The management of hypertension has represented one of the most important therapeutic successes of the past 50 to 60 years. The capability now exists to lower blood pressure (BP) effectively and with relatively minimal adverse effects in most hypertensive individuals. The debate regarding therapy has shifted from whether lowering BP is beneficial to such issues as the relative benefits and risks of individual antihypertensive medications, their long-term effects on cardiovascular disease (CVD) and chronic renal disease outcomes, and the optimal BP goals of therapy in different clinical conditions.

Based on extensive clinical trial data, general agreement has existed that lowering elevated BP to \(<140\) mm Hg systolic and \(90\) mm Hg diastolic BP is beneficial. Lower BP goals have been suggested on the basis of epidemiological and observational data indicating that CVD risk increases progressively from BP levels as low as \(115/75\) mm Hg.\(^1\) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommended a goal BP of \(\leq130/80\) mm Hg in hypertensive patients with chronic renal disease or diabetes mellitus,\(^2\) consistent with the recommendations of the National Kidney Foundation and the American Diabetes Association. Subsequently, the American Heart Association expanded this list by recommending BP targets \(<130/80\) mm Hg for patients with preexisting coronary heart diseases, angina pectoris, and acute coronary syndromes or those at high risk for CVD, and BP \(<120/80\) mm Hg for those with left ventricular dysfunction.\(^3\) Generally similar recommendations have been made by other national or international groups as well. However, the available evidence may not justify such an aggressive approach.

For example, the African American Study of Kidney Disease and Hypertension compared the effects of goal BP of \(\leq140/90\) mm Hg versus \(\leq125/75\) in blacks with chronic renal disease (glomerular filtration rate: 20 to 65 mL/min per 1.73 m\(^2\)).\(^4\) The average BP achieved in the usual BP group was 141/85 mm Hg and 128/78 mm Hg in the aggressively treated group. However, no significant difference in the rate of change of glomerular filtration rate was observed between groups. As with other studies, considerable overlap in achieved BP levels occurred between the 2 groups. More than one half of those randomized to the lower BP goal group failed to reach the specified goal. Davis et al\(^5\) in the present issue of Hypertension have provided an interesting post hoc analysis of the African American Study of Kidney Disease and Hypertension combining data on BP levels achieved by all of the trial patients. They found that those in this intensively treated group who failed to reach goal BP were phenotypically different than those in the usual care group who achieved similar BP levels. They had more comorbidities and a greater rate of deterioration of renal function than the usual care group with comparable achieved BP. They also were less adherent to therapy. Such baseline differences probably contributed to the observed relationship between the achieved mean arterial BP and rate of deterioration of glomerular filtration rate and clinical composite outcomes, thereby casting doubt on the value of using African-American Study of Kidney Disease and Hypertension data on achieved BPs to justify aggressive BP lowering.

Another trial that examined different BP goals was the recently reported Action to Control Cardiovascular Risk in Diabetes Trial (ACCORD), a randomized, open-labeled study of type 2 diabetic individuals whose systolic BPs were treated to target levels of either \(<140\) mm Hg or \(<120\) mm Hg.\(^6\) Despite an average BP difference of 14/6 mm Hg between the groups, no significant difference in the primary outcome (composite of nonfatal myocardial infarction, stroke, or death from CVD causes) was present, although the intensively treated individuals did have significantly fewer strokes than the standard-treatment group. The results in ACCORD have been interpreted as differing from those in the United Kingdom Prospective Diabetes Study in which the group with the lower BP target developed less CVD than the standard treatment group.\(^7\) However, the goal BP in the aggressive treatment group of United Kingdom Prospective Diabetes Study was \(\leq150/85\) mm Hg, and the average BP achieved in this cohort was 144/82 mm Hg, a level similar to that achieved in the standard treatment group of ACCORD.

Another relevant trial to consider was the HOT Study in which hypertensive patients with pretreatment diastolic BP in the 100 to 115 mm Hg range were randomly assigned to 3 groups and treated with felodipine and other antihypertensive medications to achieve goal diastolic BPs of \(\leq90, \leq85,\) or \(\leq80\) mm Hg.\(^8\) No significant difference in primary outcomes was present between groups, although, unlike ACCORD, the most aggressively treated diabetics had fewer CVD events than those in the least aggressively treated group. When the data were analyzed according to achieved BP in the total group of individuals, the lowest rate of CVD events was observed at an average BP of 139/83 mm Hg.

In addition, a post hoc analysis of achieved BP in the Verapamil SR-Trandolapril Study, which was designed to
compare the effects of verapamil-trandolapril versus atenolol-hydrochlorothiazide combinations in hypertensive patients with coronary heart disease, was reported recently.9 In the diabetic cohort, no significant differences were present in coronary outcomes between individuals with average systolic BP <130 mm Hg versus those with systolic levels in the 130 to 139 mm Hg range, but those persons with average systolic BPs ≥140 mm Hg had a higher rate of coronary complications. In another post hoc analysis of the Verapamil SR-Trandolapril Study, the incidence of myocardial infarction but not stroke was greater at achieved levels of diastolic BP <70 mm Hg.10

Despite problems associated with the intention-to-treat trial design, it clearly remains the best approach for analyzing the results of comparative clinical trials, such as African-American Study of Kidney Disease and Hypertension and ACCORD. The heterogeneity of populations recruited into large trials is always a problem but is difficult to eliminate, particularly if the results of a study are to be relevant to the general patient population. Importantly, as reported in the article by Davis et al9 and as is probably relevant to other clinical trials, those who do not respond well to antihypertensive therapy may differ clinically from the better responders. Such differences may complicate the interpretation of the data obtained, particularly if post hoc analyses of achieved BP are made.

Because clinical trials explore more and more nuances of therapy, other aspects of the trial design should be kept in mind. Comparison with outcome data from previous trials may become problematic when calculating statistical power and required sample size. For example, patients entering later trials, such as ACCORD, may be at lesser overall CVD risk than those in previous studies because of the expanded use of such drugs as statins, aspirin, and other platelet inhibitors. Such therapies could influence the biological and clinical responses of study cohorts when BP is lowered. In addition, the incremental benefits of antihypertensive therapies may be more difficult to demonstrate in those at lower CVD risk.

What can we conclude about BP goals from our current state of knowledge? For the general population, impressive benefits of antihypertensive therapies may be more difficult to demonstrate in those at lower CVD risk. For the general population, impressive benefits of antihypertensive therapies may be more difficult to demonstrate in those at lower CVD risk. However, because of the lack of clarity on these issues, I think that the most reasonable approach at present would be to have a general BP goal of ≤140/90 mm Hg in the majority of hypertensive individuals with lower targets to be individualized and based on clinical judgment. Some may consider this approach as overly conservative, but the issues are complex, and mixed messages on BP goals have been emanating from the clinical trials. The results of the Systolic Blood Pressure Intervention Trial, which is in progress, will hopefully help define these issues further. In the interim, with ≥50% of hypertensive persons in the United States still not controlled to <140/90 mm Hg, the greatest benefits of treatment will continue to be in that group.

Disclosures

None.

References

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