SUMMARY The proper management of mild and moderate hypertension remains a matter of considerable professional disagreement. Major clinical and population research has largely been designed to define a level of blood pressure (BP) at which treatment should be initiated. This paper reviews studies of the natural history of hypertension and the findings of intervention trials to determine whether the BP level alone is adequate to identify, diagnose, and predict the future course of hypertensive patients. Observational data suggest that patients defined by mild elevation of BP are a heterogeneous group who do not share a common prognosis. Moreover, intervention trials reveal that not all those at risk of cardiovascular disease will benefit from hypotensive therapy. Thus, BP level alone defines neither the group at risk nor those likely to benefit from BP reduction. It is therefore concluded that the management of each patient with hypertension should be determined on the basis of available clinical, biochemical, and behavioral as well as epidemiological data.

KEY WORDS • mild-to-moderate hypertension • therapy • diagnosis • age •
Veterans Administration studies • Framingham study

SINCE 75% of all hypertensive persons have mild or moderate elevation of blood pressure (BP), and since available data provide, at best, inconsistent guidance for therapy, it is not surprising that intense interest continues to surround questions of who should be treated, at what time, and by what means.1 Often the issue is joined by the seductively straightforward question: "At what level of BP should treatment be instituted?" Unfortunately, available knowledge about the nature of high BP suggests that the question may not be answerable in these terms. Results of epidemiological studies suggest that hypertensive patients, as a group, are of sufficient clinical heterogeneity to defy cleavage into two mutually exclusive subgroups on the basis of BP level alone.

In view of the heightened interest in the issue of BP management generated by the recent Hypertension Detection and Follow-Up Program findings,2,4 it seems timely to review significant population studies in an effort to place the current debate in historical perspective.

Observational Studies

The Framingham Study

Examination of the longitudinal experience of middle-aged adults in Framingham permits estimation of the probability of having a cardiovascular disease event during a 15- to 30-year period.4-6

Figure 1 depicts graphically the risk of developing cardiovascular disease in 15 years, for 35-year-old men and women under different clinical conditions. The "low risk" 35-year-old man does not smoke, has a cholesterol of 235 mg%, no ECG abnormality, nor evidence of glucose intolerance. He stands a 15% risk of developing cardiovascular disease if his systolic BP is 195 mm Hg. But a 35-year-old man with the same systolic BP of 195 mm Hg who smokes, has a cholesterol of 310 mg%, LVH on ECG, and glucose intolerance is at "high risk", with an 86% chance of experiencing a cardiovascular disease event over the ensuing 15 years. Thus, two men at the same age and level of pressure, can have a sixfold difference in their expectation of disease.

By way of contrast, a 35-year-old woman with the "low-risk" configuration of associated clinical and behavioral characteristics, has only a 6% risk of disease events in 15 years if her systolic BP is 195 mm Hg. This is equivalent to the hazard faced by a man with the "low risk" characteristics, but a systolic BP
Second, that the means employed to manipulate the pressure would not, in themselves, produce harm. Finally, that those whose BP was so artificially altered would therefore enjoy the life experience of one whose BP was naturally at that lower level.

Figure 2 depicts the ratio of nonbenefited-to-benefited persons if treatment were begun at age 35 years and continued for 15, 25, or 30 years. In the top left panel, it can be seen that almost 50 35-year-old women with the low risk configuration must have their pressure dropped from 165 to 135 mm Hg for 15 years without any benefit for every such woman who would benefit from the same treatment. Of course, the odds ratio can change dramatically when other BPs and clinical circumstances are considered. In the lower left panel, it can be seen that only three high risk men need fruitlessly undergo a BP reduction from 195 to 135 for 15 years for each patient to benefit.

In sum, this arithmetic indicates that, regardless of sex, blood pressure level, clinical status, extent of reduction, or length of follow-up, the majority of 35-year-old females of 135 mm Hg. Thus, a man and woman sharing the same age and risk, can have BPs separated by 60 mm Hg. Furthermore, this “low risk” woman with a systolic BP of 195 mm Hg has only 1/6th the risk faced by a “high risk” man with a systolic BP of 135 mm Hg.

The point of these examples is to demonstrate the enormous variety in the natural history of hypertension that is not predicted by BP level. In fact, it is clear that the range of risk within a single BP stratum is enormous. Furthermore, people with vastly different BPs can have exactly the same risk of disease while others with lower BPs can have risks greater than those faced by persons with higher pressures.

These projections suggest that, although the height of arterial pressure may distinguish groups with variations in aggregate burden of subsequent cardiovascular disease, this approach tends to lump together individuals with vastly different life expectancies. Moreover, since disease risk is not evenly distributed within blood pressure strata, it seems reasonable to expect that the benefit of any BP reduction might not be uniformly received by all the persons at a given level of BP.

To provide a quantitative dimension to this intragroup variability, the extent of disease prevention that might be realized by BP reduction has been estimated under various clinical and BP circumstances. These estimations of potential benefit depend upon the validity of three fundamental assumptions. First, that BP reductions of the magnitude defined can be achieved and maintained over a period of 15 years.

Figure 1. Risk of developing CVD in 15 years for 35-year-old men and women, by SBP level and risk status. High risk = LVH, cigarette smoker, a cholesterol of 310 mg%, and glucose intolerance. Low risk = no LVH, nonsmoker, a cholesterol of 235 mg%, and no glucose intolerance.

Figure 2. Relative benefit of various degrees of blood pressure reduction for three periods of follow-up, at two levels of associated risk, for 35-year-old men and women.
hypertensive persons can expect to be treated without hope of benefit. Moreover, at the milder levels of pressure and during shorter periods of follow-up, ongoing treatment is likely to benefit only a very small fraction of the persons exposed. These data, based on the best possible interpretation of observed natural history, permit some reasonable predictions about the likely optimal results of intervention trials. The trials themselves suggest that the modest expectations pressed by the Framingham experience have indeed been borne out by empirical investigation.

**Intervention Trials**

**Veterans Administration Studies**

Completed more than a decade ago, the VA studies were designed to determine the ability of active hypotensive agents to reduce cardiovascular disease morbidity and mortality. The power of these studies derives from their precision of design and elegance of completion. Participants, selected according to rigid criteria, were randomly allocated to either placebo or active treatment. Thereafter, save for their pharmacological category, all patients received the same follow-up care.

Under the circumstances of this study, in particular the heavy selection bias to “high risk” patients, it was possible to quickly demonstrate the value of treatment for patients with diastolic pressures in excess of 114 mm Hg. At the mild and moderate levels below that range, results were less dramatic, and indeed, in the mild range (90-104 mm Hg), no statistically significant benefit of treatment was found. Since the vast bulk of so-called hypertensives reside in that mild blood pressure stratum, it is worth reviewing the more detailed examination of the data provided by the VA cooperative study group (Freis and associates). These data (fig. 3) depict the variety of natural history that exists within a single BP stratum. For example, male veterans in the placebo group with entry diastolic pressures between 90-104 mm Hg who had no evidence of cardiac abnormality at entry had a risk less than that of a person with the same blood pressure who had evidence of cardiovascular risk abnormality at entry. Other categories of demography and clinical status produced similarly wide variations in actual disease incidence.

It is therefore not surprising to find that, when the benefit of treatment is examined, concomitant variation between subgroups appears. For example, as illustrated in figure 4, patients without cardiovascular abnormalities at entry had a risk less than ½ that of a person with the same blood pressure who had evidence of cardiovascular risk abnormality at entry. Other categories of demography and clinical status produced similarly wide variations in actual disease incidence.

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In the face of this tantalizing but inconclusive information, support was mobilized in the early 1970s to undertake further studies in several countries to fill the gaps in knowledge.

**Hypertension Detection and Follow-Up Program (HDFP)**

The HDFP study was designed to test the value of antihypertensive therapy for hypertensives drawn from the general community. Unfortunately, the meaning of its observed outcomes is somewhat clouded by the absence of a control group defined in the conventional sense. Instead of two groups differing only in their medication regimen, HDFP randomly allocated participants into special or regular care treatment cohorts. The special care (SC) group received vigorous care without cost under conditions designed to maximize compliance to a predetermined,
albeit somewhat outmoded, chemotherapeutic regime. The regular care (RC) group, by contrast, was referred to community physicians to receive treatment in the conventional fashion. Under these circumstances, it is difficult to determine whether any differences in outcomes were due to the hypotensive therapy or the nonspecific benefits of general medical care. As it turned out, deaths ascribed to noncardiovascular events fell by an amount that was about 60% of the extent of the decline in cardiovascular-related deaths. Thus, it is hard to discount the importance of the nonspecific impact of SC.

Assuming, for the moment, that the decline in mortality was entirely due to the impact of the demonstrated fall in BP, it is still clear that these results do not resolve the issues surrounding treatment of mild hypertension. First of all, although the difference in all cause mortality in the mild strata was 16%, attack rates were low, and the actual difference in survival over 5 years was about 1.5% between the two groups, with more than 92% of all participants surviving. In fact, this difference was 13 per 1000 persons over 5 years.

Moreover, as shown in figure 6, when the experience of this mild group was subjected to slightly more detailed scrutiny, the anticipated heterogeneity of the group emerges. For example, when mortality differences according to sex and race are examined, it can be seen that blacks had high attack rates and substantial benefit, while white women suffered few deaths and did not seem to benefit from a lowered BP. Furthermore, when results are depicted according to age (fig. 7) it can be seen that again, as expected, older persons were more likely to die, and had substantially fewer deaths if they participated in SC. But those persons under 50 had slight mortality and this was not reduced by achieving a lower pressure in SC.

**Conclusions**

What comfort can be drawn from these observational and intervention trials? The VA and HDFP studies as well as an Australian placebo controlled therapeutic trial confirm the expectation generated by the Framingham experience that reduction of arterial pressure can produce benefit, even at very mild elevations. However, at all levels, but more so at lower pressures, the prognostic heterogeneity of persons with the same level of pressure produces an uneven distribution of therapeutic benefit.

In the absence of a precise means to identify those who would actually benefit from treatment, there is an understandable but nevertheless inappropriate tendency to apply an epidemiologically useful parameter (BP level) to define the need for treatment in an individual case. Thus, particularly at mild levels where risk is small, a uniform treatment plan based on BP levels alone commits the vast majority to long-term intervention without hope of benefit.
The ambiguous quality of the information that plagues clinicians today can perhaps be better appreciated by contrasting the current situation to that which surrounded the evolution of a treatment strategy for malignant hypertension. It was possible to set up precise diagnostic criteria for identification of patients with malignant hypertension due to the discrete nature and course of the disease. As has been well established, the clinical course of these patients is uniformly and rapidly downhill, and if untreated, almost invariably ends fatally. In view of this clinical and prognostic homogeneity, intervention that produced a particular result in any patient with this condition could reasonably be expected to produce a similar result in all such patients. Thus, more than 2 decades ago, favorable experience with hypotensive chemotherapy in some persons with malignant hypertension led to the universal acceptance of drug therapy. The subsequent impressive decline in mortality from malignant hypertension would tend to confirm the wisdom of that therapeutic innovation.

By extrapolation from the positive findings of clinical trials to less egregious forms of the disease, it is tempting to use the same discriminating variable, namely, BP level, as the standard by which to define the need for treatment. Unfortunately, the defining marker in this case lacks the precision that was characteristic of the whole syndrome of malignant hypertension. In fact, at the mild level, BP is about as specific as temperature in predicting patient outcome or signalling the proper therapy for any single patient.

In sum, intervention studies reconfirm that patients with essential hypertension can be categorized into three subgroups with distinctly different clinical outlooks. These are: 1) hypertensives at risk of CVD and likely to benefit from hypotensive therapy; 2)
hypertensives at risk of CVD but likely to experience their unfortunate outcome despite BP reduction; and 3) hypertensives not at risk of developing CVD and therefore unable to benefit from BP reduction. Unfortunately, the simple measure of BP does not distinguish between these three groups. Thus, any management strategy based on level of BP alone, while sure to benefit some, condemns a vastly greater number to all the disagreeable effects of therapeutic intervention without any of its concomitant benefits. In the absence of diagnostic taxonomies that divide patients into prognostically homogeneous strata, it would seem wise for clinicians to employ all the relevant clinical, biochemical, and behavioral data to augment available epidemiological data in defining an appropriate individualized management strategy for every patient.

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