Measuring the therapeutic efficacy of coronary revascularization: Implications for future management

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"In certain cases of angina pectoris, when the mouth of the coronary arteries is calcified, it would be useful to establish a complementary circulation for the lower part of the arteries."

Alexis Carrell, 1910

The concept of coronary revascularization has existed for a century now, since Alexis Carrell's seminal experimental procedure, in which the left subclavian artery was suture-anastomosed to the circumflex coronary artery in the dog.^{1,2} The latter half of the century witnessed an explosion in techniques of coronary revascularization, both in cardiac surgery and interventional cardiology. With analysis of long-term outcomes, the clinical benefits of restoring coronary flow are now well-established, including improved quality of life and better long-term survival. In the past decade, however, multiple methods of coronary revascularization have emerged, creating confusion about the best technique in a given patient. Clinical approaches have been on a veritable roller coaster, leading to fractionation of therapeutic recommendations and controversy. As stated by Dr. John W. Kirklin in his 1972 Lewis A. Conner lecture before the American Heart Association³: "When [physicians] embark upon an intervention for their patient, they must do so with confidence and conviction if there is to be a high probability of success. But these very convictions can make the doctor guilty of premature conviction in *evaluating* procedures, unless he addresses this evaluation with the same seriousness and skill he uses in treating individual patients". With recent objective assessments, fairly uniform data now are emerging to guide decision-making, and relevant issues (and at least some answers) are becoming more consistent. The purpose of this editorial is to review briefly this new information, within the context of the article in this issue by Guru and associates,⁴ and to present a viewpoint, based on the authors' interpretation of current data.

Very early after the clinical introduction of surgical coronary bypass, a major study was begun, the Veterans Administration (VA) randomized trial.⁵ It should be emphasized that this was an early era both in clinical research and in the techniques of coronary bypass. We now forget that the first major randomized trial in surgery had been published only a few years earlier,⁶ and that statistical methods such as the Cox model for observational studies had not yet been described.⁷ By today's standards, surgical techniques for coronary bypass also were rudimentary. Despite these limitations, the VA trial *did* show a significant survival benefit after coronary bypass in patients with left main coronary disease, primarily because the surgical/medical treatment benefit was so large that it could be defined even with a small sample. The next 3 major trials were: 1) the Unstable Angina Trial, 2) the European Coronary Surgery Study, and 3) the Coronary Artery Surgery Study (CASS). Each of these trials examined coronary bypass versus medical therapy in non-left main patients with predominantly good ventricular function, each had recruitment problems, and all probably were underpowered.⁸⁻¹⁰ Moreover, the results of these trials, arguably, were interpreted in over-simplified and possibly counterproductive ways,¹¹ to support the concept that coronary bypass had no survival benefit in non-left main patients and to suggest that a delayed approach to coronary revascularization was appropriate in most situations. These studies also illustrated the

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Received for publication Nov 23, 2005; revisions received Dec 28, 2005; accepted for publication Dec 30, 2005.

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J Thorac Cardiovasc Surg 2006;131:944-8
0022-5223/\$32.00

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doi:10.1016/j.jtcvs.2005.12.039

limitations of randomized trials in cardiovascular disease: excessive cost, recruitment difficulties, selection of potentially unrepresentative patients at the point of randomization, the necessity of crossover design for patient care (and its negative effects on statistical power), the ability to assess treatment at only one point in time, and the potential for superficial misinterpretation of the data. To this list can be added new problems encountered in more recent trials, such as STICH: the reluctance of physicians to contribute patients in a financially stressed environment and the now excessive cost of malpractice insurance for prospective clinical research. While randomized study design minimizes baseline differences and confounding influences in patient cohorts, it should not be viewed (as in the Guru paper) as any type of “gold standard”. Randomized clinical trials require proper scrutiny and interpretation, just like any other clinical research.

By the mid-1980's, statistical methodology for observational studies had improved considerably, especially with the development of the Cox proportional hazards model. When coupled with prospective data collection, such as employed in Duke Cardiovascular Databank studies, the Cox model allowed entire clinical populations to be assessed, at minimal additional cost, over extended periods of time, and with better understanding of (and compensation for) treatment selection biases. Hlatky and associates¹² demonstrated that in a well-understood area such as coronary artery disease, and with the availability of powerful prognostic variables, an inclusive patient cohort, and nearly complete followup, predictions of survival with medical versus surgical therapies were in excellent agreement between randomized and observational publications. Observational methodology, to be sure, also had limitations, but by 1984, the results suggested a significant survival benefit after coronary bypass grafting in all patients with multi-vessel coronary artery disease.¹³ Interestingly in the Duke data, surgical survival characteristics have been stable since the mid-80's (unpublished observations, Dr. Peter K. Smith and Mr. Robert Tuttle, 2005), and early studies designed to assess the clinical benefits of multiple internal mammary artery (IMA) bypass grafting proved negative at initial follow-up.¹⁴

More recent surgical innovation addressed the potential advantages of off-pump coronary bypass. While this method had been used for some time, a major effort was made to improve technical details and to extend the procedure into patients with more complex disease. With considerable data coming in at present,¹⁵ off-pump bypass probably improves early results negligibly, and several studies suggest that long-term outcomes could be inferior,^{16,17} perhaps because of problems with myocardial protection, the tendency to under-graft, and at times, compromised graft quality. While this subject is still unresolved and is undergoing considerable debate, in the author's view, off-pump bypass probably

will not be associated with large advantages in the management of patients with coronary artery disease.

Another major effort at quality improvement was the development of percutaneous coronary interventions (PCI). Evolving over 2 decades from balloon angioplasty alone, to atherectomy, to bare-metal stents, and now to drug eluting stents, PCI has engendered an enormous developmental effort on the part of industry and cardiology investigators. This evolution has been accompanied by a reduction in early complications, to the point that PCI procedures now are rarely associated with acute problems. Advanced interventional techniques have contributed significantly to the care of patients with acute myocardial infarction and other acute coronary syndromes. Because of the perception that restenosis rates are much lower (a concept based primarily on 6-12 month follow-up data), drug eluting stents currently are being used in increasingly complex clinical settings, to the point that national rates of coronary bypass surgery are falling. PCI does have the advantage of less invasive methodology and diminished patient trauma, but do the available long-term clinical data justify this massive expansion in application?

In BARI trial studies of balloon angioplasty,¹⁸ and also in more recent analyses of bare metal stents,^{19,20,21,22} long-term death rates after PCI were significantly higher than those observed for coronary bypass. Along these lines, the BARI trial illustrated several points. First, like CASS, BARI largely enrolled low-risk patients with good outcomes. With low event rates, therapeutic differences may have been difficult to define with the trial sample size. At the outset, the surgical committee of BARI (chaired by Dr. Floyd Loop) was concerned about this problem, and negotiated for liberalizing enrollment criteria. Ultimately, the concept emerged from BARI that coronary bypass was more effective than PCI *only* in diabetics, based on a positive treatment interaction term ($P = 0.042$). However, it is also possible that “diabetes” was a surrogate for higher general baseline risk, and that the surgical outcome benefit in diabetics was a reflection (to some extent) of better results in the higher risk population.¹⁸ The more recent concept that PCI is associated with twice the relative long-term death rate as coronary bypass across the entire spectrum of baseline risk (manifested as small absolute differences in low-risk patients and large absolute differences in high-risk patients) may be the operative principle.^{19,22} This sobering fact should bring pause to the general application of PCI, especially considering the projected number of patients who may have died because of PCI over-utilization. Assessment of drug-eluting stents is under-way at present, most notably in the BARI 2D trial, comparing medical with surgical and PCI therapies in patients with Type 2 diabetes. The beginning of this trial fortuitously coincided with the introduction of drug eluting stents; the results, therefore,

Figure 1. Composite outcomes of all-cause mortality, non-fatal MI, PCI, and redo coronary bypass were significantly reduced in multi-vessel coronary disease patients undergoing multiple IMA grafting to 2 different coronary systems (as compared to single IMA grafting) at 20-years of followup.

will be very important; and 3-year outcomes in BARI 2D should be available shortly. The concept of “hybrid” coronary revascularization, utilizing combinations of minimally invasive IMA grafts and simultaneously placed coronary stents, is a recent variation on the PCI theme. It is likely that the poor performance of coronary stents may be a limiting factor with this approach,²³ but more long-term data are needed. Finally, the problem of late sudden death seen with drug eluting stents in clinical practice is very concerning, and it is hoped that scientific data will soon be available as a guide. Many are concerned that self-referral and financial incentives have played at least some role in the rapid expansion of PCI, and it would be useful to recall Dr. Kirklin’s admonitions when considering future therapeutic options.

Throughout this evolution of approaches, Dr. Bruce Lytle and associates at the Cleveland Clinic continued to espouse the advantages of bilateral internal thoracic artery bypass.^{24,25} Even when most data were to the contrary, Drs. Lytle and Blackstone applied a newer observational technique, propensity score matching, to the assessment of this problem. Propensity analysis has been a breakthrough in comparing treatments in observational studies.²⁶⁻²⁸ By liberally modeling tendencies for non-random treatment selection using all available baseline variables (significant or not), the propensity model (estimated probability that a patient will get a specific treatment) captures all measured confounders into a single variable. Propensity analysis can be considered a data reduction technique in which more confounders can be adjusted than there are deaths. It can be accompanied by a sensitivity analysis to assess whether an observed treatment effect can easily be explained by an unmeasured confounder; thus, propensity modeling allows much more aggressive adjustment for confounding variables than previously possible. Using these methods, data from multiple sources are becoming available, including the paper of Guru and associates, and most studies verify Dr. Lytle’s hypothesis. Dr. Guru’s analysis also illustrates several important design innovations, including the linking of multiple national da-

tabases. While refinements will need to be made, employing a similar technique of linking the ACC and STS databases to the National Death Index could facilitate clinical cardiovascular research in heretofore unimagined ways. It would be necessary to fulfill HIPAA requirements in order to maintain patient identifiers in the STS database, but efforts should begin in this direction. Additionally, consideration should be given to using the STS database as the platform for generating more cost-effective randomized trials in cardiac surgery. Since the first goal of establishing the STS database has been achieved, future modifications might be directed toward significantly enhancing national clinical research. The key is continued improvement in database accuracy, validity, and completeness.

The Guru study also illustrates the importance of composite outcomes. It is now understood that outcomes are multivariate and inter-related, as in the concept of competing risks.²⁹ These new insights and other very important improvements in observational analyses are in their early development. An example is analysis of dynamic or time-varying treatments. It is often the case that a treatment cannot be assigned to patients at the time of diagnosis without subsequent additional therapies being applied or withdrawn. Thus, attempting to compare dynamic treatment regimens can be extremely difficult. Some promising methods,³⁰⁻³² including time-varying propensity scores, are now available and undoubtedly will be applied to the complex situations seen in current practice. Highly sophisticated observational approaches, performed on large and comprehensive patient populations, offer great promise for the future, and as these methods are developed, the current trend toward generalizing research at the national level could rapidly accelerate clinical observations. Needless to say, the availability of virtually on-line, large-scale, and even more precise national databases in every aspect of cardiovascular disease could bring the reality of “evidence-based medicine” to daily bed-side decision making.

Returning to the Guru paper, few *now* would question the benefits of multiple IMA bypass in patients with multi-vessel coronary disease. Long-term mortality is reduced, non-fatal myocardial infarction and PCI occur at a lower rate, and the incidence of reoperation is dramatically less.³³ In the authors' study (Figure 1) with a mean follow-up to 20-years,³⁴ average event-free life expectancy was extended by almost one year, and on average, one patient in five benefited clinically. Only 4.6% of multi-vessel patients undergoing multiple IMA grafting required redo coronary bypass over 20-years, as compared to 12.6% of single IMA patients. This result is different from the Guru study, but the difference may in fact illustrate that outcomes are multivariate and interrelated. Within the U.S. healthcare system with its greater surgical availability, worse long-term results with single versus multiple arterial grafting might be manifested by a relatively higher incidence of reoperation and less of a difference in mortality. Conversely, care limitations in Canada might be associated with a lower incidence of reoperation and a higher mortality. This point emphasizes the propriety of composite outcome, but in any event, the debate about multiple IMA grafting seems to be over. Whereas, the incidence of multiple IMA grafting was low in recent STS data, the rate very likely will accelerate at this point. To modestly go out on a limb, one might even suggest that 50-75% of patients with multi-vessel disease now should be managed with multiple IMA's, including patients with diabetes and other high-risk profiles.³⁴ It should be emphasized that this concept is not substantiated for radial artery grafts, and one IMA and concomitant radial arteries should not be considered as "all arterial" surrogates for multiple IMA grafting. Certainly, the inability to differentiate between types of arterial grafts is a weakness in the study of Guru et al, and needs to be remedied in their database. Proven clinical benefits are associated only with bilateral IMA's, and with recent radial artery patency data, it is unlikely that addition of radial arteries (while perhaps useful) will produce major therapeutic benefits.

Finally, one might traverse another limb, and propose a change in the treatment algorithm for future patients with serious multi-vessel coronary artery disease. Given the excellent long-term outcomes associated with multiple IMA grafting, and the as yet irrefuted late problems with PCI, maybe the current management strategy of attempting PCI first in most patients is backwards. Perhaps multiple IMA grafting should be performed as the first procedure in most patients with serious multi-vessel coronary obstruction, and then PCI applied for the unusual situation of graft failure and recurrent single vessel disease. It is likely that outcomes would be improved with this approach, and long-term cost efficacy also could be better. Quoting again from Dr. Kirklin's lecture over 3 decades ago³: "If we are able to provide the best possible care for all patients coming to us

with heart disease, now and in the future, we must do many things, including the continual evaluation of the results of our cardiac operations and a comparison of these results with those of other patient management programs and with the natural history of the disease". In the near future, Dr. Kirklin's vision may become everyday reality.

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