An analysis of the HDFP trial

Evidence of adverse effects of antihypertensive treatment on white women with moderate and severe hypertension

PETER L. SCHNALL, MD, MICHAEL H. ALDERMAN, MD, ROCHELLE KERN, PHD

ABSTRACT Results of the Hypertension, Detection and Follow-up Program (HDFP) published in 1979 included the suggestion that systematic and effective management of hypertension benefited all individuals with high blood pressure. An analysis of these results reveals, however, that among white women aged 30 to 69 with entry diastolic blood pressure (DBP) ≥105 mm Hg, the "stepped-care" approach was associated with a mortality of 168 percent in excess of the control group ($P = 0.007$ level, $Z = 2.46$). The mortality rate in white men in the stepped-care group with entry DBP >115 mm Hg was 35 percent higher compared to controls. On the other hand, black men and women in the stepped-care group with DBP ≥105 mm Hg had a lower mortality rate compared to the control group. These data suggest that a standard therapeutic regimen may be detrimental when applied to all persons who are identified as having hypertension only by their blood pressure.

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INTRODUCTION

Some aspects of the management of patients with high blood pressure remain controversial despite the mass of data accumulated from extensive clinical trials.[1–8] The findings and conclusions of these trials are being reevaluated on the basis of additional analyses of existing data as well as the gathering of new data. The Hypertension, Detection and Follow-up Program (HDFP) was sponsored by the National Institutes of Health and conducted over a five-year period.[9] Among the trial's chief aims was the assessment of whether the findings of the Veterans Administration Cooperative Group Study (VACGS)[10–12] could be generalized to a heterogeneous, community population. The VACGS involved a selected hospital population of men, most of whom had advanced hypertensive or coronary heart disease, or both. In this paper we present the results of a re-analysis of previously published HDFP data[13] that revealed an association between "stepped care" treatment and increased mortality among white women aged 30 to 69 with moderate or severe hypertension (entry DBP ≥105 mm Hg). We discuss the implications of these findings for the treatment of hypertension in community populations.

HDFP Research Design and Findings. The HDFP was a community-based, randomized controlled trial involving 10,940 persons with hypertension (DBP >90 mm Hg) in 14 communities throughout the United States.[9] Following an initial screening and evaluation, the study sample was stratified by blood pressure level—mild hypertension (DBP 90 to 104 mm Hg) being stratum I (N = 7,825); moderate hypertension (DBP 105 to 114 mm Hg) being stratum II (N = 2,052); and severe hypertension (DBP >115 mm Hg) being stratum III (N = 1,063)—and then assigned randomly (by stratum) to one of two groups: referred care (RC) defined by the HDFP as the control group, or stepped care (SC). Those in the RC group were referred for treatment to their regular source(s) of health care. The SC patients (the experimental group) were offered "systematic, controlled antihypertensive treatment" at one of 14 HDFP health centers.[9] Drug treatment was administered to SC patients according to a stepwise protocol that called for the progressive addition of medication to an individual patient's regimen until his or her blood pressure was brought down to a specified goal level. Two features of the HDFP study design bear notice: (1) the absence of an untreated control group, and (2) the fact that the clinical intervention in the experimental group involved the simultaneous variation of both drug treatment and organization of medical care services.[1,7,8]

The HDFP Cooperative Group has reported that among those in stratum I (with DBP 90 to 104 mm Hg), the SC (as compared with RC) group showed a decrease in all-cause and cardiovascular mortality (including deaths due to stroke).[14–17] Within both strata II and III, the SC group had lower five-year death rates than did the RC group, although this difference was less than in stratum I and was not statistically significant.[15]

METHODS AND RESULTS

In examining the data reported by the HDFP Cooperative Group,

From the Divisions of Epidemiology (Dr Schnall) and Socio-medical Sciences (Dr Kern), Columbia University School of Public Health, New York, and the Departments of Medicine and Public Health, Cornell University Medical College (Dr Alderman), New York, NY.

Address correspondence to Dr Schnall, NIH-HBLI Post Doctoral Fellow, Division of Epidemiology, Columbia University School of Public Health, 100 Haven Ave, 30th floor, New York, NY 10032.

TABLE I. HDFP Five-Year Mortality for White Women with DBP >105 mm Hg*

DBP at Entry (mm Hg)	Sample Size (no.)		Deaths (no.)		Proportion of Deaths		% Change SC vs RC	Relative Risk	Probability SC vs RC
	SC	RC	SC	RC	SC	RC			
105–114	203	183	15	6	15/203 =0.074	6/183 =0.033	+124	2.2	Z = 1.54 P = 0.062
115+	69	51	10	2	10/69 =0.145	2/51 =0.039	+272	3.7	Z = 1.61 P = 0.054
Combined DBP > 105	272	234	25	8	25/272 =0.0919	8/234 =0.0342	+168	2.7	Z = 2.46 P = 0.007

* Adapted from Kass[13]

we found that among white women assigned to the experimental treatment groups (SC) in both strata II and III (white women who entered with DBPs ≥105 mm Hg) the mortality rate was higher than that in the comparable controls: an excess of 124% in stratum II and 272% in stratum III (see Table I).[13] The combined group finding for white women with DBP >105 mm Hg is statistically significant at the 0.007 level (Z = 2.46). White men in the SC group with entry DBP >115 mm Hg (stratum III) also experienced an excess mortality rate of 35% compared to their RC counterparts, although this is not a statistically significant difference. On the other hand, among both black men and black women assigned to the SC groups in strata II and III, there was a lower all-cause mortality rate than among comparable RC groups.

These findings, which have been reported in the literature but not previously discussed, indicate that the experimental stepped-care treatment (SC) of white women whose initial diastolic blood pressure equalled or exceeded 105 mm Hg was associated with an increased all-cause mortality rate and presumably an increased cardiovascular mortality rate. This excess mortality occurred within the group (SC white women) in which the lowest final blood pressure level was achieved and which contained the highest percentage of subjects whose blood pressure had reached goal levels of any of the subgroups. In addition, the mortality rate of white women with DBP >115 mm Hg in the SC group was higher than that of RC or SC white men and black women with comparable blood pressures. The only blood pressure-defined group with a higher mortality rate was the RC black men.[13]

That antihypertensive chemotherapy would have an inconsistent impact on different groups defined by demographic or clinical characteristics is consistent with what might have been expected from evidence of the natural history of hypertension. For example, analysis of the Framingham data reveals that only two of 100 treated women would be expected to benefit in terms of morbidity or mortality or both, even if a sustained reduction of systolic blood pressure from 165 to 135 mm Hg were maintained for 30 years.[18] It should be noted that this potential benefit is predicated on the assumption that the medications used to reduce blood pressure would, in themselves, be harmless.

These HDFP data do not merely reveal an absence of benefit from treatment. Rather, among white women with a moderate (DBP 105 to 114 mm Hg) or severe elevation of blood pressure (DBP >115 mm Hg), there was a higher mortality rate among those who received SC treatment. Given the small probability of this finding ($P = 0.007$), it is unlikely to have occurred by chance alone. It is also unlikely that the two groups of women (SC versus RC) were significantly different from each other initially since randomization of subjects was employed in the HDFP study design, and at baseline the overall SC and RC groups (all three blood pressure groups combined) were virtually identical.[16]

The magnitude of the difference in death rates between SC and RC white women with DBP >115 mm Hg adds to the impact of the statistical finding. In the HDFP trial the SC subgroup of white women with DBP >115 mm Hg included only 69 subjects of whom 10 died. The control group (RC) had 51 subjects who contributed two deaths. To put this in perspective, in the VACGS trial of patients with DBP 115 to 129 mm Hg, 73 subjects were in the experimental group and 70 subjects in the control group. In that study, there were no deaths and no Class A events in the experimental group (Class A events were new hypertensive complications for which antihypertensive therapy was required; for example, the development of grade III or IV retinopathy) whereas in the control group there were four deaths and 10 Class A events. The difference in event rates was considered sufficient to end the trial with the conclusion that antihypertensive treatment was beneficial.[10] Thus, in these two trials the magnitude of the impact of the intervention is similar, but in opposite directions.

DISCUSSION

This unexpected excess of mortality among white women in the SC group cannot be explained by the data published to date. It would be helpful to know the causes of death among these women, their specific blood pressure courses, their drug experience during treatment as well as center by center experience. Even this information, however, may not explain these results since the design of the HDFP had no untreated control group and involved a treatment intervention in which both drugs and the organization of health services were varied simultaneously.

Two explanations can be proposed: (1) the magnitude of the blood pressure decline was itself detrimental, or (2) the medications prescribed carried a risk that exceeded the benefit of reduced blood pressure. Support exists for both of these hypotheses. In a Norwegian study those with the greatest fall in blood pressure were most likely to experience a cardiac catastrophe.[19] In Australian, Norwegian and United States Public Health Service studies, cardiac mortality was greater in treated than in untreated subjects.[19–21] Additional evidence about the adverse consequences of antihypertensive medication comes from the recently published findings of the Multiple Risk Factor Intervention Trial (MRFIT).[22] The SI subjects (the experimental group) who had hypertension and an abnormal EKG at baseline experienced a 65% increase in coronary heart disease deaths versus the comparable UC group (the control group). Also of concern was that the SI subjects with the lowest diastolic blood pressure (90 to 94 DBP) experienced the greatest relative increase in mortality—17 deaths in the SI group compared to 12 in the UC group. These findings reinforce concerns about a standardized approach to antihypertensive drug treatment for all persons identified only by a certain level of blood pressure.

Clearly, all the hazards of antihypertensive drug therapy are not known. It has been demonstrated that diuretic-

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Clearly, all the hazards of antihypertensive drug therapy are not known. It has been demonstrated that diuretic-induced hypokalemia is associated with increased ventricular arrythmia.[23] The short-term findings of impotence (in men) and peripheral vascular disease have been well documented.[24,25] By contrast, the long-term implications of even mild hyperuricemia, hyperglycemia, and hypokalemia are poorly understood.[26] The HDFP data lend credence to the concern that drug therapy may sometimes produce harm that outweighs its benefit in the treatment of a condition, such as hypertension, in which the inherent risk of the disease is small with an uneven distribution.

Another possible explanation—that community care produced an improvement in the mortality rate by the use of other antihypertensive medications (for example, beta adrenergic agents)—seems unlikely based on the finding that in SC black men and women with moderate and severe elevations of blood pressure, all-cause mortality was lower than in matched RC groups.

Finally, these findings may be explained by chance variations among the subgroups. It is well known that making multiple comparisons increases the likelihood of finding, due to chance alone, that one or more subgroups differ substantially in their outcome from the overall study group results.[27] In assessing the possibility of a chance finding, it should be noted that the results we report are based on the testing of a conservative null hypothesis, that there is *no difference* in outcome between SC and RC in white women with moderate or severe hypertension. On the other hand, we might expect that white women with moderate or severe hypertension could be expected to do significantly *better* in SC than in RC. Clearly, the use of this alternative null hypothesis would have made the probability of the observed results even smaller (produced a larger Z score) and, therefore, would have made the observed results very unlikely to have occurred by chance. Unfortunately, no statistical test can itself resolve the issue of whether these findings are significant or due to chance. Rather, the findings of markedly increased mortality in the experimental SC group among white women with entry DBP >105 mm Hg compared to the RC group must be examined in the context of our expectations of antihypertensive drug treatment effects. Thus, it is the totally unexpected nature of the findings, their magnitude, and the clinical and social significance of their implications that leads us to conclude that they should be taken seriously.

Aggregation of population data in clinical trials may mask important differences within groups, including the presence of negative outcomes for particular subgroups. It seems possible that a thorough examination of results from the HDFP and other clinical trials of antihypertensive drug therapy using social class, age, race, and sex (separately and together) may reveal other subgroups at increased risk from treatment with antihypertensive drugs.

We do not interpret these new findings as conclusive evidence for or against antihypertensive treatment of white women with moderate and severe hypertension, particularly in light of the known limitations of subgroup analysis. Instead, they argue for increased efforts to identify more precisely those individuals and subgroups at highest risk from elevations of blood pressure, as well as those at increased risk from treatment with medications. These data strengthen the view that a scientific basis for a standardized approach to the management of population groups defined exclusively by level of blood pressure does not exist.

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