Evidence-based Medicine

Worship of Form and Treatment of High Blood Pressure

You, or at least many of your colleagues, have failed to provide optimal care to your patients with high blood pressure. The U.S. national recommendations to use low-dose diuretics or beta-blockers as first-line antihypertensive therapy are based on strong evidence from large long-term randomized controlled clinical trials.¹ Yet clinical practice seems to be disconnected from the evidence and from these recommendations. In a paper by Knight and colleagues,² calcium-channel blockers, not low-dose thiazide diuretics, were the most frequently prescribed antihypertensive medication for older adults in the early 1990s. At the same time that new evidence about the effectiveness of low-dose diuretic therapy was published in 1991–1992,^{3,4} the use of thiazide diuretics declined from 22% in 1991 to 10% in 1995.² Other authors have described similar trends for the use of anti-hypertensive agents in the 1990s.^{5,6}

Although it may be astonishing that a safe, effective and inexpensive therapy such as low-dose diuretic therapy is used so infrequently, there are a number of potential explanations. An accompanying paper by Smith and colleagues in this issue suggests that teaching evidence-based medicine skills, especially critical appraisal skills, is difficult.⁷ In this editorial, we would like to focus on two other explanations. Both hypotheses represent an excessive dependence on form rather than content, and we would like to insist on the importance of the content of the outcome and the content of the intervention.

In the hierarchy of evidence, the randomized controlled trial reigns as queen. One extreme version of evidence-based medicine suggests that in making clinical decisions, we should only read or rely on information from articles that describe randomized controlled trials, preferably ones that are doubled blinded. The defining feature of a high-quality study is thus its form, the study design as randomized trial. This emphasis on form makes it all too easy to ignore or gloss over the content. What question is the trial posing?

For hypertension, which is rarely symptomatic, the critical outcomes and thus the critical questions are the effects of specific drugs in preventing the devastating complications of untreated high blood pressure—stroke, myocardial infarction, heart failure and renal failure. We treat high blood pressure not simply to lower blood pressure, nor to have beneficial effects on cholesterol, nor to have a low incidence of side effects, but mainly to prevent cardiovascular complications of untreated hypertension.

Between 1990 and 1995, 14,525 articles were published and indexed as referring to calcium-channel blockers; 8,759 articles had calcium-channel blockers as their main focus; and indeed, 1,430 were randomized controlled trials, almost all short-term studies focusing on

outcomes such as blood pressure, side effects, or metabolic factors.⁸ If practitioners were to over-value treatments or therapies simply because they have been used frequently in randomized trials, they might well have felt confident about prescribing calcium-channel blockers in the early 1990s. Here, the form of the small randomized clinical trial may serve as a marketing tool among practitioners and scientists alike. In this new age of a super-abundance of small randomized clinical trials, it is important to remember that if a clinical trial does not provide new information about a clinically important end point, that study, despite the perfection of its form, is not an ethical study.^{9,10} Even placebo-controlled trials of the effect of anti-hypertensive agents on major disease end points, which answer the question whether hypertension should be treated, are no longer interesting or ethical since the answer is already known.⁸

An appreciation for the importance of the end point has been late in coming to discussions of evidence-based medicine, especially for the treatment of risk factors such as high blood pressure.¹¹ McAlister and colleagues drew attention to the issue in 1998,¹² and the first evidence-based users' guide on surrogate end points did not appear until 1999.¹³ The recent publication of the ALLHAT trial is a stunning reminder about the importance of staying focused on the critical end points. While alpha blockers are associated with an improved lipid profile—one that should theoretically reduce the risk of cardiovascular events, doxazosin, compared with low-dose diuretic therapy, increased the risk of stroke by 19% and the risk of heart failure by 100%.¹⁴

If the content of the outcome is important, so is the content of the intervention. For risk factors such as high blood pressure, early epidemiologic studies suggested that hypertension was associated with cardiovascular complications. Subsequently, intervention studies suggested that blood-pressure-lowering medications reduced the risk of selected outcomes. As physicians, we regularly monitor blood pressure levels during therapy. Trained in physiology, we find it easy or natural to think of our intervention as "blood-pressure lowering." This inclination is reinforced by the studies that use blood pressure as an end point.

The clinical trials that supported the use of anti-hypertensive treatment are not tests of blood-pressure lowering *per se*; they are trials of specific medications or strategies of treatment. For example, the SHEP trial, which used low-dose diuretics as first-line drug therapy, suggested that this particular treatment strategy reduced the risk of cardiovascular complications in older adults with isolated systolic hypertension.³ If other drugs such as calcium-channel blockers or alpha blockers also lower blood pressure, should we therefore conclude that they

also prevent cardiovascular complications? To do so is to generalize the findings from one class of drugs to another class of drug on the basis of the effect on the surrogate end point, blood pressure. This line of reasoning is an argument for doing a clinical trial with another class of drugs rather than using another class of drugs in clinical practice.¹¹ Indeed, the mechanisms of action of anti-hypertensive drugs—diuretics, beta-blockers, alpha-blockers, calcium-channel blockers, and angiotensin-converting enzyme inhibitors—are all so different that it would be astonishing if all classes of antihypertensive drugs had the same effects on all major disease end points.

Randomized clinical trials test specific interventions. Insofar as physicians use the same intervention and the same drug and dose in clinical practice as was used in the clinical trial, the findings are directly generalizable to study-eligible patients who would, if asked, have enrolled in the trial. While it is often reasonable to generalize findings for a drug to other populations with the same condition, we prefer to use the specific agent that was evaluated in large long-term trials. Generalization from one proven member of a class of drugs to another unproven member of the same class may be problematic.¹⁵ From the point of view of public health, it is prudent to use the proven agents rather than those that are theoretically similar or theoretically superior on the basis of some ancillary drug effect. Moreover, each prescription written for a drug proven to be safe and effective in large long-term trials may function as a vote on behalf of the conduct of trials of sufficient scope and duration to answer key public health questions.

One approach to sort through the plethora of randomized clinical trials that are published nowadays is to focus on the study content by asking whether the trial is posing a serious and important scientific question. For the treatments of cardiovascular risk factors such as blood pressure, lipids, and glucose, we need large long-term trials that directly compare therapies or strategies of treatment. ALLHAT is an excellent example of the kind of trial that will help answer the critical questions about antihypertensive treatments. Based on the evidence available to date, if your drug-treated hypertensive patient is not on a low-dose diuretic, why not?—**BRUCE M. PSATY, MD, PhD** and **CAROLINE RHODES, MD**, *University of Washington, Seattle, Wash*, and **CURT D. FURBERG, MD, PhD**, *Wake Forest University School of Medicine, Winston-Salem, NC*.

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