Beyond randomized clinical trials: applying clinical experience in the treatment of patients with coronary artery disease

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FOUR LARGE randomized controlled trials have compared the results of coronary artery bypass graft surgery (CABG) with medical therapy of coronary artery disease.1-4 Although the randomized controlled trial is the most scientifically valid method of comparing therapies, these trials have left unanswered many of the important questions that confront clinicians and patients daily. Furthermore, additional trials will probably not be funded comparing medical and surgical approaches, so that alternative methods must be used to study these therapies. We believe that scrupulous analysis of carefully collected clinical data offers a complementary approach to the randomized controlled trials. Although such trials have generated some consensus about patient management,5-7 the lessons learned from clinical data bases at Duke, the Seattle Heart Watch,8 the University of Alabama,9 and the Coronary Artery Surgery Study (CASS)10 provide further significant insights into the management of patients with coronary disease. In this essay we will first discuss briefly why randomized controlled trials are not suitable to answer all questions of therapeutic interest. We will then discuss the strengths and limitations of observational approaches.

Randomized controlled trials of CABG have four important limitations. First, limited resources have led investigators to focus on particular questions of scientific interest, restricting patient enrollments to relatively small, homogeneous portions of the general population seen in clinical practice. Because of the restricted populations, randomized controlled trials as they have been conducted are limited in their ability to examine the differential impact of CABG in specific subsets of patients. In fact, only a small minority of patients seen in clinical practice for suspected coronary artery disease would have been eligible for any of the trials. Women and patients with severe symptoms have been underrepresented,11 and the trials have evaluated few patients over age 65 and no patients with marked impairment of left ventricular function, two populations likely to derive greater benefit from CABG than the "average" patient.9,12,13 Of the population referred for cardiac catheterization at Duke because of suspected coronary artery disease,11 only 13%, 8%, and 4%, respectively, would have been eligible for the Veterans Administration (VA), European Coronary Artery Surgery Study, or CASS. Clinical data bases have the advantage of enrolling all patients so that the spectrum of illness can be studied.

Second, even among patients eligible for the randomized controlled trials, enrollment has been so selective that investigators are uncertain about the ability to generalize from the populations of these studies to other apparently similar patients. In most of the large randomized controlled trials, only a fraction of the eligible patients was entered into the study. Only the CASS trial, in which 37% of eligible patients were randomized,14 has been able to examine this problem, since it was the only trial to collect a detailed data base of information about eligible patients who were not enrolled. Thus clinical data bases can complement randomized controlled trials by providing information about "randomizable" patients who are not entered into the study.

Third, treatments for patients with coronary artery disease have changed so rapidly that even the most recent data from the large trials may not apply to patients treated today. The last patient randomized in a major trial in coronary artery disease was enrolled in 1979. Since that time, the medical and surgical therapy of coronary artery disease has changed dramatically, with new drugs (calcium channel–blocking agents),

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new doses or administration routes of old drugs (high-dose β-blocking agents, intravenous nitroglycerin), new uses for old drugs (aspirin and dipyridamole to maintain graft patency after CABG), more frequent use of internal mammary grafts, and the introduction of interventional cardiac catheterization techniques. Percutaneous transluminal coronary angioplasty, which is currently used for many patients with coronary artery disease, has never been evaluated in a randomized controlled trial. The overall effect of these changes in patient management is that patients in 1986 are living longer than equally sick patients cared for in the 1970s. If a new randomized controlled trial could be started this year, the initial results would not be available until the 1990s, by which time other dramatic changes in therapy are likely to occur. By design, clinical data bases should be constructed so that they track changes in therapy over time.

Fourth, because randomized controlled trials are performed in selected centers with various degrees of expertise, it is unclear whether the results can be generalized to the practice setting of an individual physician. Operative mortality, for example, has varied more from institution to institution than could be explained by the status of the patients before surgery. Clinicians can now keep track of their own experience through readily accessible clinical data bases, so that the results of randomized controlled trials can be compared with local results.

Because of these four weaknesses, clinicians in 1986 must critically evaluate not only evidence from the randomized trials but also reports from nonrandomized studies, other scientific observations, and personal experience in their own institutions when advising patients with coronary artery disease about therapeutic decisions. The importance of using information beyond the randomized controlled trial can best be understood by considering the example shown in table 1 of two patients from the same randomized controlled trial subgroup: patients with three-vessel coronary disease and a resting ejection fraction over 50%. Patient 1 is a 64-year-old man with frequent exertional angina, peripheral vascular disease, a previous inferior infarction, resting ST segment depression, a resting ejection fraction of 51%, and a 95% stenosis of the proximal left anterior descending artery. Patient 2 is a 51-year-old man with one episode of angina per week, no peripheral vascular disease, no previous infarction, a normal electrocardiogram, a resting ejection fraction of 64%, and a 75% distal left anterior descending lesion. Using data as published from the randomized controlled trials, the clinician would put both patients into the same category (“three-vessel disease, normal left ventricle”) and expect their medical and surgical survival to be similar. Table 1 demonstrates the survival times with medical and surgical therapy estimated from past experience with our patients at Duke. These estimated probabilities of survival at 1, 3, and 5 years are based on statistical models developed from our entire population of patients. The difference in survival with medical therapy is dramatic and the predicted benefit from surgery is quite different between the two patients. Because the randomized controlled trials have reported benefits only for the “average” patient, the clinician relying on this information alone is often ill-equipped to estimate the benefit of therapy for an individual patient.

The use of the observational data base as a registry of information about the natural history of the disease is generally accepted. Many critics, however, have questioned the role of data bases in assessing the value of therapy. The major problem of the data base is the nonrandom nature of the treatment received. The possibility is always present that an unrecognized imbalance in baseline characteristics could exist that might explain any observed differences in outcome between the therapies being compared. When therapy is assessed with a data base, statistical methods are used to reduce bias introduced from the nonrandom treatment allocation by measuring all characteristics about the patients that are known to be important and “balancing” the distribution of these characteristics among the treatment groups. This need for sophisticated analytic capability considerably increases the organizational complexity of data bases designed to address therapeutic questions.

If observational data bases use the same methods of data collection, quality control, and follow-up as randomized controlled trials, the central issue in their use

| TABLE 1 | Predicted survival (%) of two patients with ejection fraction >50% and three-vessel disease |
|---------|-----------------|-----------------|-----------------|-----------------|
|         |         |         |         |         |
| Patient 1 | Medical | Surgical | Medical | Surgical |
| 1 year    | 82      | 94      | 98      | 98      |
| 3 years   | 64      | 82      | 96      | 98      |
| 5 years   | 42      | 82      | 92      | 97      |

1° Age 64, frequent angina, resting ST segment depression, peripheral vascular disease, previous myocardial infarction, ejection fraction 51%, 95% proximal stenosis of left anterior descending artery.

2° Age 51, infrequent angina, normal ECG, no peripheral vascular disease, no previous myocardial infarction, ejection fraction 64%, 75% distal stenosis of left anterior descending artery.
for treatment comparisons becomes the ability of analytic methods to adjust for baseline differences (bias). Multivariable statistical methods such as the Cox proportional hazards model have provided powerful tools for making these adjustments. Several examples now exist documenting the ability of observational studies to achieve the same results as randomized controlled trials in well-characterized diseases.\(^{23, 24}\) Nevertheless, in each new situation the completeness with which important baseline differences have been characterized must be questioned. No single observational treatment comparison can be regarded as definitive. When observational trials agree, as in the benefit of CABG for patients with coronary disease and impaired left ventricular function or older age, we can have more confidence in the results.\(^{12}\) The strength of scientific observation improves with replication. When observational studies with adequate design disagree, randomized trials are necessary to resolve the differences.

The need for replication is not limited to observational studies, however. Recent reports of multiple randomized controlled trials have demonstrated the possible lack of consistency from one randomized trial to another. The most glaring example of this problem in the CABG literature has arisen in patients with three-vessel disease and normal left ventricular function.\(^{25, 26}\) The CASS trial found no improvement in survival with CABG in this subset of patients, while the European study found a highly significant difference. Similar examples regarding other cardiovascular therapies also exist. In a recent "meta-analysis" by Yusuf et al.,\(^{27}\) the estimated benefit of \(\beta\)-blockers in randomized trials after myocardial infarction ranged from an odds ratio of 1.5 to 0.6. Only when the multiple randomized trials were analyzed jointly did the therapeutic effect of \(\beta\)-blocker therapy become convincing.

The dramatic technical progress of the computer industry in providing improved computational capabilities while simultaneously reducing the cost has made it realistic for practitioners to develop their own observational data bases. We have identified several characteristics common to successful clinical data bases.\(^{28}\) First, important data items should be delineated and collected prospectively. The quality control mechanisms of a data base should be the same as those used in a randomized controlled trial. Second, patients must be followed compulsively at regular intervals. Again, the methods of complete, accurate follow-up should be no different between data bases and randomized controlled trials. For a clinician to be aware of his or her clinical experience, these first two principles will allow for adequate collection and tabulation of data.

If the data base is used to evaluate therapy, a third essential component should be included: a team of investigators, including clinicians, clinical epidemiologists, biostatisticians, and computer scientists. The team working together provides the greatest opportunity for reducing bias. The interchange can keep the judgment of involved clinicians from being too biased, while continually keeping the statistician abreast of relevant clinical issues.

Since 1971, as part of the patient care process, physicians at Duke have prospectively collected for each patient the medical history, results of physical examination, pertinent laboratory tests, and results of cardiac catheterization.\(^{29, 30}\) This information is then used to generate the test report.\(^{11}\) The computer data base improves medical care and serves as both a medical record and a research tool. By linking the baseline status of each patient with long-term outcome and collating the information from multiple patients, the data base becomes a collective reservoir of clinical experience, permitting immediate recall of the experience of the institution unfettered by anecdote or opinion. In this way, the data base functions as a computerized textbook of medicine for the individual patient. Estimates of outcome based on this collected clinical experience have recently proved to be more accurate than those made by expert cardiologists with an average of 18 years of experience beyond training.\(^{18}\)

We have recently reviewed the influence of randomized controlled trials on our practice at a time when the data base has been available.\(^{31}\) Several examples were identified in which our collective experience seemed to influence practice before randomized controlled trial results were known. Long before the results of the randomized portion of the CASS study were available, our clinicians were exposed to information documenting the excellent survival of medically treated patients with mild stable angina and good left ventricular function. Accordingly, a minority of patients in this category have been treated surgically at our institution and the practice pattern has not changed since the CASS results were published.

In a similar fashion, nonrandomized treatment comparisons from the CASS Registry are influencing practice across the nation. Although CABG was not found to influence survival in patients with mild stable angina and normal left ventricular function, improved survival with surgery has been found for older patients,\(^{12}\) patients with left ventricular dysfunction,\(^{11}\) and patients with severe angina.\(^{32}\) Although the appropriate
cautions about nonrandomized treatment comparisons have been included in each of the CASS Registry reports, clinicians will use the information from these analyses since no randomized controlled trial data exist for these populations.

Although randomized controlled trials have provided important information for managing patients with coronary artery disease, their costs, the difficulty in generalizing their results, and the rapidly changing technologies and therapies make it imperative that additional information be available to clinicians making therapeutic decisions for their patients. Observational data bases can provide additional information, but the clinician should be aware of associated problems and limitations. We believe that randomized controlled trials and carefully collected and analyzed clinical data bases are not competitive but complementary. Clinicians who will manage patients with coronary artery disease through the next decade must have information from both randomized controlled trials and clinical data bases.

References

14. CASS Principal Investigators and their associates: Coronary Artery Surgery Study (CASS): A randomized trial of coronary artery bypass surgery. Comparability of entry characteristics and survival in randomized patients and nonrandomized patients meeting randomization criteria. J Am Coll Cardiol 3: 114, 1984
19. Rahimtoola SH: Left main equivalence is still an unproved hypothesis but proximal left anterior descending coronary artery disease is a "high-risk" lesion. Am J Cardiol 53: 1719, 1984
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