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Comparative Effectiveness Research: The View from NHLBI

Michael S Lauer, MD, FACC, FAHA

Director, Division of Prevention and Population Sciences, National Heart, Lung, and Blood Institute, 6701 Rockledge Drive, Room 10122, Bethesda, MD 20892, Phone: 301 435 0422, Fax: 301 480 1864, Email: lauer@nhlbi.nih.gov

“Let me tell you how *I* like to _____.”

Cardiovascular medicine trainees hear their faculty utter this phrase often. Let me tell you how *I* decide when, how, or whether to prescribe statins, or to order some type of noninvasive test, or to send a patient to the catheterization laboratory, or to recommend medical or surgical revascularization. Trainees amuse themselves by noting the enormous variability in how their faculty fills in the blank; for some scenarios there seem to be as many approaches as cardiologists!

What may be amusing, and confusing, for trainees is, in fact, the basis of serious health care and research policy debates. Enormous variations in practice have been well documented for many cardiovascular procedures.(1) Patients in some parts of the United States are 10 times as likely as similar patients elsewhere to be referred for stress imaging or coronary revascularization.(2,3) Furthermore, there seems to be little association between the patterns of cardiovascular practice and cardiovascular health; people who live in regions where more cardiovascular tests and procedures are performed do not live longer or have fewer cardiac events.(4) Health policy experts cite practice variation as symptomatic of uncertainty, waste, inefficiency, and poor performance of the health care enterprise.(5,6)

Why is there so much practice variation? While it may be easy to dismiss it as “the art of medicine,” the main causes are uncertainty and lost translation. Uncertainty because for many common clinical scenarios, definitive evidence does not exist demonstrating that one approach is better than another. We do not know, for example, if a patient with new onset chest pain will have a different outcome if referred for one type of noninvasive test as compared to another. (7) Even when definitive guidelines are disseminated, evidence-based practices are often slow to be widely incorporated into routine practice.

A number of health policy experts and professional groups have identified “comparative effectiveness research” (CER) as a solution to the problem of unjustified practice variation. (8,9) The Congressional Budget Office defines CER as “a rigorous evaluation of the impact of different options that are available for treating a given medicine condition for a particular set of patients.”(10) Comparative effectiveness research (CER) may compare competing drugs (e.g. atorvastatin versus simvastatin), competing modalities (e.g. anti-arrhythmic drugs versus defibrillators, or stents versus coronary bypass grafting, medical therapy versus revascularization), or may primarily focus on costs and benefits of specific options. CER

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includes traditional randomized trials, pragmatic trials, cost-effectiveness analyses, and observational studies.

During the past few years as health care costs seem to spiral out of control, CER has taken center stage on Capitol Hill. As of this writing, there are at least 10 bills introduced into the 100th US Congress that directly address CER. Senator Max Baucus (D-MT) introduced the “Comparative Effectiveness Research Act of 2008” that proposes to establish a private, nonprofit corporation called the “Health Care Comparative Effectiveness Research Institute.”(11) The Institute would be governed by a Board with representatives from multiple sectors, would be charged with identifying national priorities for CER, and would be allowed to enter into contracts with different entities for conducting research.

While the phrase “comparative effectiveness research” is relatively new, CER has long been a high priority for the cardiovascular community and for the NHLBI. Over many decades, NHLBI has funded or co-funded numerous landmark comparative trials that have had major impact on practice. Just a few examples, nearly all well known to practicing cardiovascular specialists, include the Coronary Artery Surgery Study (CASS), the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT)(12), the Women’s Health Initiative (WHI)(13), and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).(14) More recent and ongoing major NHLBI-funded comparative trials include Occluded Artery Trial (OAT)(15) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD).(16) A major trial now in planning is the Systolic Blood Pressure Intervention Trial (SPRINT), which will compare aggressive and conservative management strategies for prevention of complications of systolic hypertension.

NHLBI’s interest in CER is not limited to randomized trials. The Cardiovascular Research Network (CVRN) is taking advantage of a rich electronic data structure covering over 10 million patients to analyze three important therapeutic questions: 1) How is hypertension recognized, treated, and controlled within community practices?; 2) How is warfarin used to prevent adverse thrombotic events in atrial fibrillation and venous thromboembolism; and 3) What are the clinical characteristics, outcomes, and costs for patients receiving implantable defibrillators for primary prevention of sudden cardiac death.(17) The CVRN represents a viable example of Paul Ellwood’s call for “Outcomes Management” in his 1988 Shattuck Lecture.(18)

NHLBI’s commitment to CER is longstanding and was recently explicitly recognized as a critical component of our Strategic Plan(19), which states that we hold it as a high priority “to generate an improved understanding of the processes involved in translating research into practice...[and to] evaluate the risks, benefits, and costs of diagnostic tests and treatments in representative populations and settings.” We are pleased that the health policy community and the public at large have a renewed interest in CER. We are eager to be active not only in initiating, catalyzing, and supporting CER but also in participating in the national policy debate about how CER is best prioritized and directed.

The national CER debate includes a number of critical questions, all of which are relevant for the cardiovascular community. What should be the relative roles of randomized controlled trials versus observational studies? Given some of the well-known observational failures, such as the impact of hormone replacement therapy on outcomes, can observational studies ever be trusted for developing guidelines or public health policies? How should CER priorities be established, even within one field like cardiovascular medicine? Should diagnostic tests, like CT angiography, also be considered a target for CER just like more conventional therapeutic strategies? Should government-sponsored CER primarily be directed by existing federal agencies (like NIH, AHRQ, and the VA) or should a separate entity be established? How can

optimal coordination be achieved among existing federal agencies as well as between federal agencies and private sector research sponsors? Can research methodologies be improved, making it possible to perform large scale trials at substantially lower costs or to generate more trustworthy outcomes from observational studies? Should cost-effectiveness be part of CER, or should it be explicitly divorced from it given political sensitivities?(8,20)

NHLBI is and plans to be an active player in addressing all of these questions. We are funding work that attempts to reconcile differences between randomized trials and observational studies; as an example, parallel analyses are being performed of the WHI trials, observational study, and Nurses Health Study.(21) Nonetheless, because multiple “bad experiences” with ultimately debunked observational findings, we recognize that controlled trials must remain the gold standard for evidence, with observational studies primarily functioning for hypothesis generation and extension of trial findings to routine care. Using our Strategic Plan(19) as a guide, we are actively engaged in ongoing dialogues with investigators, clinicians, professional societies, community groups, and other government agencies to define those areas of uncertainty where high quality CER is most likely to have a major impact on public health and clinical practice. We are particularly excited about expanding CER beyond traditional therapeutics; this past summer we held a workshop on CER opportunities in diagnostic imaging, which is now one of the most rapidly growing technologies within the Medicare program. We have explicitly recognized the importance of cost, as our Strategic Plan recognizes as a critical challenge the need “to identify cost-effective approaches to prevention, diagnosis, and treatment.”(19)

NHLBI also recognizes that high quality comparative effectiveness research is only of value if it is incorporated into routine practice. We have a longstanding history of synthesizing the literature and generating practice guidelines for primary prevention of vascular disease, including management of hypertension, obesity, and hypercholesterolemia. We are now preparing updated guidelines in these specific areas, as well as engaging in an ambitious effort to write integrated guidelines that will provide coherent, cohesive recommendations for all lifestyle and medical approaches to primary prevention. We look forward to working with clinicians, academic leaders, and professional societies to assure rapid and widespread implementation of these guidelines.

Cardiovascular medicine is at a cross roads. On the one hand, NHLBI and the cardiovascular community have a long, proud tradition of initiating and performing outstanding CER that has led to strong evidence-based guidelines and dramatic improvements in clinical outcomes. On the other hand, cardiovascular medicine is in the crosshairs of critics who decry widespread variations in practice, failure of physicians to adhere to guidelines, and promotion of expensive diagnostic technologies in the absence of any evidence of better patient or public health. As we work closely with our cardiovascular colleagues and with the public, NHLBI sees CER as a critically important tool to render obsolete the phrase “Let me tell you how *I* like to _____.”

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