INTRODUCTION
In the next 20 minutes I will talk about the power of clinical trials and guidelines to influence cardiology practice. I will also amplify concerns others have raised about the threat that financial conflicts of interest pose to the industry–academic relationships that are so essential for medical progress. I will close with a few thoughts about the cost implications of the many cardiovascular treatment advances we celebrate. Although most of my comments reflect circumstances in the U.S., many of the issues I raise resonate around the world.

Powerful scientific and socioeconomic forces continue to transform medical practice and research, especially in this country. In the past 15 years, the parallel clinical trial, practice guideline, and continuing education movements combined to create one of the greatest paradigm shifts in the history of medicine. What I call the “trial-guideline-education process” is having profound effects on cardiology research and practice—effects almost as significant as the invention of the stethoscope in France in 1816 and the electrocardiograph in Holland in 1902 (1). Although the impact of the trial-guideline-education process is especially evident in America, it’s growing in Europe and elsewhere. The interesting thing for us is that we’re alive—witnessing this phenomenon revolutionize cardiology in real time.

CLINICAL TRIALS AND PRACTICE GUIDELINES
The modern randomized clinical trial was invented in the middle of the twentieth century, but its prehistory dates back exactly 250 years—to 1753—when British naval surgeon James Lind showed that citrus fruit cured scurvy. Although it took two centuries for clinical trials to gain momentum, a few individuals along the way promoted quantification as a tool to evaluate treatments. For example, in the 1830s, French physician Pierre Louis (2) challenged those seeking new therapies to support their conclusions with statistics, not subjective impressions. He explained, “Let those who engage hereafter in the study of therapeutics … demonstrate, rigorously, the … degree of influence of any therapeutical agent on the duration, progress, and termination of a particular disease.”

But Louis’s modern-sounding message didn’t have much impact. Most drugs introduced in the nineteenth century proved to be ineffective, and eventually almost all vanished without a trace. Harvard anatomist and author Oliver Wendell Holmes (3) anticipated this in 1860 when he wrote, “I firmly believe that if the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind—and all the worse for the fishes.” Gradually, things improved as experimental pharmacology replaced empirical polypharmacy and as new government regulations helped filter out useless and unsafe drugs.

Turning to more recent history and to cardiac drugs, the advances of the past 50 years are astonishing. For perspective, consider this advice for angina that Paul Dudley White (4), America’s leading cardiologist, published in 1951: “The most effective drug [for angina] after nitrates is alcohol … when nitrates are not available an ounce or two of whisky … may give quite rapid relief.” When White wrote this, penicillin was a new drug, polio was epidemic, and there were no effective oral diuretics.

The pace of medical discovery accelerated rapidly after World War II as America and a few other countries endowed biomedical research and as pharmaceutical companies collaborated with clinical investigators and statisticians to conduct controlled trials (5). British researchers published the first clinical trial using individual randomization in 1948. Their pioneering study showed that streptomycin could cure pulmonary tuberculosis, a powerful conclusion that changed practice and closed countless TB sanitariums. In the U.S., in 1951, the newly organized National Heart Institute, now the National Heart, Lung, and Blood Institute (NHLBI), funded the world’s first international, multi-center cardiovascular clinical trial. It was designed to test the effectiveness of aspirin, cortisone, and adrenocorticotropic hormone (ACTH) in treating acute rheumatic fever and in preventing rheumatic heart disease (6).

The clinical trial movement grew slowly until the 1970s when the National Institutes of Health (NIH) and industry began plowing huge piles of money into this type of research (Fig. 1). In this fertile climate a new type of clinical investigator emerged, a precursor of the modern “trialist,” who used computers and statistics to sift through mountains
of data collected from patients following a therapeutic intervention. These researchers, and those who funded their research, were looking for treatment effects invisible to the clinician’s eye.

During the 1980s, the trial process matured rapidly in response to creativity and criticism. Today, despite some lingering concerns (Table 1), well-designed trials are generally viewed as trustworthy trails to the truth. But clinical trials don’t lead to absolute truth in the same sense that an element, like sodium, has an exact atomic weight. This helps explain the noisy debates that sometimes follow the publication of trials that could have significant implications for practice.

During the last decade, the number of cardiovascular trials grew phenomenally because heart disease is so prevalent and has such enormous economic implications—both in terms of costs to society and potential for corporate profits. Today, the number of cardiovascular trials is mind-boggling. For example, a recent PubMed search for the term “acute myocardial infarction” limited to clinical trials published in English since 1990 returned 1,740 references. And consider this: on average, a new cardiovascular trial is launched every other day (7) (Fig. 2). Despite the terrific reference tools available in this era of the Internet and evidence-based medicine, it’s impossible for anyone to retrieve and review—let alone understand—the vast amount of data published weekly by our supercharged clinical trial industry. And trial results are just one part of an avalanche of potentially relevant information that threatens to bury busy clinicians.

This leads me to a bit of pragmatic advice for cardiologists who—like me—feel overwhelmed by all this new knowledge. I mean no disrespect to trialists or the dynamic trial movement when I say that doctors don’t have to memorize acronyms or detailed trial results to provide quality care. Fortunately, there are many talented academics working hard to synthesize trial results into reviews for practitioners. And if you do want to know about a particular study, Cardiosource (www.Cardiosource.com), the College’s new educational Web site, is an efficient path to a comprehensive compendium of clinical trials.

Although I don’t think cardiologists have to memorize acronyms or detailed trial results, we do have to keep up with what I’ll call the “current common wisdom of cardiac care.” The American College of Cardiology–American Heart Association (ACC/AHA) guidelines, invented almost two decades ago—and now updated regularly—are one shortcut to some of this common wisdom. It took several years for the guideline movement to mature and gain the trust of physicians. Those who invented the approach a generation ago promoted guidelines as a way to help achieve certain goals (8) (Table 2).

Today, guidelines are woven into the fabric of modern medicine—especially in cardiology and in America. The ACC/AHA guidelines are authoritative, evidence-based documents that synthesize and organize vast amounts of relevant information. Practitioners, payers, and policy makers respect and use our guidelines because they fulfill most of the criteria that define optimal guidelines (Table 3). Although full-text guidelines can be intimidating because of their size and substance (the recent update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction was 93 pages long and included 552 references), executive summaries and pocket

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**Table 1. The Most Common Criticisms of Clinical Trials**

- the problem of underpowered trials
- the unknown effects of polypharmacy
- the decision to change a trial in progress
- the short duration of follow up
- the choice of arbitrary end points
- the use of surrogate end points
- the practice of post-trial subgroup analysis
- the unsupported claims of class effect
- the gap between statistical and clinical significance
- the implications of publication bias
- the consequences of conflicts of interest
versions distill their essence (9). Patients also have access to them through Cardiosource and the College’s Web site (http://www.acc.org).

Various approaches have been developed to help incorporate guideline recommendations into patient care. The ACC-sponsored Guidelines Applied in Practice (GAP) projects have shown that some methods designed to influence individual practice patterns and encourage institutional changes, such as the use of standard orders in post-infarct patients, lead to improved outcomes (10). Although guidelines are a valuable adjunct to traditional clinical decision-making methods, they must never become the Pied Piper of physicians, leading each of us to write the same prescription for every patient. It is important to emphasize that guidelines complement clinical judgment, they don’t replace it. Clinical trials and practice guidelines address populations and average patients. Doctors take care of unique patients—one at a time (11).

CONFLICTS OF INTEREST

Although the trial–guideline–education process has helped to inform decisions and enhance care, it presents some challenges. I will focus on one: financial conflicts of interest that pose a threat to the vital but vulnerable interface between academic medicine and industry. I won’t address conflicts that practitioners face except to say that in this country the American Medical Association (AMA), the Pharmaceutical Research and Manufacturers of America (PhRMA), and other organizations have produced guidelines that help define and defend the ethical boundaries between individual doctors and industry.

A custom blend of altruism and self-interest motivates each individual, institution, and company involved in every phase of health care, whether it’s inventing drugs, conducting trials, developing guidelines, educating doctors, or performing procedures. As medical professionals, we must assure patients and the public that altruism is our primary motivating force. And because academics influence so many important parts of the trial–guideline–education process, they have a special responsibility to ensure its integrity. Academics help design and carry out clinical trials. They also publish papers, write editorials, give talks, and create guidelines that influence practice. These are valuable activities, and the significant time and energy academics devote to them must be acknowledged—and compensated.

Today, a significant portion of this compensation comes from industry, either directly or indirectly through an institution or sponsoring organization. Industry’s role in funding our nation’s academic enterprise has grown for several reasons, including the fact that subsidizing research and education with patient-care dollars is now obsolete. In this context, academic centers under stress (and many are

Table 3. Ideal Guidelines Will Be:

- created by informed and unbiased experts
- based on the best available published evidence
- concise and clearly written
- documented with appropriate references
- clinically relevant and useful in practice
- flexible enough to acknowledge that each patient is unique
- realistic about the cost implications of the recommendations
- accompanied by explicit conflicts of interest statements
- accepted as authoritative by all interested parties
- used consistently and appropriately in all relevant contexts
- proven to enhance clinical outcomes in pertinent populations
- reviewed and revised regularly by unbiased experts
Is academic medicine for sale?

Several things compel us to confront the potential, real, and perceived conflicts of interest that threaten the important and ever-expanding academic–industry interface. Two months ago, in the Journal of the American Medical Association, Yale researchers reported a detailed study of conflicts in biomedical research. They concluded (12): “Financial relationships among industry, scientific investigators, and academic institutions are widespread. Conflicts of interest arising from these ties can influence biomedical research in important ways.” I doubt these statements surprised many readers, because so many other authors have raised similar concerns (13–18). Two years ago, Marcia Angell (19) wrote an editorial in the New England Journal of Medicine with the provocative title, “Is academic medicine for sale?” If we ever hope to answer this question with an emphatic “No!” we need to do a better job of defining, identifying, and managing conflicts of interest.

The challenges are real because economic incentives energize certain critical components of the clinical trial industry. In fact, the U.S. government purposely infused a big dose of entrepreneurialism into academic research in 1980, when the Bayh–Dole Act, named for two senators, was signed into law. This legislation (that allowed universities to patent and commercialize inventions resulting from federally funded research) was a powerful catalyst of innovation and technology transfer—with tremendous benefits for patients and the public. But the Bayh–Dole Act also increased the chance that research institutions and some of their staff members would confront conflicts of interest.

Conflicts of interest are unavoidable in the trial-guideline-education process that evolved during the past half-century. But their impact can be minimized if we reach consensus on thresholds beyond which real conflicts are more likely to occur, set reasonable dollar limits for specific services, and require detailed disclosures. Academic medicine, corporate bioscience, organizations, our government, and other interested parties should develop common standards that reflect a shared commitment to ensuring the integrity of the trial-guideline-education process. Disclosure statements should be required not only for obvious end-product activities, such as publications and presentations, but also for other functions like committee and editorial work, where conflicts might influence outcomes. To be effective, these statements must be explicit and accessible, and they must be used when appropriate.

We can’t treat conflicts of interest like some family secret no one talks about. We must become more comfortable asking and answering pertinent questions about the sources and substance of industry funding that might influence individual practitioners—because these relationships are vital to medical progress and optimal health care. We can’t allow publicity or profit potential to blur our focus on patients or compromise the credibility of the trial-guideline-education process. Fortunately, there are several signs that we’re addressing the challenge. Recent examples include the Association of American Medical Colleges guidelines on conflicts of interest in clinical research, the Accreditation Council for Continuing Medical Education standards for commercial support, and the joint statement by cardiovascular journal editors on conflicts of interest (20,21).

Along with many other organizations, the ACC also navigates these turbulent waters. The Journal of the American College of Cardiology competes with other leading journals to publish clinical trial results, and our annual meeting features them (22). With the AHA, the College creates and distributes guidelines that influence prescriptions and procedures (23). The ACC prides itself on being the premier source of continuing medical education for cardiovascular specialists. This means the College has a special obligation to ensure the integrity of the trial-guideline-education process. Because the ACC, like other professional societies, depends on industry to help support our mission, we must be alert to the potential for bias. Acknowledging all of these things, the College continues to enhance its conflict-of-interest policies and procedures.

The profession and the public must understand that industry support—like government funding—is vital to the vast academic enterprise that discovers, digests, and distributes new knowledge. If we want to ensure medical progress, there’s no viable alternative. At the same time, capitalistic incentives catalyze invention and innovation that can benefit patients. And it’s unrealistic to expect industry to be financially disinterested in the trial-guideline-education process. Companies sponsor clinical trials because they hope to find proof of efficacy they can translate into profitable products. If a trial shows that a pill or device is beneficial, why shouldn’t the company that makes it seek publicity, market penetration, and profit?

Understandably, as one part of this dynamic process, companies seek experts and opinion leaders to help disseminate positive trial results and to interpret their implications for patient care. We need to keep bias out of these important educational functions. For a generation, statisticians have worked tirelessly to protect clinical trials from bias. Others involved later stages of the trial-guideline-education process must be sure bias doesn’t seep into these critical components of knowledge transfer that can influence practice in profound ways.

THE COST CONSEQUENCES OF TRIALS AND GUIDELINES

The phenomenal successes of the world’s biomedical research enterprise present another challenge. No country can
afford all the effective new pills, products, and procedures produced by our energized academic–industrial complex. Two decades ago, the pioneers of the guideline movement argued that their tool would not only enhance care but would also save money by discouraging unnecessary tests and treatments. While that has happened in certain situations, evidence-based guidelines have also fueled increases in health care costs. These cost increases aren’t always due to innovations in diagnosis and treatment. Sometimes, they reflect decisions to redraw the boundaries between “normal” and “abnormal” values, as a result of epidemiological or natural history studies. For example, lowering target cholesterol or blood pressure levels in entire populations has profound implications for prescription drug use. We expect that higher up-front costs for preventing cardiovascular disease will pay dividends later. Nevertheless, the cost trajectory of cardiology’s extraordinary track record of invention and innovation is problematic as we look to a future filled with promise.

Cost concerns are one reason Medicare and other payers to use the trial-guideline process to inform their reimbursement decisions. In cardiology, last year’s Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) and the subsequent updated ACC/AHA/North American Society of Pacing and Electrophysiology (NASPE) arrhythmia device guideline are examples of this phenomenon (24,25). This trial showed that putting a prophylactic implantable defibrillator in patients with a 30% or lower ejection fraction at least one month post infarct resulted in a 5.6% absolute risk reduction for death. This trial triggered a series of related events because the findings were compelling and the financial implications were enormous.

This life-saving device is an excellent example of the promise of inventions and the power of trials. But the cost implications are staggering. There are estimates that each year in the U.S., as many as 150,000 patients will meet MADIT-II criteria for a defibrillator. Although the actual domestic market will be smaller, there is consensus that this single technological safety net will cost more than a billion dollars a year. This explains why the Center for Medicare and Medicaid Services (CMS) solicited testimony from the ACC and other experts to help them relate our new device guideline recommendation to reimbursement policy. This is a situation where evidence rather than self-interest (which is potentially present at several levels) must drive discussions and decisions. Having said that, reimbursement decisions are inevitably somewhat subjective and context sensitive. Although solid scientific or statistical evidence doesn’t recognize national boundaries, each country will have to decide how to address the cost consequences of the potent products of the trial-guideline-education process.

The invention and trial-proven effectiveness of defibrillators, left ventricular assist devices, drug-eluting stents, and powerful new drugs seem to represent win–win situations in a culture that applauds medical breakthroughs and celebrates corporate profits. But these therapeutic triumphs that have helped define modern cardiology shouldn’t distract Americans from something we haven’t invented: a way to care for 41 million citizens without health insurance. Today, the U.S. has a health–cost crisis. Difficult decisions can’t be postponed indefinitely, and tough choices must be made as we enter a future filled with even more potent pills, powerful devices, and promising procedures. Although the ACC continues to update our practice guidelines to reflect important treatment advances, the public—through its policy-makers—will ultimately have to choose how America copes with the cost consequences of medical progress and an aging population.

In this country, the incredible advances in the diagnosis, treatment, and prevention of cardiovascular disease during the past half-century owe much to the billions of dollars NHLBI and industry have invested in basic research and clinical trials (26). The close relationship between clinical trials, practice guidelines, and continuing education that developed during the second half of the twentieth century has saved and enhanced the lives of countless millions. We owe special thanks to the hundreds of thousands of patients who entrusted their lives to trialists in order to advance medical knowledge and help others.

Today’s productive trial-guideline-education process depends on truth and trust, and we must protect each element of it from bias and excessive self-interest. Although there’s no vaccination to eliminate conflicts of interest, we’re getting closer to a commonsense prescription to manage them. This is very important because a healthy and productive academic–industry interface is so vital for medical progress. Future doctors and patients are depending on us to further enhance the trial-guideline-education process as it continues to mature. I think we are on the right track, and I hope you agree.

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