Why We Can’t Translate Clinical Trials Into Clinical Practice in Hypertension

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How Ought We Make Medical Decisions, Or Why Is Knowing More About Our Patients Better Than Knowing Less?
The Problem: The “Top–Down” Approach to the Evaluation and Therapy of Hypertension

We live in an era, like many in the recent past, where new approaches to the diagnosis and treatment of medical conditions have greatly altered our daily activities as physicians. However, the increasingly used epidemiologic approach to medicine, based on the assessment of the average behavior of large populations, is often used as a substitute for the information previously available to the physician, rather than as an aid to achieving a broader perspective on it. Indeed, the results of epidemiologic-based observational and interventional studies (ie, “large” clinical trials) are today not only considered a valid basis for therapeutic decisions, but claim to be the most valid, or even the only valid basis on which individual patients should be treated. What has resulted is the phenomenon of “guidelines” derived from “expert” panels. These “consensus” statements (the oft-quoted description of ‘a camel as a horse made by a committee’ seems apt) are increasingly “taught” to or rather imposed on the unsuspecting clinician, whose role has increasingly been relegated to complying with these guidelines. Accordingly, the physician’s attempt to make different therapeutic decisions for different individual patients on the basis of physiologic, biochemical, or other individual characteristics measured in his or her patients is actively discouraged and may not even be allowed in many institutional, governmental, health maintenance organization (HMO), or other “guideline”-based clinical settings.

There are a lot of things wrong with this top–down, ex cathedra approach to dictating care for each individual based on group-averaged results and often weak demographic associations obtained from large clinical trials. It appears to follow the general trend in society at large to consider people as members of groups in the aggregate, rather than as individuals. Accordingly, the focus of epidemiologic physicians on people in the aggregate, as a mass, rather than as individuals, has aesthetic appeal in public health, media, and government circles, who already have adopted this approach, and who magnify its role in medicine. At the same time, physicians who actually take care of patients may be intimidated by their own lack of mathematical or statistical training, and so accept the pronouncements derived from epidemiologic studies even when they diverge from their own, often much deeper clinical experience.

These and other factors severely limit the scientific and clinical applicability of large trial, epidemiologic-based results to the day-to-day practice of medicine. To discuss all of these factors in their totality would require a much longer analysis. However, the implications of these issues for clinical decision making have not been adequately recognized and critiqued by clinicians. It seems reasonable, therefore, especially in light of continuing public dissemination of increasingly strident and seemingly “definitive” conclusions derived from large clinical trials, that certain limitations of this approach be openly aired to the practicing physician and educated lay public.

The Language of Large Intervention Trials—An Intellectual Sleight-of-Hand

The practicing physician may naively thinks that the results of large clinical drug intervention trials in hypertension tell him or her what to expect if the patient is placed on and continues to be treated with a particular drug over a period of time. What the results actually reflect, however, is almost entirely different. In fact, none (that’s right, none) of the large clinical trials claiming to test the efficacy of one drug versus another in hypertension have ever directly done so. What is reported to the physician, health or policy administrators, public officials, or media personnel are group labels (eg, drug X, drug Y). The group


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designation using the name of a single drug or drug class merely represents what drug was allocated initially to subjects randomized to that group, and masks all of the other drugs that may be concomitantly added both in the study protocol itself, or even other drugs used by each subject’s other nonresearch physicians anytime during the course of the trial. It does not even mean that the subject was actually on drug X or Y for more than a single dose during the years involved in most trials. This consideration goes much deeper than the more technical controversies about an “intention-to-treat” analyses, and there are, of course, valid statistical reasons for performing and analyzing the data from large clinical trials in this fashion. The point is, however, that the results just do not mean what physicians, to say nothing of the lay public, press, and patients themselves, are told that they mean.

A second issue results from comparing the data provided by the epidemiologic study with the conclusions drawn either by the authors of the study, or subsequently by other investigators claiming that as a result of the data, the physician should somehow alter his or her clinical practice. In traditional science, arbitrary conclusions do not warrant broad acceptance. If more than one conclusion, or even opposite conclusions, can be drawn from the same data, then the public, “official” conclusions, as well as the advice for medical practice that often follow, are rightly viewed as arbitrary, and have the potential to distort and discredit medical science. Unfortunately, examples of this are common, especially among the epidemiology of drugs in hypertension.

The results of the Hypertension Optimal Treatment (HOT) randomized trial were used to “mandate” lower goal blood pressures (BP) in hypertension, both systolic and diastolic, compared to levels previously recommended for the “average” patient with hypertension. Given the distribution of BP achieved on therapy in this study, pressures at which the “minimum” number of clinical outcome events occurred were quoted as new desirable target pressures to achieve. Up to that time, however, to say that BP should be lowered below some value, it was necessary to show that a statistically significant difference in outcomes occurred above versus below that BP value. The HOT data showed, however (with the exception of the diabetic group), almost exactly the opposite of the publicly pronounced conclusions “based” on this data. No significant differences in cardiovascular events were observed over a wide range of achieved systolic (130 to 150), or even 160 mm Hg) and diastolic pressures (80 to 90 mm Hg). Nowhere is the “desirable” BP goal associated with any statistically significant lower incidence of anything compared to BP above or below it. One wonders whether the data were reported in this manner specifically because no significant differences were actually observed. Regardless, the widely disseminated conclusions about the validity of more stringent goal BP persist, unproven by the very data on which they claim to be based. These conclusions may indeed be correct—it is just that what the physician and the public were told the HOT trial meant was not what the HOT trial showed.

More recently, at least one of the authors of the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), an editorial accompanying its publication, and The New York Times all announced publicly that diuretics should be the drug of first choice for all hypertensives, a conclusion they claimed was based on data from that study. The lay public and most physicians probably thought that is what the ALLHAT study actually demonstrated. Although an accompanying editorial in this issue analyzes this trial in more detail, other reasonable medical conclusions to be drawn from the same data include, 1) converting enzyme inhibitors should be the antihypertensive drug of first choice, as equivalent effects on the primary end point of the study were achieved in this drug group with even less BP control than that achieved with the “diuretic” group; 2) diuretics should not be the first drug choice in hypertension, as the increased metabolic side effects reported in ALLHAT for diuretics compared to the calcium antagonist or angiotensin converting enzyme (ACE) inhibitor studied—elevated blood glucose, diabetes mellitus, hypercholesterolemia, and hypokalemia—are all associated with an increased morbidity and mortality over periods longer than the term of this study; and 3) that both calcium channel antagonists as well as ACE inhibitors should again be recommended as equivalent “first-line” antihypertensive drugs (they were already listed as first-line drugs in the 1988 Fourth Report of the Joint National Committee [JNC-IV]). The only stated rationale for their “demotion” was the lack of “evidence-based data” that they were as equally protective as diuretics and β-blockers. ALLHAT provides this evidence-based data for the hard end points it evaluated. Which conclusions do you like best? The data are consistent with them all.

Even more disturbing is the tone struck in reporting current drug trials in hypertension. This contrasts with traditional science, where the experimental procedures used, and the limitations they impose on the interpretation of the results obtained are critical to judging the contribution of any given scientific experiment. This has led to the appropriately tentative and modest nature of scientific conclusions, in which terms like “the results suggest that, are consistent with the hypothesis that,” or “support the concept that,” are characteristic phrases in most scientific reports. Hence, it is either irresponsible media hype, “spin”, or worse even, an example of intellectual hubris when the practicing physician and the public are told (often by the physicians leading the trial itself) that a trial or combined (meta-) analysis of trials in hypertension, “proves” that a particular drug should be prescribed preferentially for all hypertensive individuals, or that a study “proves” the superiority of or mandates the use of any individual therapeutic agent. These are almost never necessary conclusions derived from the data obtained, but rather are one of many possible interpretations, some of
which may even suggest opposite conclusions (discussed previously). One reason for the plethora of clinical trials with different drugs in hypertension may be just this, that no definitive conclusions about different therapies have been reached since the very original clinical trials did conclusively prove one and only one thing: that treating hypertension, for the “average” subject (discussed later), is better than not treating it. There may be exceptions to these considerations, but they are exceptions (or as Dr. John Laragh had inscribed on the board behind his desk, "expectione probot regulum").

Some Common Sense About Basic Statistics: Should We Be Impressed By the Large Numbers of Subjects in “Large” Clinical Trials?

Large clinical intervention trials in hypertension are large because the effects they hope to demonstrate are small. This is an admitted fact, is not controversial, and is a requirement for planning trials, to have them sufficiently “powered” to achieve statistically significant results. What that means, however, is that the larger the trial, the smaller the statistical probability that any individual subject of a large clinical trial would benefit from any one of the treatment arms to be tested compared with another. When thousands of people are placed in different therapeutic groups, the conclusions, even when the primary end points differ among the groups (which they did not in the recent ALLHAT trial), are by definition clinically negligible. Hence, at least in hypertension, drug intervention trials are of little or no relevance to the practicing physician who wants to know the best treatment strategy for the next hypertensive patient he or she sees. The “average” hypertensive patient is an unhelpful illusion when it comes to drug therapy.

In a larger sense, the very fact that clinical trials in hypertension need to be so large ought to alert the physician in practice, as it should also have already alerted the epidemiologist constructing the trial, that either 1) the question as formulated by the primary hypothesis is the wrong question, and that somehow, a more clinically relevant question would be capable of being addressed more definitively with many fewer subjects; or 2) that the population to be studied has been insufficiently characterized, and the resulting heterogeneous mix of people obscures physiologically distinguishable groups of subjects whose different responses to different therapies masks the relevance of any one therapy in any particular group of subjects.

What does the “wrong question” mean? For example, it only takes 10 to 20 subjects, probably less, to determine that penicillin is superior to placebo in the treatment of a febrile illness such as pneumococcal pneumonia. However, it is not at all clear whether a large clinical trial would ever show a statistically significant difference between penicillin and placebo in the treatment of subjects with the sole entry criteria of a fever per se. This latter study would be asking the wrong question, as most fevers derive from viral or other less penicillin-sensitive bacterial infections. Thus, lumping different types of subjects having different underlying causes of fever would obscure those for whom penicillin would be (and is, as we know from pre-epidemiologic data) a “wonder drug.” In a parallel manner, to test the efficacy of any antihypertensive drug class on all subjects lumped together just because they share an elevated BP, is to ask the wrong question. Examples of alternative, clinically more relevant questions in hypertension that would not take all that many subjects to satisfactorily determine are: 1) which drug classes most effectively offset the actions of the renin-angiotensin system, or, which drugs lower pressure and subsequent clinical events best in predominantly renin-dependent subjects? Is there a relation between the two questions? Conversely, 2) which drugs provide the greatest long-term total body sodium volume loss, provide the most positive potassium and magnesium balance, and so on? Which drugs lower pressure and improve outcomes best in sodium volume forms of hypertension? These questions are aimed at already accepted physiologic factors regulating BP in normal and hypertensive subjects, and they have already been definitively answered in hypertensive animal models, and in smaller clinical studies for decades.

If we had an easy way of knowing which of these physiologic factors are more important than others in individual hypertensive subjects, we could better individually characterize the overall hypertensive population. Then we would know which drugs to use as initial therapy in which patients. There is much published literature on matching the right drug to the right patient on the basis of underlying hypertensive mechanisms. This literature has also been largely ignored for too long. In an era that has finally come to recognize its failure in providing broad, effective control of hypertension in the population as a whole, it is time to stop treating everyone as an “average” person, and return to the more historically valid behavior of physicians in practice—to diagnose and treat each hypertensive subject individually.

Ironically, the statistical requirements of large clinical trials usually prevent exactly this kind of information from being discovered. Thus, most trials do not allow analysis or comparison of those subjects for whom drug no. 1 normalizes pressure as monotherapy (achieves “goal” BP), compared to those in whom drug no. 2 by itself normalizes pressure. This would provide information useful in the kind of clinical judgments that practicing physicians have to make all the time. Who is the patient that a diuretic is best for, or that a calcium channel antagonist or an ACE inhibitor is best for? But the statistical randomization that is supposed to guarantee equivalence among the different treatment arms would be “broken” if patients responding best to monotherapy with a diuretic, and therefore not needing other drugs, are not the same kinds of patients.
(older, younger, salt-sensitive, renin-dependent, and so on) who respond best to other drug classes. Although this information is exactly what the physician could use to help him or her choose therapy with drug no. 1 vis-a-vis drug no. 2 in different patients, clinical drug intervention trials in hypertension routinely do not seek and usually will not provide these data.

**You Can’t Fool Mother Nature: Different Hypertensive People Are Different—The Heterogeneity of Hypertension**

On the basis of the above, we recognize at least two critical unexamined assumptions in the present “trials” atmosphere. One is the assumption in hypertension trials that “BP is BP is BP—is the same in everybody.” Thus, what every physician experiences in the course of his or her clinical practice, that the same dose of the same drug may lower pressure significantly in one patient, and not at all in the very next, equally hypertensive patient, is somehow forgotten in the face of average results obtained in the physiologically undefined populations studied in most large clinical trials. This unquestioned heterogeneity automatically limits the relevance of any results derived for a group as a whole to any individual in particular, for whom the recommendations derived from lumped group data may be totally inapplicable, and even counterproductive.

A second fallacious assumption is that the (at least initial) treatment of hypertension in a primary care or general internal medicine setting should differ in quality from that provided in specialty care centers. Calling the prevalence of hypertension a “public health” problem is not an excuse to stop thinking and abandon the best standard that each physician can provide for each of his or her patients. When more sophisticated testing for curable secondary forms of hypertension, are less available or less familiar to primary care or general internal medicine physicians, referral to clinical hypertension specialists is clearly reasonable. But with the broad availability of many easily obtained blood tests such as the recently developed reliable renin assays now provided, all physicians can assess the relevance of different physiologic factors in individual hypertensive subjects before recommending diet or drug therapy. This tool also screens for both unilateral renovascular hypertension and primary aldosteronism. As stated at the beginning of this editorial, knowing more about our patients is better than knowing less. This is especially true for the primary care physician and general internist who see the majority of hypertension present in our population.

**Summary About the Present and for the Future**

Can we salvage any benefit from the epidemiologic approach to antihypertensive therapy? Is there a reasonable chance that if one drug is used initially for all hypertensive subjects, and if the number of subjects treated is large enough, then some medical benefit could accrue to the society as a whole even if not to each individual hypertensive subject in particular? “Probably” not. Given what we already know of the scientific foundations of clinical hypertensive disease, and of the multiple drug classes available, the idea that one drug, any of them, should be the initial choice for all hypertensive patients is irrational. Empirically this already has been proven inadequate in practice, is wasteful of time, of the number of patient visits to achieve BP control, and of the number and doses of different drugs needed, compared to an individualized approach based on a reasonable clinical and laboratory assessment of each patient.

So where does this leave us? For medical practice to benefit from the growing use of randomized controlled clinical trials, especially intervention trials in hypertension, there needs to be an increased understanding on the part of the practicing physician, the media, and the public in general 1) about what these trials can tell us and what they cannot. Furthermore, 2) the amount of money spent on these trials (now more than a hundred million dollars for a single trial), the sponsoring agency (ies), and the media dissemination of the “results,” should not affect candid assessment of the importance (or lack of importance) of the data obtained. This seems obvious to us when drug companies sponsor trials, but an equal vigilance is required for studies underwritten by public institutions, including our government who often have already publicized views on the very issues being investigated, who have already provided much “educational” material designed to influence our therapeutic choices, who financially support and thus have much influence over the academic research infrastructure, who pay the salaries of investigators and support their research livelihood and who work for the same people that pay for much of the country’s medical care.

More constructively, 3) the epidemiologic “trialist” community needs to alter its approach, to seek to add to, rather than appear to substitute for, the accumulated biochemical, physiologic and pharmacologic knowledge about hypertension we already possess. With that change in attitude, not only should the distorting public pronouncements, hype, and “spin” surrounding clinical trials recede, but what should follow are 4) true collaborative efforts at physiologically and clinically “informed” clinical trials, where the issues raised here and others as well are taken into account in the structure of future research.

Like all science, progress in medicine has been incremental and additive. The utility of the initial medical history of an illness was aided by the development of the physical examination and then by the increased availability of various laboratory, chemical, and radiologic procedures. Arguing about which way of obtaining information to diagnose and treat human disease in general or hypertension in particular represents the best source of “evi-
“Public evidence” is both silly and dangerous; silly by definition, and dangerous because it stops us from using knowledge in a coordinate manner to provide the patient with what we have all been rightly proud to call modern medicine. Thus, the powerful tools offered by an epidemiologic approach to hypertension need to be more properly integrated into the overall fabric of pathophysiology and clinical science to create the best medical practice, and should not be used to rip it apart. Lastly, as Nobel laureate Richard Feynman reminded us: “... reality must take precedence over public relations, for nature cannot be fooled.”

References


