

Major Clinical Trials of Hypertension What Should Be Done Next?

The National Heart, Lung, and Blood Institute Working Group on Future Directions in Hypertension Treatment Trials*

Abstract—The National Heart, Lung, and Blood Institute assembled an ad hoc working group to evaluate opportunities for new major clinical trials in the field of hypertension. The mandate of this working group was to consider the possible designs of major randomized clinical trials focused on clinical outcomes that might merit significant investment by the National Institutes of Health. The group concluded that the ideal pragmatic clinical trial would have a factorial design and include a population at elevated risk of cardiovascular disease events. Subjects would be randomized to a target of systolic blood pressure <130 versus 130 to 150 mm Hg for adequate separation of means. Initial treatment with thiazide diuretic would be followed by randomization to angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β -blocker, calcium channel blocker, or aldosterone antagonist. A third drug could be added according to a protocol. DNA, proteins, and metabolites would be collected in a sample adequate to assess differential impact of treatment on outcome as a function of genotype, proteomic, and metabolomic expression. Subclinical markers and images would also be measured in a sample of patients to develop evidence of ability to predict ultimate effect on clinical outcomes. This ideal trial would take place within a network, funded for at least a decade, aimed at connecting primary care providers with hypertension specialists. Within the network, substudies or independent studies would be coordinated to develop a continuously improving base of knowledge about the effective delivery of hypertension care. (*Hypertension*. 2005;46:1-6.)

Key Words: clinical trials ■ drug therapy

New knowledge of prevention and treatment for cardiovascular disease, coupled with a better understanding of implementation strategies for therapy, has reduced its age-specific mortality and morbidity rates.¹ The diagnosis and treatment of hypertension have been a significant part of this success story. Nevertheless, we have fallen far short of our potential to improve longevity and functionality by more effectively managing hypertension.

This report emanates from an ad hoc working group assembled by the National Heart, Lung, and Blood Institute (NHLBI) to evaluate opportunities for new major clinical trials in the field of hypertension that could improve the public health. The mandate of this working group was to consider possible designs for major randomized clinical trials focused on clinical outcomes that might merit significant investment by NHLBI of the National Institutes of Health (NIH).

Trial Concepts

The planning committee for the working group concluded that major clinical trials funded at least in part by the NIH are needed, and that these trials should measure clinical outcomes while informing mechanisms through substudies. Such stud-

ies could be designed to answer questions in 4 content areas. First, what should constitute the criteria for level of blood pressure (BP) that should drive therapy (“how low to start treatment/how low to go”)? Second, which specific regimens should be used? Third, has the time come to orient trials around genetic differences in drug response or subclinical markers of disease? Fourth, what hypertension control strategies should be implemented at the community level? Through an informal process, the committee arrived at a set of recommendations for consideration by NHLBI and the broader community.

Threshold for Treatment

The threshold theme has 2 main variations. First, among people newly diagnosed with hypertension, at what level of BP or estimated cardiovascular risk should pharmacological treatment be initiated (ie, how low to start)? Second, among patients in whom the decision has been made to treat, should there be a BP target or goal level, and if so, what should that target be (ie, how low to go)? Although guidelines have long made assumptions about these questions, the definitive evidence base is lacking, and clinicians have not fully accepted the current Joint National Committee on Prevention, Detec-

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tion, Evaluation, and Treatment of High Blood Pressure (JNC7) guideline recommendation of treating stage 1 systolic hypertension or treating to achieve a goal systolic BP <140 mm Hg.^{2,3} These questions have great public health significance because persons with systolic BP in the prehypertension and stage 1 hypertension range represent a large proportion of the general population and of BP-related morbidity/mortality.

A trial testing the optimal threshold for treatment would evaluate the effect on cardiovascular events of lowering systolic BP from untreated levels of 130 to 149 mm Hg or 130 to 159 mm Hg, or when the treated systolic BP is \geq 140 mm Hg. The design might involve treatment to stated goals using a wide variety of open-label antihypertensive drugs, as in the NHLBI-sponsored Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.⁴ Alternatively, it could use a limited titration with a masked design, as used in the Systolic Hypertension in the Elderly Program (SHEP).⁵ Finally, allocation to a fixed 2- or 3-drug combination versus placebo (with individual drugs added to avoid unacceptably high BP levels) with no specific BP goal could be considered. A potential limitation of studying different BP treatment goals is the apparent difficulty of achieving a separation between treatment groups (see the Hypertension Optimal Treatment [HOT] trial,⁶ the African American Study of Kidney disease and hypertension [AASK],⁷ the Modification of Diet in Renal Disease [MDRD] study,⁸ and the United Kingdom Prospective Diabetes Study [UKPDS]⁹); in studies in which BP is unblinded, practitioners seem to treat more aggressively in the control group compared with results in clinical practice, although the AASK and MDRD trials were able to achieve good separation in a special population with moderate renal dysfunction.

The risk level of the population studied provokes interesting considerations. From the perspective of proof of principle, it would be ideal to have a higher-risk population to increase the power of the study to detect outcome differences. Participants could be selected to have increased risk of events by virtue of criteria such as those used in the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) study,¹⁰ although patients with diabetes should be excluded, because this threshold and goal issue in people with diabetes is being tested in the ACCORD trial (systolic BP goal <120 mm Hg versus <140 mm Hg in diabetic patients with systolic BP >130 mm Hg).⁴ Alternatively, or in addition to oversampling on the basis of global cardiovascular disease risk assessment, markers of chronic kidney disease (eg, microalbuminuria or reduced glomerular filtration rate [<60 mL/min per 1.73 m² or metabolic syndrome]) could be used.^{11,12} However, there is also a compelling need to understand the impact of long-term treatment on people at low risk to understand the balance of risk and benefit across the broadly defined population at risk.

Drug Comparisons

The second theme was the potential need for trials to determine optimal treatment regimens for a broadly representative patient population. A wide variety of behavioral and pharmacological interventions could be contemplated. How-

ever, to simplify the discussion, the term "treatment regimens" is used here to indicate antihypertensive therapy intended for use in adults with primary ("essential") hypertension.

The background for considering drug regimens must account for the recent NHLBI sponsorship of ALLHAT and the summary of available evidence in JNC7. ALLHAT focused on selection of first-step drugs and was interpreted by the majority of participating investigators as showing the superiority of thiazide-type diuretics for reducing the risk of \geq 1 major cardiovascular event compared with an angiotensin-converting enzyme (ACE) inhibitor, a calcium blocker, and an α -blocker; the thiazide-type diuretic also was unsurpassed with regard to any cardiovascular or chronic kidney disease outcome, tolerability, and BP control. In addition, in the United States, these are the least expensive drugs by a considerable margin, although now that β -blockers and ACE inhibitors are generic, they are much less expensive than branded drugs.

The ALLHAT findings, along with aggregate results of other trials, influenced the JNC7 to recommend that diuretics should be first-step treatment for most hypertensive patients. Other ALLHAT findings indicated that only 26% of patients had their BP controlled on just 1 drug, at least for the hypertensive patients studied in this trial: older patients with predominantly systolic hypertension, with increased representation of blacks, diabetics, and those with diagnosed cardiovascular disease. This observation was reflected in the JNC7 recommendation to initiate treatment with 2 drugs (along with lifestyle advice) in those whose pretreatment levels were >20 mm Hg above the systolic goal or 10 mm Hg above the diastolic goal, although that particular strategy has not been tested specifically.

Thus, major post-ALLHAT issues relate to particular drug regimens and tend to center on the question of what class of drugs should be favored for adding to diuretic monotherapy when needed. There is also a question of what strategy for implementing multidrug regimens leads to the best medical and economic outcomes: a stepped-care approach or initially combined regimens. Because 2 classes of drugs (angiotensin type 1 receptor blockers [ARBs] and aldosterone antagonists) were not candidates for inclusion in ALLHAT (because they were not widely used when the study was designed in the early 1990s), there is special interest in their possible role.

One possible approach would be to revisit an "ALLHAT-like" question of first-step drug choice. However, given the cost advantages and convenience of basing hypertension strategy on thiazide diuretics, comparing a new, more expensive antihypertensive drug would be a reasonable target for the pharmaceutical industry but does not seem appropriate for NHLBI funding. In addition, the VALUE trial reported that the ARB valsartan was not superior to amlodipine in a head-to-head trial, with hydrochlorothiazide added as a second step if needed.¹³ The trial raised the possibility that drugs may differ in BP response (here, amlodipine was superior) and in effect on clinical events per unit of BP drop (here, valsartan may have been superior).¹⁴

Several approaches may be taken to define the step-2 drug that should be added to a thiazide-type diuretic. One design

would focus on a particular biological effect, such as the differential effects of ACE inhibitors and ARBs on stroke.^{15,16} Mechanistic considerations, supported by animal experimentation and interpretations of relevant trials, suggest that ARBs increase angiotensin II levels and stimulate angiotensin type 2 receptors, producing an anti-ischemic effect in the brain.¹⁷ However, the focus on stroke as the outcome, and on populations at especially high risk of stroke and below-average risk of coronary events, would limit applicability and generalizability. Enriching the study sample for stroke risk based on older age, higher systolic BP, black race, or left ventricular hypertrophy could be justified. It might be possible to examine this question in some fashion by maintaining separate ACE inhibitor and ARB arms.

Other approaches would specifically compare each of 2, 3, or 4 drugs as add-on therapy to a diuretic. Each of these designs would enroll a population at high risk of cardiovascular disease generally, and all major cardiovascular events would count in the primary end point. Choices for comparison would include β -blockers, calcium channel blockers, ARBs, ACE inhibitors, and aldosterone receptor antagonists.

A major issue in designing such a trial would be the choice of agent within the class. Recent studies have cast doubt on the “class effect,”^{18–20} and specifically in the field of hypertension, uncertainty remains about the degree to which benefits of specific drugs might depend on pleiotropic properties in addition to BP lowering. Interesting issues include whether ACE inhibitors and ARBs should be the subject of separate randomly allocated arms, or whether a renin-angiotensin system blockade arm might be initiated with an ACE inhibitor, with ARBs reserved for patients with ACE inhibitor intolerance. Recent heart failure trials demonstrated that significant differences in outcomes can be produced by varying the type of β -blocker and dosing regimen.^{21,22} An intriguing suggestion would be to subrandomize to either hydrochlorothiazide or chlorthalidone in the thiazide base for the trial because ALLHAT used chlorthalidone, which is not the most commonly used thiazide diuretic.

Recent evidence supports the inclusion of a high-risk group defined by chronic kidney disease or diabetes, especially because ACE inhibitors and ARBs appear to have particular benefits in these diseases and have been recommended in recent clinical practice guidelines.^{23,24} This would enable the use not only of cardiovascular events but also chronic kidney disease progression as part of the primary end point. Although focusing solely on this population at risk of both adverse outcomes has considerable attraction from the point of view of density of the burden of disease, such a trial would exclude the majority of people with hypertension. Furthermore, controversy continues over the magnitude of change in glomerular filtration rate or albuminuria that would be clinically relevant to be included in the primary outcome.

Another topic of great interest concerns the issue of how to initiate drug treatment. The JNC7 and the European Society of Hypertension guidelines disagree,²⁵ with JNC7 advocating a diuretic-based stepped care and the European Society of Hypertension preferring “clinician choice” among the commonly accepted first-step drug classes. A trial comparing these strategies would create so much overlap in regimens

that differences in clinical outcomes would be unlikely, and if clinical outcomes differed, the explanation would almost certainly lie in differential time to control of BP; this end point can be measured with a much smaller sample size.

Another important question is whether traditional stepped care, with up to 3 steps specified and titrated to goal, is superior to initial treatment with combination therapy, as advocated in JNC7. Although this could be conducted as a clinical events trial, the outcomes of BP control and cost of care in a relatively small sample could provide much of the information needed to make rational clinical decisions. The recently initiated HORIZON trial will provide significant insight by comparing the combination of an ACE inhibitor and calcium channel blocker with stepped care.

A final issue is how to better manage hypertension. Multiple novel approaches to delivery could be compared with traditional physician-led management of high-risk hypertensives; an example of a novel intervention would be nurse-centered care, with both arms having access to the same guidelines. Although this could be conducted as a cardiovascular events trial, most participants felt that it would be more appropriate to evaluate the impact of alternate modes of care on BP control and costs, assuming that differential effects on BP control and greater efficiency would translate into clinical benefit, whereas a minority of participants felt that documentation of improved outcomes in studies of health care delivery is imperative.

Considering all of these proposals, in terms of a trial requiring a substantial national investment, among the drug comparison options, the choice of step-2 drug fits most closely with priorities and likely impact, with a preference for the most generalizable and broadest design, which could incorporate secondary questions about the strata with stroke-related or chronic kidney disease-related special characteristics. There was also strong endorsement for trials of health services delivery systems, along the lines of 2 previously released NHLBI requests for applications (“Trials Assessing Innovative Strategies to Improve Clinical Practice through Guidelines in Heart, Lung, and Blood Diseases” and “Interventions to Improve Hypertension Control Rates in African Americans”).

Global Risk

Two concepts could be considered addressing the issue of reducing “global” (multifactorial) cardiovascular disease risk. The first recognizes that risk in persons with hypertension is related not only to BP, but that other factors contributing to global risk should be considered in determining the need for pharmacological and nonpharmacological intervention.

An increasingly discussed and controversial approach to the global risk issue is the “polypill” concept, in which multiple therapies attacking different biological targets would be incorporated into a single pill.²⁶ In this approach, patients with a threshold level of global cardiovascular risk would be randomized to either usual care or a pill containing aspirin, statins, ACE inhibitors, a low-dose diuretic, and perhaps vitamins. Concerns about this approach center on the large potential for crossover in this population and the difficulty of determining which part of the pill would be responsible for

any observed benefit. Additionally, multiple logistical issues exist with the development of a polypill, including patent and formulation issues that would be cumbersome in an NIH-sponsored study.

The second concept would use a multifactorial approach of identifying a target population for a trial, which might be based on the metabolic syndrome, according to some definition that identifies a group without any single risk factor at a level that mandates treatment for everyone. In such a design, individuals with metabolic syndrome might be randomly allocated to a strategy of blood pressure lowering, even if the baseline BP was within the JNC7-defined normal or prehypertensive range. The industry-sponsored Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial is using a similar design with an ARB and a postprandial insulin secretagogue in patients enrolled through screening to identify insulin resistance.²⁷ Alternatively, computer-based global cardiovascular disease risk assessment could identify subjects eligible for inclusion in a hypertension treatment trial as the basis of a predefined threshold (eg, 2% per year risk for a major cardiovascular event). This would reduce the cost and duration of a clinical trial by reducing the inclusion of low-risk patients who will contribute few end points. Thus, global risk assessment, which is an integral component of Adult Treatment Panel III, can improve the efficiency of a large clinical trial by reducing sample size or reducing follow-up duration.

Dietary Intervention

There is considerable interest in examining the impact of macronutrient variations in diet on BP and its related outcomes. Americans and their physicians are troubled and confused by claims made by diets with highly variable macronutrient content. The NHLBI has made significant progress with the development of the DASH dietary pattern,²⁸ which results in lower BP and may assist in weight control. The PREMIER trial provided evidence that the DASH dietary pattern, when combined with drug therapy, was superior to advice only and similar to drug therapy only in reducing BP, but it is under further study.²⁹ The consensus of the working group was that dietary interventions needed additional work on pragmatic delivery aspects in smaller populations before being evaluated in a broad, outcome-based trial.

Delivery of Hypertension Care

Studies evaluating the delivery of care for hypertension have generated considerable enthusiasm. Multiple such studies are under way, many funded by the NIH, but numerous questions remain to be answered, including issues concerning management prompts, feedback on performance based on groups of patients or the individual patient level, and the use of financial incentives and disincentives. In most cases, these studies of how therapy should be delivered would be smaller by their nature than trials aimed at determining which therapies should be recommended. Furthermore, concern exists that current mechanisms of funding such trials are inadequate and that coordination among the efforts is insufficient to produce an iterative improvement in the national effort to deliver therapy for hypertension. Ideally, compo-

nents of proven successful methods could be combined over time in a coordinated manner rather than through isolated experiments in different practice settings. Perhaps at critical junctures, these healthcare delivery interventions derived from iterative steps could be tested for their impact on health outcomes.

The Possibility of Networks

The enormity of the challenge of hypertension demands a coordinated approach if progress in improving the public health is to be accelerated. In addition to the "landmark" clinical trials, the aggregated evidence from smaller pragmatic trials, mechanistic trials, research on the delivery of health care, and economic and policy analyses must be woven into a coherent plan for patients, providers, and payers. Although the National High Blood Pressure Education Program Coordinating Committee provides the mechanism for the distillation of this effort, a more coordinated infrastructure could significantly accelerate the process. Whereas the proposed primary trial would substantially affect treatment, many smaller projects would make significant contributions to this base of evidence.

Perhaps more than any other factor, the need to translate the findings into practice seems to be underserved. Despite all of the available knowledge about the need to control BP with behavioral and pharmacological therapies, a large proportion of Americans remain undertreated, and the research in this arena has not adequately influenced the funding mechanisms that would allow changes in the structure and process of care delivery for hypertension.

The NIH Roadmap process, which was initiated to establish a plan for new directions for the institutes, identified "reengineering the clinical research infrastructure" as a key part of the plan.³⁰ Built into this plan is a goal of developing interoperable networks that would bring together biological and epidemiological specialists with providers, patients, families, and the medical products industry. Ultimately, through a "network of networks" linked through modern information technology, common diseases such as hypertension could be studied more rapidly and effectively from a variety of angles via sharing of data and derivative practices. However, many obstacles exist. For example, constructing these networks could be impeded by the current Health Insurance Portability and Accountability Act regulations, which have impaired the ability to share information needed to understand the epidemiology of diseases.^{31,32}

A network linking specialists in hypertension and related fields (basic researchers, behavioral scientists, nutritionists, cardiovascular practitioners, and epidemiologists) with primary care physicians, nurses, and the public health delivery system could have an impact well beyond the value of any single study. Patients and their families could also join this network to provide the perspective of those affected by hypertension. To the extent that the network was linked by a common informatics platform, findings from studies could be embedded into a common framework for advances in understanding efficacious therapies and practices and effective delivery of these therapies.

Principal Recommendations

The ideal pragmatic clinical trial would have a factorial design including the following elements.

1. Inclusion of a population at elevated risk of cardiovascular disease events with untreated systolic BP between 130 and 159 mm Hg or treated systolic BP between 140 and 159 mm Hg.
2. Randomization to a target of systolic BP <130 mm Hg versus 130 to 150 mm Hg for adequate separation of means.
3. Initial treatment with thiazide diuretic.
4. Subsequent randomization to ACE inhibitor or ARB, β -blocker, calcium channel blocker, or aldosterone antagonist; alternately, begin with 2 drugs (thiazide plus a randomly assigned accompanying drug, especially for the intensive BP control arm). The less-intensive arm could also receive randomization of the second drug.
5. Addition of a third drug according to a protocol.
6. Collection of DNA, proteins, and metabolites in an adequate sample to assess differential impact of treatment on outcome as a function of genotype, proteomic, and metabolomic expression.
7. Measurement of subclinical markers and images in a sample of patients to develop evidence of ability to predict ultimate effect on clinical outcomes.

This trial would take place within a network, funded for at least a decade, aimed at connecting primary care providers with specialists in the biology and therapeutics of hypertension. The network would define common nomenclature and data standards for recording information in the practice and research of hypertension treatment. The informatics infrastructure would include Internet-based data collection and study management. The same Internet system would be used to disseminate study findings, guidelines, and expert opinion to researchers and clinicians, and ultimately to patients.

Within the network, substudies or independent studies would be coordinated to develop a continuously improving base of knowledge about the effective delivery of hypertension care. These studies would provide knowledge about the best way to use existing diagnostic and therapeutic technologies to reduce risk in people with hypertension.

The efficiency of the network for doing research would attract supplemental industry funding to offset costs of the primary government work and to advance new therapies in trials that should not be funded primarily by the government.

Core elements of the network would include regional coordinating centers committed to sharing data and analyses, interoperable data sharing with other cardiovascular and noncardiovascular networks, and distributed image and ECG collection to regional core labs.

Appendix

Workshop Participants

The NHLBI Working Group on Future Directions in Hypertension Treatment Trials

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