Antihypertensive Drug Treatment
Potential, Expected, and Observed Effects on Stroke and on Coronary Heart Disease

Stephen MacMahon, Jeffrey A. Cutler, and Jeramiah Stamler

The effects of prolonged differences in diastolic blood pressure (DBP) on the risks of stroke and of coronary heart disease (CHD) were estimated from nine major prospective observational studies involving about 420,000 men and women who were followed up for intervals of 6–25 years. The results indicate that a prolonged difference of about 6 mm Hg in DBP was associated with approximately 37% fewer strokes and 23% fewer CHD deaths and nonfatal myocardial infarctions. The effects of equivalent reductions in DBP produced by antihypertensive drug treatment but maintained for only a few years have been estimated in several overviews of randomized trials involving a total of 30,000–40,000 patients. The results of the overviews indicate that treatment reduced the risk of stroke by about 40%, suggesting that most or all the long-term potential benefits for stroke due to lower DBP were achieved within about 3 years of beginning treatment. The risks of nonfatal myocardial infarction and CHD death may have been reduced by about 10% among patients allocated to active treatment; the 95% confidence limits for the difference ranged from about zero to about 20%. Whatever the true effect of treatment on CHD, it would appear somewhat less than the difference in risk estimated from the observational studies for a prolonged difference in DBP of the same size. This apparent shortfall in benefit may reflect a long time-course for changes in DBP to have their full effects on CHD, possible adverse side effects of the principal trial treatments, or both. (Hypertension 1989; 13(suppl I):I-45–I-50)

The morbidity and mortality results from trials of antihypertensive drug treatment have been the subject of long-standing debate in the medical literature. Much of this controversy appears to have occurred as a consequence of two factors. First, there has been little consideration of the size of the benefits likely to accrue from several years of modest blood pressure reduction. Expectations about the effects of treatment will undoubtedly have important implications for the interpretation of the trial results. Second, the majority of the trials have been individually too small to detect reliably or exclude those moderate but potentially worthwhile effects of treatment on major morbidity and mortality from vascular disease that may be the most plausible outcome of treatment.

The sensitivity to detect moderate but worthwhile benefits of treatment on major disease events can be increased by combining the results of all relevant randomized studies in an overview, such as that reported in the article by Cutler et al in this issue. This approach has the added advantage of avoiding the biases that can be introduced when inference about treatment effects is based on the results of a few selected and potentially nonrepresentative trials. In interpreting the results of such overviews of antihypertensive treatment trials, estimates from prospective observational studies of the eventual effects on vascular disease of prolonged differences in blood pressure may be useful. These estimates may provide a reasonable upper limit for expectations about the effects of similar blood pressure differences maintained for substantially shorter intervals in the trials of antihypertensive treatment.

In this report, we consider the morbidity and mortality results from several overviews of randomized trials of drug treatment for hypertension in which diastolic blood pressure (DBP) was reduced, on average, by approximately 6 mm Hg among
patients allocated to study treatment] in the context of data from several prospective observational studies on the effects on stroke and on coronary heart disease (CHD) of prolonged blood pressure differences of the same size. From these data, it is possible to consider the proportion of long-term benefits of lower blood pressure that is achieved within a few years of beginning treatment with antihypertensive drugs (in particular, diuretic-based regimens). In these analyses, DBP rather than systolic blood pressure (SBP) was used because the trials of antihypertensive drug treatment have, for the most part, provided more complete data on DBP than on SBP.

Potential Effects of Prolonged Differences in Blood Pressure on Stroke and on Coronary Heart Disease: Evidence From Prospective Observational Studies

Due to blood pressure tracking, differences in blood pressure between individuals of the same age tend to be maintained over time. Thus, age-specific cross-sectional differences in blood pressure between individuals at baseline in prospective observational studies will be correlated with long-standing blood pressure differences, which may have existed since childhood.4-5 With appropriate analysis (see below), the effects of prolonged blood pressure differences on vascular disease can be estimated from the relation between baseline blood pressure levels and subsequent disease risks.

The effects of prolonged differences in DBP on stroke and on CHD risk have been estimated from data collected in nine major prospective observational studies6-14 involving approximately 420,000 individuals followed up for intervals of 6–25 years. These studies were conducted in adult populations from North America, Hawaii, the Caribbean area, and the United Kingdom. Data were obtained from each study for participants aged 25 years or older, of either sex and of any race, who had no known history of myocardial infarction (or stroke, if data were available) and who were not receiving treatment for diabetes. These criteria correspond approximately to the minimum exclusion criteria adopted in many of the trials of antihypertensive treatment.

Follow-up data on deaths from CHD were available for all nine studies, and data on deaths from stroke were available for five of these studies.6-8,10,12-14 Three studies also provided data on nonfatal myocardial infarction,9,10,12 and two of these provided data on nonfatal stroke.10,12 The results of each study suggest approximately log-linear increases in the risks of both stroke and CHD with increasing levels of DBP at baseline. Throughout the observed range of DBP, the risks appear continuous, with no obvious “threshold” level of DBP at which the risks were suddenly elevated. Similarly, there is no obvious level below which the risks did not continue to decrease, although even in the largest studies, there were too few strokes in individuals with DBP below 80 mm Hg to allow precise characterization of this relation at low blood pressure levels. Overall, the relation between DBP and stroke was about 50% steeper than that between DBP and CHD, but in most studies, the incidence of CHD was several times more common than that of stroke. The relations observed in these nine studies are typified by those observed in the largest of the studies, the follow-up study of some 350,000 men screened for the Multiple Risk Factor Intervention Trial.6 (Figure 1).

The effects of prolonged blood pressure differences on the risks of stroke and CHD were estimated from each of the studies in Cox regression analyses, with adjustment for other major confounding risk factors (age, plasma cholesterol, and smoking status) and for the limited reliability of differ-
The effects of blood pressure reduction with antihypertensive drugs will also depend on any independent effects of particular agents on risks. Diuretic agents, which were the most widely used class of drugs in the trials of antihypertensive drug treatment, appear to produce a number of adverse metabolic effects that could be expected to offset estimated effect of a 6 mm Hg difference in usual DBP on stroke. In all seven studies that provided data on stroke, this difference in blood pressure was associated with a lower incidence of stroke, the differences ranging from 33% to 41%, with a mean of 37% for all studies. Although modest heterogeneity could not be excluded, there were no striking differences in the sizes of the effects either on stroke or on CHD between men and women or among those studies in which fatal events alone were reported and in those in which fatal and nonfatal events were reported.

Expected Effects of Shorter-Term Reductions in Blood Pressure on Stroke and on Coronary Heart Disease

The results of prospective observational studies indicate that, in the long term, a 6 mm Hg lower usual DBP would be expected to result in almost one quarter fewer CHD events and almost 40% fewer strokes. These estimates are likely to represent an upper limit for expectations about the effects of similar differences in blood pressure maintained over shorter intervals. The actual effects of a reduction in DBP in a middle-aged adult population will also depend on the degree to which blood pressure reduction can reverse or prevent the progression of the pathological processes responsible for the increased risks of stroke and CHD associated with higher blood pressure levels. Unless there is complete and rapid regression of these processes, the short-term effects of blood pressure reduction are likely to be somewhat less than the effects of prolonged blood pressure differences.

For example, it is uncertain whether the atherosclerotic and preatherosclerotic endothelial changes\(^{19,20}\) that appear to be produced by high blood pressure are quickly affected by reductions in blood pressure. If not, any atherogenic effects of pretreatment blood pressure levels on the coronary arteries may continue to exert some influence on the risks of myocardial infarction and CHD death after the initiation of treatment for blood pressure reduction. If so, the short-term effects of blood pressure reduction on CHD would be somewhat less than the effects of prolonged differences in blood pressure of similar size. Any such effect, however, is likely to be more pronounced for CHD than for stroke, as atherosclerosis does not appear to have a direct role in the etiology of cerebral hemorrhage,\(^{24}\) and, judging from the weak association between blood cholesterol and strokes of supposed thromboembolic origin,\(^{21,22}\) atherosclerosis probably has a lesser role in cerebral infarction than in myocardial infarction.

The effects of blood pressure reduction with antihypertensive drugs would also depend on any independent effects of particular agents on risks. Diuretic agents, which were the most widely used class of drugs in the trials of antihypertensive drug treatment, appear to produce a number of adverse metabolic effects that could be expected to offset...
some benefits of blood pressure reduction. An increase of about 5% in total cholesterol has been observed in several studies involving diuretic drugs. Although there is some controversy about the long-term effects of such treatment on serum lipids, the results of the Medical Research Council trial suggest an increase in total cholesterol of about 3% after several years of treatment with bendroflumethiazide. There is evidence to suggest that a 3-5% increase in serum cholesterol may increase the risk of CHD by 6-10% during several years of treatment. As discussed in the article by Cutler et al in this issue, it has also been suggested that treatment with diuretic drugs may increase the risk of arrhythmic cardiac death, particularly in patients with preexisting electrocardiographic abnormalities, although this suggestion remains controversial. Any such adverse effects of treatment with diuretic drugs could result in the outcome of treatment for CHD being somewhat less than that estimated for a prolonged blood pressure difference in observational epidemiological studies. However, these particular adverse effects would not be expected to produce important effects on the risks of stroke.

Finally, the effects of treatment on the risks of CHD and stroke may also be influenced by any reduction in SBP, if the effects of such reduction were independent of those produced by reductions in DBP. Unfortunately, complete data on changes in SBP are not available from several trials, and it remains uncertain whether reductions in SBP independently contribute to the observed effects of treatment in the trials.

**Observed Effects of Shorter-Term Blood Pressure Reduction in Randomized Trials of Antihypertensive Drug Treatment**

There have now been several overviews conducted on the randomized trials of antihypertensive drug therapy. Only one of these has included trials in severe hypertension and in patients with a clinical history of stroke in addition to trials in mild-to-moderate hypertension (R. Collins, unpublished observations). Another review, which is summarized in the article by Cutler et al in this issue, was restricted to those trials in predominantly mild-to-moderate uncomplicated hypertension. Yet another review was restricted to community-based trials. Cutler et al have chosen to include in their overview the results from the hypertensive stratum of the Multiple Risk Factor Intervention Trial, while the other overviews have excluded this study because of the potential confounding effect from concurrent interventions for smoking cessation and cholesterol lowering in that trial. The results reported from the overviews are, however, consistent in most respects.

Overall, about 600 strokes and 1,400 CHD deaths and nonfatal myocardial infarctions were included in these overviews. Among those patients randomized to study treatment (predominantly diuretic-based regimens), DBP was reduced during follow-up by a mean of about 6 mm Hg compared with patients allocated to the control group (many of the latter did receive active treatment at some stage during follow-up). The average period between randomization and the occurrence of fatal or nonfatal vascular events was about 3 years (i.e., about one half the scheduled trial follow-up interval). If treatment during this short interval produced effects on stroke and CHD that were as large as those estimated from observational epidemiological studies for a prolonged blood pressure difference of the same magnitude (i.e., about a 37% lower incidence of stroke and a 23% lower incidence of CHD), then the overviews should have adequate statistical power to detect such effects. If, however, the short-term effects of treatment were somewhat less than those estimated for long-term blood pressure differences, either as a consequence of chronic disease processes or as a consequence of adverse side effects of treatment, then the overviews may have inadequate statistical power for reliable assessment of treatment effects. For CHD, for which a lesser effect in the trials may be particularly plausible, the overviews would not be able to determine reliably any true effects of treatment that were one third to two thirds of the estimated long-term effects of a 6 mm Hg lower blood pressure (i.e., a reduction of about 7-14%).

The results of the overviews indicate that a 6 mm Hg reduction in DBP maintained for just a few years was associated with a highly significant reduction in stroke of about 40% (Table 2). The reductions in fatal and nonfatal stroke were independently significant and were of similar magnitude. Furthermore, there was clear evidence of benefit in patients with DBP below 110 mm Hg at baseline as well as in patients with more severe hypertension. These results indicate that, for stroke, most or all the potential long-term benefits of a 6 mm Hg lower DBP were achieved within just a few years of beginning treatment for blood pressure reduction, thus indicating that the effects of high blood pres-

### Table 2. Estimates of Effects on Stroke and on Coronary Heart Disease Risk of a 6 mm Hg Lower Diastolic Blood Pressure Maintained for Several Years

<table>
<thead>
<tr>
<th>Overview</th>
<th>Coronary heart disease</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutler et al</td>
<td>9% (-1%, 19%)</td>
<td>36% (26%, 46%)</td>
</tr>
<tr>
<td>Hebert et al</td>
<td>9% (-1%, 18%)</td>
<td>40% (29%, 49%)</td>
</tr>
<tr>
<td>Collins et al</td>
<td>12% (2%, 21%)</td>
<td>42% (33%, 50%)</td>
</tr>
</tbody>
</table>

Results are from three overviews of randomized trials of antihypertensive drug treatment.

*Reduction in the typical odds of vascular disease events among all patients allocated to study treatment in randomized trials of antihypertensive treatment.

†Unpublished observations.
pressure on the cerebral vasculature are quickly reversible after reduction in blood pressure.

For CHD, the results of the overviews are less clear (Table 2). The results suggest that benefit is more likely than not. However, the true effect of treatment during the short duration of the trials appears likely to be less than the 23% associated with a prolonged 6 mm Hg lower DBP. The exact size of the treatment effect for CHD is uncertain; the 95% confidence limits for CHD in the overviews are consistent with both no material effect of treatment and moderate benefit that may be as great as an 18–21% reduction in CHD. The point estimate of treatment effect for CHD varies between a 9–12% reduction, depending on the inclusion or exclusion of data from the MRFIT trial and of data on self-reported myocardial infarction from the Hypertension Detection and Follow-up Program. If the true effect of treatment on CHD is a reduction of about 10%, then it would appear that a 6 mm Hg reduction in DBP maintained for a few years by treatment with diuretic-based therapy produces about one half the potential long-term benefits of a 6 mm Hg lower DBP. If such a difference between the observed and potential effects of blood pressure reduction were not largely due to chance, it could reflect chronic processes in the relation between DBP and CHD or some adverse effect of the drugs studied. Indeed, an increase in total plasma cholesterol of as little as 3–5% could account for the majority of the apparent shortfall in benefit.

Conclusions

Prospective observational studies indicate that even modest differences in blood pressure eventually result in large differences in the risks of stroke and CHD. A prolonged difference of 6 mm Hg in usual DBP was associated with almost 40% fewer strokes and almost one quarter fewer CHD events. The results of randomized trials of antihypertensive drug therapy indicate that a similar difference in DBP maintained for just a few years produced most or all the potential long-term benefits for stroke. For CHD, however, the trial results, even in combination, were inadequate for reliable determination of the exact proportion of long-term potential benefit for CHD achieved by a few years of treatment. The best estimates suggest that about one half the benefit may be achieved. However, only by the conduct of further trials, perhaps with agents that do not adversely affect blood cholesterol or other risk factors, will it be possible to determine whether treatment can confer worthwhile benefits for CHD.

In the meantime, the possibility should not be dismissed that patients at risk of CHD may derive worthwhile cardioprotective benefit from antihypertensive treatment; however, in general, efforts to prevent CHD in hypertensive patients should be directed toward the management of all risk factors, including blood cholesterol for which there is strong evidence of a beneficial effect of intervention.24

Acknowledgments

The authors are grateful to the following investigators who provided us with data from their studies: 1) MRFIT Screenees: J. Neaton and D. Wentworth, School of Public Health, University of Minnesota, Minneapolis; 2) Chicago Heart Association: A. Dyer and C. Ballew, Department of Community Health and Preventive Medicine, Northwestern University Medical School, Chicago; 3) Whitehall: G. Rose and M. Shipley, Department of Epidemiology, London School of Hygiene and Tropical Medicine, London; 4) Puerto Rico: P. Sorlie, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Bethesda; 5) Honolulu: R. Abbott, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Bethesda; 6) LRC Prevalence: I. Mebane and J. Nelson, Division of Heart and Vascular Disease, National Heart, Lung, and Blood Institute, Bethesda; 7) Framingham: P. Sorlie, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Bethesda; 8) Western Electric: A. Dyer and C. Ballew, Department of Community Health and Preventive Medicine, Northwestern University Medical School, Chicago; and 9) People’s Gas: A. Dyer and C. Ballew, Department of Community Health and Preventive Medicine, Northwestern University Medical School, Chicago.

References

dietary, and biochemical characteristics. J Chronic Dis 1974; 27:345–364

KEY WORDS • antihypertensive agents • clinical trials • prevention • coronary heart disease • stroke
Antihypertensive drug treatment. Potential, expected, and observed effects on stroke and on coronary heart disease.
S MacMahon, J A Cutler and J Stamler

Hypertension. 1989;13:I45
doi: 10.1161/01.HYP.13.5_Suppl.I45

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/13/5_Suppl/I45