The Heart Surgery

EDITORIAL

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Twenty-Two Years and It Just Keeps Going, Going, Going: The Veterans Affairs Cooperative Study of Coronary Artery Bypass Surgery for Stable Angina

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Peduzzi, et al. recently reported the 22 year follow-up from the Veterans Affairs Cooperative Study of Coronary Artery Bypass Surgery for Stable Angina [Peduzzi 1998]. Like influenza and taxes, this study just will not go away. It has been so long since the VA study began, however, that younger surgeons may not recall that the original report of survival data at 36 months of follow-up [Murphy 1997] aroused such vociferous objections from surgeons, as well as from surgically oriented cardiologists, that the New England Journal of Medicine published a special section of correspondence on the topic [NEJM 1977].

In Peduzzi's current publication, as in the original report, VA investigators conclude that the study provides "strong evidence" that coronary bypass operations have "no benefit in long-term survival or relief of angina" and have "an obvious detrimental impact on cost-effectiveness." They base this conclusion on the observation that although survival was initially better in the surgical cohort, the survival curves in the medical and surgical groups converged after eleven years.

Although the investigators acknowledge that the study has "obvious limitations," they avoid drawing attention to serious flaws that invalidate its conclusions. Despite all the time, energy and Federal grant money that went into this multi-institution, multi-year study, the most glaring deficiency of the VA study has always been the quality of the surgical results. Regardless of repeated insistence by VA investigators that the study's surgical results were comparable to those being reported from other centers in the early 1970s, there are five major reasons why the surgery performed in the VA study was not representative of actual clinical practice then, and is even less so now:

1. The study was carried out in a very low-risk population, which makes it all the more difficult to demonstrate a surgical benefit. All operations were primary, elective procedures for chronic stable angina; 44% of patients were less than 50 years old (average age 50 years; range 30-66 years); and patients could be excluded for subjective reasons such as left main stenosis, "poor" ventricular function, previous surgery, etc. Furthermore, since 50% stenoses were considered significant in that protocol, many patients really had non-critical coronary disease. Since angiography in those days was not what it is today, even the lax criterion of 50% stenosis is suspect because the angiographic studies were so poor. The impressions of Goffredo Gensini—one of the pioneers of coronary angiography—are quoted by Rene Favoloro:

   "Some of the early films hardly show the outline of the coronary arteries at all.... If you assume ... that a ... significant number of patients had surgery when either the runoff was inadequate or the bypass was unnecessary, it would not be surprising to find no difference between medical and surgical therapy. In fact, these patients, when randomized to surgery, would ... have poor results." [Favaloro 1998]

2. In this low-risk population, operative mortality was 6.1% for double-vessel disease (6 of 98), and 7.3% for triple-vessel disease (9 of 124). (The actual overall mortality was 5.8% of those operated, because there was no mortality in 46 patients with single-vessel disease and 20 patients assigned to surgery did not undergo any operation). Those mortality figures were almost four times as high as results at that time for comparable patients at recognized centers [Collins 1973, Anderson 1974, Ullyot 1975].
3. Revascularization was inadequate, since the average number of grafts was 1.9, and no patient received more than three grafts. In most specialized centers in those days, the average was 2.5 grafts [Reul 1975, Geisler 1977, Favaloro 1998], and today it is, of course, much higher.
4. Only 14 of 268 patients received internal mammary artery (IMA) grafts, and two of these 14 patients actually received Vineberg implants rather than bypass grafts.

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5. Graft patency was only 69%. Twelve percent of patients had all grafts occluded, including 19% of patients with single grafts! Only 54% of patients had all grafts patent. In a contemporary report from another center, the graft patency rate was 87%, with 94% of patients having at least one patent graft, and 81% having all grafts patent [Geisler 1977]. The actual graft patency rates at that center were probably even higher since then, as now, only selected symptomatic patients were studied outside a randomized study. Of the 332 surgical patients in the VA study, 137 suffered a myocardial infarction (MI) during follow-up, which is not surprising in view of the inadequate graft patency rate, the insufficient number of grafts, and the virtual absence of IMA grafts. The relationship between graft patency and clinical outcomes is well established [Alderman 1996].

Problems With Randomized Studies That Compare Medicine With Surgery

It is commonly observed that patients in randomized trials fare better with either treatment than do historical controls and this is also true in the VA study. This may not be simply the result of trial patients receiving more attentive, more standardized, and more effective therapy, but rather because—as a result of pre-randomization bias—they constitute a low-risk subset.

Pre-randomization bias causes physicians who feel strongly about high-risk patients to refer them for specific therapy rather than for randomization. Low-risk patients are randomized, however, because physicians do not have strong feelings about their therapy. Even participating investigators also have human instincts and biases that can influence the selection of patients for randomization.

The frequent use of non-quantitative criteria in the VA study would have made it easy to act on such biases. Patients could be excluded because of subjective criteria such as "poor" left ventricular function or "unstable" angina. Once in the study, "high-risk" patients were defined as those with triple-vessel disease and "some abnormality of left ventricular function." The latter term meant any one of the following: some abnormality of contractility, abnormal left ventricular size, cardiothoracic ratio >0.49, ejection fraction <0.45, or LVEDP >14mm Hg. Even with these rather loose definitions, only 38% of patients were considered "high-risk."

Moreover, randomized trials that compare surgical with medical therapy, rather than one drug regimen with another, have unique pitfalls about which I have written more extensively elsewhere [Bonchek 1982]. Pre-randomization bias is particularly strong. Second, the inevitable crossovers to surgical therapy leave the medical group composed only of patients in whom medical therapy is successful. When 66% of patients cross over to surgery, as happened eventually in the VA study, statistical manipulations cannot adequately compensate since the study groups were small. Third, there obviously can be no placebo for surgery. Fourth, a drug is an unchanging compound that is equally effective in all hands, while surgical technique evolves continuously, and its effectiveness varies between surgeons and institutions.

The rapid evolution of surgical technology and techniques can invalidate even a study that compares one surgical approach with another. In 1976, as the VA Coronary Bypass Study was winding down, VA investigators proposed a randomized study of the Bjork-Shiley mechanical heart valve versus the Hancock bioprosthetic valve. The study was doomed to irrelevance by the foreseeable evolution of prosthetic heart valves. (The Bjork-Shiley valve was subsequently removed from the U.S. market, and the standard Hancock model was supplanted by the hydraulically superior modified orifice model.)

Even so, this meaningless study has continued stubbornly onward at public expense. Why do such obviously flawed randomized trials keep going and going and going? Is it because once they have begun that they generate their own central bureaucracy and peripheral constituency, so that terminating them involves a loss of financial support that is a form of academic financial suicide [Bonchek 1979]?

Summary

In their recent publication, VA investigators conclude that surgery conveys no long-term survival benefit because even though survival was initially better in the surgical group, the mortality curves cross after eleven years [Peduzzi 1998]. To the contrary, I conclude that surgery is so beneficial that it is useful even when it is done poorly in a selected, low-risk subset! When one considers that a low-risk population was subjected to an unacceptable operative mortality rate and a disastrous early graft closure rate, it is remarkable that there was ever any benefit from surgery. Had the surgical results in the VA study been better, the survival curves for medicine and surgery would have been much further apart and they would never have crossed, even in these low-risk patients. And, of course, this analysis does not even take into account the large numbers of "survivors" who remained alive only because they crossed over from medicine to surgery.

After 22 years, there is no longer any justification for euphemisms about the VA study. It was an early study with multiple, major defects that did not even provide state-of-the-art angiographic and surgical results. Even among patients with chronic stable angina, study patients were an extraordinarily low-risk subset, which made it all the more difficult to demonstrate a surgical benefit. This flawed study is irrelevant and misleading, and it should be allowed to sink into oblivion. Despite the routine referral of elderly, high risk and multiple comorbid candidates in today's surgical practice, the modern results are far superior to those obtained several decades ago in these VA training institutions. It is time to close the VA Cooperative Study of Coronary Artery Bypass Surgery and to relegate its publications to the archives.

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