped care. Reported incidence of cancer, diabetes, kidney stones, ulcers, and liver disease were identical in the two groups.

The report also contains a section on the participants' understanding of the problems of high blood pressure, which again reveals similar responses, with 97% of patients in both groups agreeing that individ-

<table>
<thead>
<tr>
<th>Cause of death (ICDA codes)</th>
<th>Total</th>
<th>SC</th>
<th>RC</th>
<th>SC</th>
<th>RC</th>
</tr>
</thead>
<tbody>
<tr>
<td>All noncardiovascular diseases</td>
<td>154</td>
<td>179</td>
<td>109</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>Renal disease (580–599)</td>
<td>15</td>
<td>10</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (250)</td>
<td>5</td>
<td>10</td>
<td>4</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Neoplastic diseases (140–239)</td>
<td>61</td>
<td>74</td>
<td>45</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Breast cancer (174)</td>
<td>(2)</td>
<td>(5)</td>
<td>(2)</td>
<td>(4)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal diseases (530–537)</td>
<td>11</td>
<td>20</td>
<td>9</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Respiratory diseases (460–519)</td>
<td>13</td>
<td>17</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Infectious diseases (000–136)</td>
<td>6</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Accidents, suicides, and homicides</td>
<td>(800–999)</td>
<td>26</td>
<td>25</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Other diseases</td>
<td>17</td>
<td>20</td>
<td>11</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

DBP = diastolic blood pressure.

*From death certificates of HDFP patients (ICDA code is International Classification of Diseases Adapted code).

**TABLE 2**

<table>
<thead>
<tr>
<th>Target organ damage at baseline</th>
<th>SC</th>
<th>RC</th>
<th>% Reduction in deaths in SC group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>n</td>
<td>No. of deaths</td>
<td>n</td>
</tr>
<tr>
<td>Yes</td>
<td>173</td>
<td>36</td>
<td>175</td>
</tr>
</tbody>
</table>

SC = stepped care; RC = referred care.
TABLE 3
Employment status, annual hospitalization rates, and disability (%) at baseline and at 5 year follow-up in stepped care (SC) and referred care (RC) groups

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Year 5</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>SC</td>
<td>RC</td>
</tr>
<tr>
<td>Employed</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td>Not employed</td>
<td>36</td>
<td>35</td>
</tr>
<tr>
<td>Retired (nonmedical)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Annual hospitalization rate</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Hospitalized more than one time</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Disabled (more than 7 days/year)</td>
<td>21</td>
<td>21</td>
</tr>
</tbody>
</table>


uals with hypertension should see a doctor regularly, and 93% in both groups believing that the long-range benefits of medication for high blood pressure include a lesser chance of developing a heart attack. As far as self-perception of health is concerned, 19% of those in the referred care and 20% of those in the stepped care group evaluated their health as "excellent," 45% and 46%, respectively, reported it as "good," 27% and 26% said it was "fair," and only 9% and 7% reported it was "poor."

The report concludes that the improved cardiovascular status resulting from better control of hypertension in patients receiving stepped care may have indirectly caused a decrease in noncardiovascular deaths.

Complications refractory to comprehensive medical care. Development of left ventricular hypertrophy (LVH) in patients with normal electrocardiograms at baseline was 37.5% greater in the referred care than in the stepped care group. Among patients with an increase in R wave amplitude at baseline, at 5 years there was a 66.7% greater occurrence of LVH with ST-T segment changes in the referred care compared with the stepped care group.

In those patients with electrocardiographic evidence of tall R waves or LVH at baseline, the rate of regression toward normal was 54.3% in the stepped care and 42.9% in the referred care group (p < .01). Reversal of enlarged cardiac silhouette on chest x-rays was noted in 47% of those in the stepped care and in 38% of those in the referred care group (p < .01). It appears unlikely that this regression of highly abnormal electrocardiographic and chest x-ray findings in a significantly larger number of patients receiving stepped care could have occurred with an improved general health care program. It is equally unlikely that a comprehensive medical care system could effect a 45% reduction in death from stroke and, among patients free of target organ damage at entry, a 25% decrease in incidence of fatal coronary heart disease and nonfatal myocardial infarction in the stepped care compared with the referred care group.

Noncardiovascular mortality in hypertension intervention trials. In contrast to other interventional studies, HDFP patients were unselected with respect to comorbidity and hypertension-related or unrelated risk factors at baseline. Trials such as those undertaken by the United States Public Health Service (USPHS) Hospitals, and the Australian Mild Hypertension and the Oslo studies, excluded mildly (90 to 94 mm Hg) hypertensive individuals or did not compare those with and without baseline target organ damage. Therefore, they did not yield information on these subgroups, which were studied in detail in HDFP. All three studies failed to show any reduction in noncardiovascular mortality in patients under active treatment. It is relevant to note that the overall mortality was unusually low in these three studies: Two of 193 patients under active therapy (1%) and four of 196 placebo-treated patients (2%) in the USPHS Hospitals Study died. There were nine fatal events from all causes in 1721 Australian patients in the active treatment group and 19 fatal events among 1706 patients in the placebo group. In the Oslo Study total deaths numbered 10 of 406 patients under active treatment and nine of 379 patients receiving no treatment. In comparison with these very low numbers, HDFP reported a total of 349 deaths in the stepped care and 419 deaths in the referred care group, corresponding to a 6.4% and 7.7% mortality, respectively (p < .01).

The Gothenburg Study recruited hypertensive patients without any regard to coexisting risk factors and morbidity. The authors found that the lower mortality from cardiovascular causes in the treatment group was not compensated for by an increased mortality from other causes. They recognized a tendency to lower mortality from noncardiovascular causes, and concluded that if this tendency were to be found in a larger series, it could be due to some overall effect of antihypertensive treatment. The lower noncardiovascular mortality in the treatment group was similar to that found in the HDFP (2.8% in the stepped care and 3.3% in the referred care group).

Lack of effect of comprehensive care on blood pressure control. In describing the placebo group of the USPHS Hospital Study, the authors emphasized that these patients received placebo in a very positive health care setting, including regular systematized follow-up within a system that provided comprehensive medical.
care. This care did not produce a fall in the mean diastolic blood pressure.

Noncardiovascular mortality in two epidemiologic studies. In two prospective epidemiologic studies, the Evans County and the Framingham cohorts, a modest positive association between hypertension and risk of dying from noncardiovascular causes was demonstrated for the era before antihypertensive drug therapy became widely accepted. For the purpose of this article, we have carried out analyses of the Evans County cohort, which disclosed excess noncardiovascular mortality in hypertensive individuals as compared with normotensive subjects as ascertained in a community-based survey begun in 1960 and continued to 1980. The ratio of age-adjusted noncardiovascular mortality of men with hypertension compared with that of nonhypertensive men was 1.06 in lower social class white men, 1.34 in high social status white men (neither of these statistically significantly different from 1), and 1.73 in the black men (p < .05).

Among men in the Framingham study population who were 45 to 74 years old, the age-adjusted noncardiovascular death rate was 1.2 times higher in hypertensive compared with normotensive individuals between 1955 and 1973 (72.2 per 10,000 men vs 59.4 per 10,000 men). Among women in this study group, all-cause mortality rates in hypertensive and normotensive individuals were 50% lower than in men and noncardiovascular death rates were similar in normotensive and hypertensive women.11

Discussion. The design of the HDFP was thought to be flawed because patients who receive comprehensive medical care have lower mortality than those who get less intense care.1,2

It is impossible to completely differentiate between the impact of general medical care for hypertensive patients and that of stepwise antihypertensive care in the HDFP. The counter argument can be summarized as follows: Noncardiovascular mortality decreased significantly in the stepped care group, which is proof of a comprehensive medical care effect; therefore, the HDFP results with respect to reduced cardiovascular mortality are not due to antihypertensive medication per se. This ignores the data that show hypertension to have a deleterious effect on noncardiovascular mortality.

When data from five recently completed hypertension intervention trials were reviewed, it became evident that strict exclusion criteria for three of the studies prevented the admission of hypertensive patients with target organ damage. Among 2320 patients randomly assigned to the active treatment groups only 21 deaths occurred; among 2281 patients randomly assigned to the control groups only 32 deaths were recorded. It would be unreasonable to expect noncardiovascular mortality to show any significant difference between the two treatment groups when the total number of deaths was so low (53 or 1.2%), probably as a result of the strict exclusion criteria, in all three studies.

Neither the Australian nor the Oslo study followed patients with diastolic blood pressures below 95 mm Hg. In the USPHS study, baseline mean diastolic blood pressure was 99 mm Hg, with the mode in the range of 90 to 95 mm Hg. The total number of deaths in this study of 389 hypertensives was small: only four deaths occurred in the placebo group and only two in the actively treated group. The HDFP experience, with its 2045 hypertensive subjects with diastolic blood pressures in the range of 90 to 94 mm Hg, showed a 34% decrease in total mortality.

It is not surprising to clinicians that patients with uncontrolled hypertension, when randomly assigned to a control group of an intervention trial, would suffer from increased noncardiovascular complications, particularly if these patients have a variety of coexisting risk conditions and morbidity at baseline. If untreated hypertension diminishes cardiac reserve, then these patients are at higher risk of death when faced with life-threatening consequences of various noncardiac diseases.

A test of total health care exclusive of blood pressure control was carried out in the 7 year study of the USPHS Hospitals.7 As expected, blood pressure was not reduced, but in fact rose to an unacceptably high level in 24 of 196 control patients.

It is interesting to consider how noncardiovascular diseases affected hypertensive patients before effective means of treating large numbers of patients became available. Data from the Framingham Study indicated that death rate from noncardiovascular causes among white male hypertensive patients in the first 18 years (1955 to 1973) was higher than in age-matched normotensive men; this was in addition to the well-known increased mortality from cardiovascular disease among hypertensive men (cardiovascular deaths per 10,000 159.9 vs 58.0 in normotensive men).11 Complementary to these observations are the slightly higher than expected noncardiovascular mortality rates among hypertensive white men and the significantly higher noncardiovascular mortality rates among black men with hypertension in comparison with normotensive men in Evans County between 1960 and 1980.

There can be little doubt that the reduction in cardiovascular events achieved by the stepped care program...
of the HDPP, including reductions in stroke, LVH, radiographic evidence of cardiomegaly, fatal and non-fatal myocardial infarction, and angina pectoris, were attributable primarily to control of blood pressure, possibly with some additional contribution of comprehensive medical care. The reduction in rates of noncardiovascular death may be due to a similar mechanism: improvement of cardiac reserve in patients compromised by other major disease entities.

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Addendum

In a cohort of California men and women from 60 to 79 years old, Khaw and Barrett-Conner (Am J Epidemiol 120: 550, 1984) reported that systolic blood pressure was a significant independent predictor of cancer mortality in men. In women there was a similar but not statistically significant trend. They raise the possibility that hypertension might decrease cancer survival. “In fact, the positive relationship between systolic blood pressure and cancer may suggest some benefit” from antihypertensive treatment.

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