Preventing Vascular Events Due to Elevated Blood Pressure

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E levated blood pressure (BP) demonstrates a consistent, strong, and graded relationship across the entire spectrum at levels >110 mm Hg systolic with several cardiovascular disease outcomes including cardiovascular death, myocardial infarction (MI), stroke, heart failure, and renal dysfunction. The population attributable risk due to elevated BP is large and consistent in all ethnic groups and regions of the world. In many countries (eg, United States, Canada, and Japan), strokes (especially hemorrhagic strokes) have been declining, which can be attributed, to a significant extent, to better BP control, although other factors (eg, changing diets and social and economic circumstances) are also likely to be important. By contrast, over the last 2 or 3 decades, the prevalence of heart failure has been increasing despite the increase in the proportion of patients with hypertension receiving BP-lowering therapy. This overall picture marks a decrease in heart failure in younger individuals, which is more than counterbalanced by an increase in the elderly.

Undoubtedly, BP lowering reduces heart failure to a substantial degree, but the randomized trials that have generated this evidence have generally lasted usually for an average of 5 years. At first glance, a 5-year trial may seem to be of long duration, but in fact it represents a relatively short duration of treatment (because the average time of treatment in these trials before an event occurs is approximately half the duration of the trial, which is only ~2.5 years) compared with the need for lifelong therapy over several decades. Over this period, BP control often gets poorer as patients get older, long-term adherence to antihypertensive therapy declines, and new cardiovascular events (eg, a heart attack or renal dysfunction) or noncardiovascular events (eg, arthritis) develop, which either directly or indirectly (eg, through the use of nonsteroidal antiinflammatory drugs, which can affect BP levels) lead to poorer BP control, changes in patients’ risk, or changes in the types of drugs that can be used safely. Thus, neither the long-term impact of BP lowering nor the exact type of drug to be used in individual patients can be adequately predicted by the relatively short-term trials. Nevertheless, these trials provide useful information (but not absolute rules) to serve as a guide for clinical practice.

In the last 3 decades, a large number of important and well-designed trials of BP lowering have been conducted, which have been well summarized in previous overviews. The first generation of these trials convincingly demonstrated the value of BP lowering, initially in those with very high BP, then among those with moderately elevated BP. The second generation of trials addressed whether there were important differences in clinical outcomes between different agents. Of these trials, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study is among the largest and most ambitious. It randomized 42,000 individuals with elevated BP to 4 initial choices for BP-lowering drugs: chlorthalidone, amlodipine, lisinopril, and doxazosin. The doxazosin arm was terminated prematurely after a median of 3.3 years because there was a significantly higher risk of a composite of cardiovascular disease events with doxazosin versus chlorthalidone. Of these, the most marked difference was in heart failure (4-year rate of 8.13% with doxazosin compared with 4.45% with chlorthalidone). At this time there was no difference in the primary outcome of fatal coronary heart disease (CHD) or nonfatal MI and in total mortality. In 2002, the results for the other comparisons were reported and indicated no difference in the primary outcome (CHD death or nonfatal MI) or in mortality between the chlorthalidone, amlodipine, and lisinopril arms. However, some differences in secondary outcomes were reported. In this issue, Davis et al provide a detailed account of the impact of these treatments on heart failure (fatal or hospitalization). They report a significantly higher rate of heart failure with amlodipine (relative risk of 1.35) and a nonsignificantly higher rate with lisinopril (relative risk of 1.09) versus chlorthalidone. These results should be interpreted in the context of the design of the study and other data in the trial and in the context of other related data from similar studies.

In ALLHAT, both the primary outcomes (fatal CHD and nonfatal MI) and the most important secondary outcome (total mortality) were similar across the 3 groups. From a “purist’s” point of view, a lack of statistical significance in the primary analysis at the conventional label of statistical significance does not allow us to make confident statements about any observed differences in other outcomes (in statistical jargon, “used up all the alpha” or, in lay terms, “we have placed a bet and not won, and so we are not allowed to place further bets in the same race”). Therefore, the lack of a clear difference in the primary outcome theoretically makes interpretation of secondary outcomes challenging. However, such a view may be too restrictive. Surely, one can learn from analyses of secondary outcomes, but perhaps one should give such analyses credibility only if they achieve some extreme...
probability value (although there is no consensus about what probability value would be persuasive, the $P<0.0013$ calculated by Davis et al in the article as an adjustment for multiplicity is likely to be a reasonable threshold) and, furthermore, if they are consistent with external data. With respect to the comparison between amlodipine versus chlorthalidone, both conditions are met: The statistical difference is extreme ($P<0.001$), and the possibility that calcium channel blockers either increase or have less of an impact on heart failure compared with diuretics or angiotensin-converting enzyme (ACE) inhibitors has been reported in numerous trials and is supported by an overview of all large trials.\textsuperscript{11} By contrast, the slightly higher rate of heart failure in the lisinopril group compared with chlorthalidone (relative risk of 1.09; $P=0.09$) does not meet conventional or adjusted levels of statistical significance and is not supported by other similar trials.\textsuperscript{12} The post hoc subdivision of the events by time (<1 year versus later) is methodologically suspect and is not supported by other data, and therefore it is not particularly persuasive.

What therefore are the implications of ALLHAT and other trials? With regard to heart failure, diuretics are at least as good as other treatments. However, physicians treat patients to avoid a range of complications, and therefore it is worth examining the impact of these drugs on several serious and common outcomes. These data indicate similar effects for the prevention of CHD and total mortality between most drug comparisons in individual trials. However, the degree of BP lowering was 2 to 3 mm Hg less with ACE inhibitors in some trials (eg, ALLHAT). After adjustment for the degree of BP lowering, a meta-analysis of all trials raises the possibility of a somewhat larger risk reduction in MI with ACE inhibitors than with other BP-lowering drugs.\textsuperscript{13} The impact on strokes also appears to be similar between agents after adjustment for the degree of BP control. How does a physician integrate the current information into practice? First, we are fortunate to have several classes of agents (diuretics, \(\beta\)-blockers, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, and \(\alpha\)-blockers) that are effective and relatively safe (ie, no irreversible and common major side effects). Second, in a large proportion of patients with elevated BP, multiple drugs are often needed to achieve an adequate level of BP reduction. Therefore, what really matters is not which single drug to use, but instead which combination of drugs to use. My preference is to use a combination of a diuretic and an ACE inhibitor in most patients, given the results of various trials of diuretics in hypertension and the special benefits of ACE inhibitors in patients with heart failure and after MI\textsuperscript{14} and in other high-risk patients with vascular disease\textsuperscript{15} or renal dysfunction.\textsuperscript{16} Some may prefer the combination of an ACE inhibitor and amlodipine,\textsuperscript{12} and this too is a reasonable choice. Some individualization of therapy based on specific clinical situations (eg, in patients with a MI, a \(\beta\)-blocker\textsuperscript{17} and an ACE inhibitor would be preferred) and cost, as well as whether or not the drugs are tolerated, is sensible.

In recent years, the focus has moved from control of a single risk factor to reducing overall risk.\textsuperscript{18} This has 2 implications. First, greater benefit can be realized by combining BP lowering with lipid lowering and smoking cessation rather than any single approach taken to its extreme. Second, on the basis of the epidemiological associations, even people with “normal” BP levels may benefit from BP lowering as long as they are at significant risk for future events.\textsuperscript{1} Although this approach of using a combination of BP lowering and lipid lowering to produce large reduction in the risk of events in those with average levels of risk factors is likely to be valid, it requires evaluation in well-designed trials.

From a public health perspective, with the increasing epidemic of obesity, the rates of hypertension in the population are increasing. Both obesity and hypertension are likely a “recent” phenomenon (during the last 100 years) and may be due to maladaptation to our changing environment, which is associated with marked decreases in utilitarian physical activity.\textsuperscript{19} Although hypertension can be prevented by sodium restriction, weight loss, and physical activity,\textsuperscript{20} societal policies and interventions are also needed. Otherwise, we may face the grim spectre of almost all adults in urban and industrialized settings needing medications for control of hypertension and other risk factors, as well as a growing burden of heart failure in the elderly. Therefore, although the benefits of BP-lowering therapies are immediate and important, they should be complemented by societal interventions that lower the entire BP distribution. Such a combined approach will lead to an important reduction in the burden of cardiovascular disease at all ages in most societies.

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