Editorial Commentary


Daniel W. Jones, John E. Hall

The recent publication in *Hypertension* of the complete version of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) provides clinicians and scientists with a valuable resource.1 For the first time, the National Heart, Lung, and Blood Institute (NHLBI)-sponsored National High Blood Pressure Education Program Coordinating Committee presented the national blood pressure guidelines in two forms. The express version, published May 2003, was designed as a succinct guide for the busy primary care clinician.2 The complete version provides the scientific basis, rationale, extensive figures and charts, and references to support the JNC 7 recommendations. The complete version will be of value to specialists, academicians, scientists, and clinicians who seek the evidence that bolsters the report’s recommendations.

There was a 6-year hiatus since JNC 6 was published, which is a much longer interval than that of previous reports. This was partially because of the anticipation of the completion of several important new clinical trials and epidemiology studies. The announcement of the formation of the writing committee for JNC 7 closely followed the publication of results of the NHLBI-sponsored Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study.3 JNC 7 streamlined the classification of blood pressure and introduced the term “prehypertension,” which has received much attention. Prehypertension replaces the older terms of “normal” and “high normal,” which suggested complacency and that little action was needed. The term is used to encourage clinicians and patients to take this level of blood pressure more seriously. The recommendation to begin lifestyle therapy at such low blood pressures is based on strong epidemiological data indicating that the risk associated with blood pressure begins at or below these levels.1

This new concept of prehypertension is, indeed, important. However, the clear central theme of the JNC 7 guidelines is the benefit of lowering blood pressure to optimal goal levels. Although the guidelines call for the use of diuretics in most patients, the key emphasis, based on data from the newer clinical trials, is on the fact that lowering blood pressure is more important than the choice of the antihypertensive agent(s).

At least two issues motivated the change in nomenclature for blood pressure classification.4 First, an attempt to simplify the message regarding treatment and control was desired. Despite much effort by the National High Blood Pressure Education Program and others, and despite clear evidence of the benefit of lowering blood pressure, blood pressure management in the United States has not been good.

The second issue is related to the growing prevalence rates of hypertension and poor blood pressure control. Data from the most recent National Health and Nutrition Examination Survey (NHANES), presented in JNC 7 for the first time, show an increasing prevalence of hypertension and continued poor control rates (<35%) for hypertension in the United States. The hope is that simplifying the classification system will encourage clinicians (and patients) to focus on what is most important: lowering blood pressure to optimal levels.

The simpler classification of only two stages in the hypertensive range should also encourage clinicians to control blood pressure to optimal goal levels in all patients with hypertension. The recommendation to consider initiating combination therapy in some patients with stage 2 hypertension (≥160/100 mm Hg) should help dispel the mistaken notion that most patients can be controlled with one agent.5

One additional change related to the classification of blood pressure in this report is the guidance to make decisions on initiation of drug therapy based on blood pressure levels alone, without necessarily considering global cardiovascular risk. The objective is to treat the blood pressure. Although this recommendation has been criticized by some, this key decision to focus on simplicity of approach may be useful to the busy clinician. Many of the changes in JNC 7 from previous versions are intended to make the guidelines as clear and easy to follow as possible.

The two-step publication process for the publication of the JNC 7 report has created interesting circumstances. For several months there has been ongoing dialogue and debate over key issues while the writing committee was completing its work on the complete version. This focused discussion has been possible because of the publication of the essentials of

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1. The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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4. © 2003 American Heart Association, Inc.

5. Hypertension is available at http://www.hypertensionaha.org

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the guidelines several months before completion of the formal comprehensive document. Much of the discussion has centered on the question of how closely and clearly the guidelines reflect evidence from recent clinical trials. It is likely that this opportunity for discussion has led to a stronger comprehensive report.

For several years, the completion of several new major clinical trials was anxiously anticipated. Many of these “new trials” were designed to shed light on the issue of the usefulness of newer antihypertensive classes versus older classes and on potential blood pressure-independent effects of some drugs. Before completion of these new trials, conventional wisdom suggested that older drugs fell short of completely reversing risk from hypertension because of adverse metabolic effects. Many presumed that the newer drugs were superior to older drugs because of the absence of adverse metabolic effects and blood pressure-independent effects that prevented cardiovascular disease. Results from the recent trials did not bear out these predictions. Most of these newer trials were reported recently in the form of a meta-analysis by the Blood Pressure Lowering Treatment Trialists’ Collaboration.

Some general principles from recent trial results incorporated into the JNC 7 guidelines are summarized.

1. Generally, lowering blood pressure to optimal goal levels appears to be more important than specific drug selection. The Trialist Group in their meta-analysis demonstrated a linear relationship between the change in systolic blood pressure and reduction in morbidity and mortality for stroke, coronary heart disease, and cardiovascular disease.

2. At least 5 classes of drugs provide benefit in reducing mortality. Several mortality studies support the claim of benefit for thiazide and thiazide-type diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, β-blockers, and calcium antagonists (both dihydropyridine and non-dihydropyridine). Absent from this group are the α-blockers.

3. The trials testing superiority of different classes of antihypertensive drugs have produced mixed results. In general, however, reduction in cardiovascular morbidity and mortality rates is dependent on the reduction of blood pressure. Most differences between drugs noted in the superiority trials are in secondary endpoints.

4. A drug useful for the management of a co-morbid condition may not necessarily be the best drug to prevent that co-morbidity. Perhaps the biggest surprise in the newer trials was the lack of superiority of ACE inhibitors in preventing congestive heart failure. The trial designs of several of these studies have been criticized. Some of the trial designs precluded the use of diuretics with ACE inhibitors. It has been noted by many that this does not mimic usual clinical practice. However, the superiority of diuretics over ACE inhibitors in preventing congestive heart failure appears to be clinically significant in more than one study. The failure of a particular agent to prevent disease even though it is useful for treatment of cardiovascular disease may seem puzzling. However, in the area of infectious diseases we are accustomed to this phenomenon. In general, one does not look to antibiotics to prevent infectious diseases and does not expect vaccines to effectively treat infectious diseases. Another issue in cardiovascular disease prevention is the difficulty of demarcating the beginning of the disease process and, therefore, the opportunity to prevent rather than treat.

5. The ideal drug(s) for a given patient may depend on selected patient characteristics. The new clinical trials have continued to demonstrate different clinical outcomes of therapies based on age, ethnicity, and co-existing medical conditions. Populations at particular risk for stroke, for example, may benefit more from drugs with better efficacy in stroke prevention.

6. Combination therapy is needed in many (or most) hypertensive patients to achieve optimal blood pressure levels. In many of the newer trials, 2 or 3 drugs were necessary to achieve goal blood pressure in most patients.

JNC 7 appears to effectively incorporate the data from these newer clinical trials into its recommendations for clinicians. The new guidelines are clear and emphasize to the clinician the importance of lowering blood pressure. But some ask, “what should be done about the disparity between the ‘evidence’ from basic and clinical research demonstrating differences among drug classes on blood vessel reactivity, inflammation, and other key factors that may influence development and progression of cardiovascular disease?” Indeed, why did the new clinical trials fail to demonstrate blood pressure-independent effects suggested by some basic and clinical studies?

Several possible explanations exist. One possibility is that there are actually no clinically relevant beneficial effects of any antihypertensive agents that are independent of reductions in blood pressure. Another possibility is that clinical trials, as they are currently designed, do not have the ability to demonstrate these blood pressure-independent effects. For reasons of economy and efficiency, almost all mortality trials select participants at higher risk by age, risk factors, or known cardiovascular disease. It is thought that selection of these higher-risk participants enables the drug effects to be demonstrated sooner. However, one obvious limitation of these trials in demonstrating blood pressure-independent effects is the presence of abnormal blood vessels in almost all the participants. It is also possible that many of the clinical trials are not performed long enough to permit more subtle influences on cardiovascular disease morbidity and mortality to be unmasked.

Overcoming these limitations will not be easy. Vascular disease begins in most at a very early age. Mortality trials with very young participants are likely never to be financially feasible. Perhaps the development of reliable intermediary markers of vascular injury will one day answer the question of whether blood pressure-independent effects of antihypertensive agents contribute to beneficial clinical outcomes. Studies in populations at lower risk in which studies can be performed more efficiently may help. Special attention to the accurate assessment of blood pressure and its various components, including blood pressure variability and pulse pressure, for example, will also be necessary to unravel this complex situation.
In the meantime, clinicians should focus on ensuring that their patients’ blood pressure is controlled to optimal levels, as recommended by these new JNC 7 guidelines. While we wait even longer to understand whether blood pressure-independent effects of antihypertensive agents are clinically relevant, we can apply the evidence that is certain: lowering blood pressure is useful in preventing cardiovascular disease.

References
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