Clinical Trials for Hypertension
Expectations Fulfilled and Unfulfilled

Norman M. Kaplan

Current projections predict that, by the year 2025, 29.2% of the adult population worldwide will have hypertension, a total of 1.56 billion people. Such figures are hard to visualize, as are the billions of dollars being spent on the Iraqi invasion. Enough to say that hypertension is now and has long been the most common risk for the most common causes of death in all but the most primitive populations in the world.

Despite such knowledge, the disease is poorly treated in almost all countries including the United States despite the increasing availability of effective and innocuous medications. A detailed analysis of the reasons responsible for our failure to control most hypertension is not the aim of this Hypertension Highlight, but rather the place of randomized, controlled trials (RCTs) in coming to where we are and where we ought to be.

The Value of RCTs

Proof of the life-saving value of treating hypertension has come almost exclusively from RCTs. Initially, the study of only small numbers of severely hypertensive patients was needed to show benefit in only a short time; over the years, as progressively milder hypertension was tested, the trials have had to be both larger and longer.

As of late 2006, the value of treating levels of blood pressure (BP) as low as 160 mm Hg systolic and 90 mm Hg diastolic in the overall population has been proved. However, this proof has almost exclusively come from RCTs of patients over age 55 years and, in most trials, with relatively high risk status. As succinctly stated by Williams, "Younger people do not usually have clinical events and trials are done in those that do."

Nonetheless, most hypertensive subjects are over age 55 years, and most have other risk factors, so the evidence now available clearly has wide applicability. However, we need much more evidence on the value of treating the younger and still low-risk population in order “to prevent the evolution of disease, rather than struggle to treat its consequences.”

The proof of principle that treatment of low-risk patients will at least slow the evolution of the disease has been shown. Now the harder-to-accomplish proof of the ability to prevent hard end points in such patients must be pursued.

Comparative Trials

Once RCTs clearly showed that drug treatment was better than placebo, around 1990, almost all of the subsequent trials have compared one drug against another, partly to document scientifically the greater benefits of one against another but largely to provide pharmaceutical marketers with grist for their mills for profit. One small piece of evidence that money comes before and increasingly drives science is the number of original articles published in indexed journals from a drug company-sponsored trial, for example, the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study, versus the number from a government-sponsored trials, for example, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT): 105 for the LIFE Study and 24 for ALLHAT. To be sure, the LIFE Study measured more hard end points, but ALLHAT surely was more clinically valuable.

Problems With Comparative Trials

Whatever the motivations behind them, hundreds of variously believable comparative trials have been published over the past 15 years. Even among those with the highest scientific merit, 2 problems have become evident: first, none that were putatively designed to compare 1 drug against another drug have been “pure”; in many, the majority of patients in each category ended up on ≥2 drugs to provide predefined “safe” BP. Second, almost none accomplished equality of BP reduction. Therefore, almost all of the additional benefit claimed by the investigators and loudly touted by the pharmaceutical sponsors can be attributed to a greater reduction in BP by one drug (or drug regimen) over the other. Perhaps the most obvious example in recent times is the Anglo-Scandinavian Cardiac Outcomes Trials–Blood Pressure Lowering Arm (ASCOT-BPLA). The calcium channel blocker-based regimen was superior to the β-blocker–based regimen for most (but not the primary) end points, but it also lowered BP significantly more.

Another comparative trial, the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) Trial, had unequal BP reductions over the first 6 months, likely responsible for a more favorable benefit of the comparator regimen, based on a calcium channel blocker, to the sponsor’s regimen, based on...
an angiotensin receptor blocker (ARB). To the investigators’ credit, no misleading claims about the outcomes were made. They “strongly suggested that an unequal BP reduction in the 2 study groups in the early phase of the trial confounded comparison for cause-specific outcomes.” Likely, at least in part, to assure the sponsor’s pain, they performed a posthoc analysis of the outcomes of the 46% of the total study population who remained on monotherapy, either valsartan or amlodipine, for the first 6 months. Fortunately, the 2 groups were comparable for initial BP levels and for subsequent BP reduction and control rates, with no difference in BP levels during the first 6 months. These patients, as expected, had milder hypertension, both as to levels of BP and as to a number of other risk factors. The rates of myocardial infarction, which were lower with amlodipine-based therapy in the entire trial, were equal in the 2 monotherapy groups.

Along with much more data, these findings further confirm the dictum: almost, if not all, of the differences in outcomes between different drugs can be attributed to differences in BP reduction. Furthermore, they support an even more fundamental dictum: the benefits of all antihypertensive drugs largely reflect their reduction in BP.

**Exceptions to the Dicta**

There may be exceptions to these dicta. Two are likely. First, the dihydropyridine CCBs may protect better against stroke but less well than angiotensin-converting enzyme inhibitors against heart failure and heart attacks with equal degrees of BP reduction. Second, renin inhibition by either angiotensin-converting enzyme inhibitors or ARBs seems to prevent or delay the new onset of diabetes better than diuretics or, to an even greater extent, β-blockers. The potentiation of the appearance of diabetes by β-blockers is likely involved with their failure to protect, as well as other classes, against stroke and no better than other classes against heart attack. The potentiation of diabetes by diuretics is likely a reflection of their potassium wasting effect and may be overcome with lower doses of diuretic or either extra potassium or concomitant renin inhibition.

On the other hand, the claims of exaggerated exacerbation of heart attack by CCBs, based on incorrectly interpreted observational data, have been convincingly refuted by multiple RCTs. Similarly, multiple claims of superiority of angiotensin-converting enzyme inhibitors and ARBs for renoprotection seem to have been largely negated by comparisons against other classes of antihypertensive drugs, despite an appealing experimental basis for the claims.

**Continuing Confusions Over RCTs**

Despite, or perhaps because of, multiple meta-analyses of the results of many RCTs, confusions persist over the relative values of different drug classes. At this time, perhaps the major area of confusion is over the claim that ARBs do not provide protection against myocardial infarction, rather, that they increase the risk when compared with other classes. Experts presumably examining the same data come to completely opposite conclusions: some say they do and others say that they do not.

A great part of the confusion over RCT data relates to the lack of head-to-head comparisons of individual drugs from the same or different classes that are both large and long enough to provide outcome data and that importantly accomplish equal degrees of BP reduction. The only 1 that meets these criteria that is currently available is the LIFE Study, but the comparator drug to the ARB was a β-blocker, a class of drugs now known to be less protective than other classes.

**What Should the Future Hold**

RCTs have been of great value for identifying effective therapies and saving both lives and money. Nonetheless, in the hypertension area, RCTs have not provided the clear evidence needed to most effectively control the disease. The future needs include the objectives described below.

First, we must discourage single drug company–sponsored short (usually 4- to 12-week comparative) trials of BP efficacy involving small numbers of patients. By the definition of Food and Drug Administration approval, all of the drugs are almost identical in overall efficacy. Such trials serve no purpose except for marketing.

Second, we must perform proper RCTs on patients who are young, at relatively low overall risk, and, most importantly, still prehypertensive. Such trials require lots of money, best provided by federal governments, but more practically (but unlikely) to be provided by pooled funds from all pharmaceutical marketers, logically based on their current financial share of the antihypertensive market. At the same time, RCTs should address therapy of those over age 80 years who will make up an increasingly larger part of the hypertensive population. The ongoing Hypertension in the Very Elderly Trial (HYVET) has shown disturbing preliminary results and more such RCTs should examine this population.

Third, we must reform the Food and Drug Administration’s process of drug approval. As delineated by Wood, these reforms are best based on granting extended periods of exclusivity for marketing of drugs that are new and innovative rather than “me too,” that have proved long-term safety, and that have fulfilled postmarketing commitments. In addition, more limited periods of exclusivity should be provided for the performance and use of surrogate and biologic markers that can be converted to clinically meaningful end points.

Fourth, we must protect physicians and their assistants from the lures of pharmaceutical marketers. The British have a rational mechanism in the National Institute for Clinical Excellence to assess whether and how new drugs are to be used in the National Health Service. Those drugs not approved are not paid for. On the other hand, pharmaceutical companies should not be denied reasonable access to healthcare professionals.

Fifth, we must accelerate the incorporation of data from RCTs into clinical practice to overcome physicians’ inertia to adequately control hypertension, assess their performance in a nonintrusive manner (mainly by monitoring of computerized records), and by paying them by the effectiveness of their management. Once again, the British are well ahead of the United States in paying for performance.

The British National Health Service provides comprehensive health care to all “allocated according to need, as defined by medical professionals, not according to the capacity to...
pay.”25 As described by Klein,25 the National Health Service is being transformed “to exploit the dynamics of the market in the emphasis on patients’ choice, payment by results, and competition.” Imagine what we in the United States could do if we continued to spend 2 times the amount of money per person as the British but used their rational system of payment and delivery of care.

Sixth, we must use home BP monitoring to assess the adequacy of therapy and to improve patient adherence to lifetime medication. All of the future RCTs and individual physician’s performance should be based on home BP monitoring. Objections to the routine use of home monitoring because it is “a time-consuming procedure”26 fail to recognize the critical need for adequate but not excessive treatment, the inadequacy of office-only BP monitoring, and the frequent long-term variability of BP that should mandate changes in therapy. Diabetic subjects, individually and in trials, do home glucose monitoring as often as 4 times a day, and adjust their insulin dosage accordingly. Hypertensive subjects surely can monitor their BP and thereby obtain the better control that many diabetics have achieved.

Last, we must provide and extensively disseminate unbiased information about RCT results. With 1500 new articles published and 55 new trials completed each day, there is no way for health professionals “to sift, digest, and act on new research likely to benefit their patients.”27 With multimedia that can influence public acceptance of even trivial information, it must be possible to provide more effective advice to healthcare providers and their patients.

All in all, RCTs have been useful. They can be made much more useful as an integral part of a revitalized American healthcare system.

Disclosures

N.M.K. has received speakers bureau fees from: Pfizer for at or more than $10,000; Boehringer-Ingelheim for at or more than $10,000; and from Key Pharma for less than $10,000. N.M.K. has received honoraria from Pfizer for at or more than $10,000; Boehringer-Ingelheim for at or more than $10,000; Boehringer-Ingelheim for at or more than $10,000; and from Key Pharma for less than $10,000. N.M.K. is on the consultant/advisory board of Novartis and receives less than $10,000.

References

Clinical Trials for Hypertension: Expectations Fulfilled and Unfulfilled
Norman M. Kaplan

Hypertension. 2007;49:257-259; originally published online December 4, 2006;
doi: 10.1161/01.HYP.0000253034.35704.92
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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/49/2/257

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/