A critique of the VA cooperative study

William C. Sheldon, M.D.
Department of Cardiology

Floyd D. Loop, M.D.
Department of Thoracic and Cardiovascular Surgery

William L. Proudfit, M.D.
Department of Cardiology

Publication of the preliminary results of the VA cooperative study of medical versus surgical treatment of chronic stable angina pectoris[1] has added fuel to the raging debate over this issue, but has not resolved the question regarding survival. Emotionalism has carried the issue beyond the scientific realm into the lay press, even into the halls of Congress. The study has shown no superiority of one form of treatment over the other and leaves us with the unsettling conclusion that both forms of treatment may be equally good or equally bad. However, a critical analysis of the study raises serious questions whether a prospective randomized multicenter study of a surgical procedure can be carried out effectively in a free society.

Prospective randomized clinical trials of pharmacologic agents have been carried out with notable success, establishing the randomized study as a valuable clinical method for studying the results of drug therapy. Inherent in these studies have been certain key ingredients: (1) carefully designed protocol assuring identical populations for study groups; (2) therapeutic intervention of high quality and reliability; (3) fully informed consent from participating subjects; (4) careful and continuous monitoring of

the data; and (5) provision for early termination of all or any part of the study upon demonstration of clear benefits or excessive risk.

The VA cooperative study raises serious questions in many of these areas.

The carefully designed protocol

Of 2804 patients who fulfilled the initial clinical criteria for inclusion in the VA study, 564 were rejected as unwilling, unreliable, unable to cooperate, or for "other" reasons.[2,3] Of 1392 patients eligible for randomization after arteriography, 348 were rejected for similar reasons. We are not told how many of the rejected patients were subsequently operated on. Is it possible that considerations other than the randomized protocol influenced the selection of patients for the study?

The VA protocol did succeed in developing a pair of study groups virtually identical with regard to certain clinical and anatomical criteria. In order to assure that the angina pectoris in these patients was both "chronic" and "stable," a number of exclusionary criteria were necessary, not all of which were clearly defined (*marked* cardiac enlargement, ventricular aneurysm, *generalized poor* contractility, *marked* elevation of the left ventricular end-diastolic pressure, *large* ventricular size, and poor ejection fraction). These exclusions resulted in a study group with a uniquely favorable prognosis. Patients in the medical series are thought to have fared better than patients in other medical series studied by coronary arteriography in the 1960s.[4] However, when patients with left main coronary artery disease are excluded from earlier series (e.g., Proudfit's surgical candidates),[5] the survival of the remaining patients is quite similar to comparable subsets in the VA medical series. The quality of surgical treatment would have had to be superior in order to show a better prognosis than medical treatment, not the case in the VA study.

The quality of the surgical intervention

Probably the greatest deficiency of the VA cooperative study is the quality of the therapeutic product. Was a surgical procedure meeting the minimal standard of excellence administered equally to each of the randomized subjects? What standards were used to measure the quality of the surgical product? Was the operation applied optimally to each of the subjects?

The VA cooperative study began in 1970, but was "restarted" in 1972 when it was apparent that the mortality and morbidity of coronary arteriography was unacceptably high and when significant differences were observed among participating hospitals with regard to hospital mortality. Changes in professional personnel, inadequate number of patients randomized, and deterioration of the quality of performance were given as reasons for excluding 10 hospitals and adding two hospitals to the list of participants in the study prior to 1972.[2] The participating hospitals randomized an average of 17.6 patients per year in 1972–1974 (8.4 patients per year for surgical treatment). It has been stated that the hospital mortality ranged from 2% to over 12%[6] and averaged 5.6% (3.4% for the top five VA hospitals). These facts do not suggest that a standardized surgical procedure was available

for study in 1972. For a group of 1400 consecutive surgical patients operated on at the Cleveland Clinic in 1973, excluding those with severe left main coronary artery lesions as in the VA study, the operative mortality was 0.6%.[7]

None of the published reports of the VA cooperative study cite the incidence of perioperative myocardial infarction in the series of patients without left main coronary disease, an uncanny omission considering the nature of the therapeutic intervention and the possible impact of this complication on the outcome.[1-3,8-10] In public presentations, the authors have variously "estimated" this incidence to range between 11% and 18%.[6,11] In our 1973 series, the incidence of perioperative infarction was 4%.[7] In the VA series, 49% of surgical randomized patients had three-vessel involvement, but only 21% had triple-graft procedures.[1] It is evident that many did not have complete myocardial revascularization by current standards.

Postoperative graft patency in the VA series was 69%,[1] again casting doubt that a standardized therapeutic product was effectively delivered. Graft patency in our 1973 series was about 87%. Considering these discrepancies, the disparity between the 88% 3-year survival in the VA surgical series and the 95% 3-year survival in the Cleveland Clinic 1973 series is not surprising.

Adherence to protocol and management of data

During the course of the study it became evident that there were potential problems in the interpretation of coronary arteriograms which led to a modification of the protocol. All angiograms were reviewed again, and a central reading laboratory was designated to code "at least 200 and possibly all" of the baseline angiograms.[2,3] In July 1977, the Director of this laboratory informed one of the co-chairmen of the study of the inferior quality of many of the coronary arteriograms and of his concern that patients may have been selected for surgical treatment on the basis of inadequate information.[12] These second readings were completed by December 1975, nearly 1 year after the last patient that was randomized had been operated on. It is reasonable to ask whether any of these patients may have received an inappropriate operation as judged by the reclassified angiograms. Even as late as September 1977, 34 patients remained unclassified with respect to the number of diseased vessels or the state of the left ventricle, and could not be included in analyses of subgroups characterized by these parameters. Such data management does not lend credibility to the study.

The problem of crossover patients is particularly difficult to deal with for reasons which the authors of the VA study have clearly delineated. Nevertheless, there were nearly three times as many nonadherers in the medically randomized group (17%) as in the surgical group (6%) which requires explanation.[1] The published figures leave uncertainty regarding the number of deaths and the method of handling crossover patients. It is stated that adherence to assigned treatment was 90.9% at 21 months, implying that 54 of the 596 were considered dropouts at 21 months. Later, it is stated that 72 patients (18 surgical and 54 medical) did not adhere to assigned treatment

after a minimal follow-up period of 21 months (87.9% adherence). None of the several publications regarding this study provide clear data with respect to the number of deaths and dropouts for medical and surgical groups for each of the follow-up intervals.

Informed consent

The matter of informed consent is especially difficult. Even in 1970 there was substantial evidence that bypass graft surgery was associated with significant improvement in symptoms,[13] and during the ensuing years this has been amply documented in a variety of ways. Surely the subjects were informed that they had a 50% chance of assignment to a treatment group that might achieve little if any benefit upon survival. Were they also informed that assignment to medical treatment might offer a less than 50% chance for symptomatic improvement? Were patients who were randomized in 1970–1971 informed of the reasons for restarting the study in 1972 and were they released from their obligation as subjects in the randomized study? Were those patients who were randomized in 1972 fully informed of the state of the art of surgical treatment among the participating VA hospitals that existed at that time?

Problems in recognizing differences between low risk groups

If two forms of therapy are to be compared, any differences will be most evident in high risk groups and least evident in low risk groups. If any form of medical intervention were to affect prognosis in coronary artery disease, surely this would be most evident when tested in a high risk group. The exclusionary criteria applied in the VA cooperative study resulted in matched medical and surgical groups of remarkably low risk. Therefore, any benefit of one form of treatment over the other might not be evident, especially over a short follow-up interval of 21 months. Poor surgical results (operative mortality, perioperative infarction, graft patency) would tend to obscure further any possible benefit of this form of therapy.

Differences in medical and surgical treatment were evident only in the VA high risk subgroup with left main coronary artery disease.[14] Among this small group (60 patients) the benefit of surgical treatment was evident, despite an operative mortality of 14% and a 12.3% incidence of perioperative infarction. Only because of the extremely poor prognosis in the medical subset was the benefit of surgical treatment evident. To conclude on the basis of this study that bypass graft surgery benefits only patients with left main coronary artery disease is to deny the existence of a prognostic spectrum that has been demonstrated in virtually all other natural history studies based on arteriographic and ventriculographic criteria. Better surgical results might have identified other subgroups that might have benefited from surgical treatment.

The cost of health care continues to escalate. Hospital costs soared from $10 billion in the 1950s to $150 billion in 1976, and coronary artery surgery costs approximately $1 billion annually.[15] Priorities must be considered, however. Coronary atherosclerosis is the greatest cause of death and disability in the western world. Medical treatment is not inex-

pensive. The costs of medication and repeated hospitalizations recur year after year for the life of the patient. Recent studies have suggested that surgical treatment may reduce the number of hospitalizations needed with medical treatment alone and considerably reduce the costs over the long term.[16,17]

When performed proficiently, bypass graft surgery offers symptomatic relief at no added risk in terms of mortality.[18] Nonrandomized studies have suggested that patients with multivessel disease (in addition to left main coronary artery involvement) may realize improvement in survival as well as symptoms. The VA cooperative study has raised more questions than it has answered. An effective randomized control study of a surgical procedure requires criteria for patient selection that are both realistic and carefully defined, quality performance in each of the participating hospitals, rigid adherence to the protocol, fully informed consent of the participating subjects, and scrupulous management and reporting of data. The VA report is deficient on all counts.

References

1. Murphy ML, Hultgren HN, Detre K, et al: Treatment of chronic stable angina; a preliminary report of survival data of the randomized Veterans Administration cooperative study. N Engl J Med **297:** 621–627, 1977.
2. Hultgren HN, Takaro T, Detre K: Medical versus surgical treatment of stable angina pectoris; progress report of a large scale study. Postgrad Med J **52:** 757–764, 1976.
3. Detre K, Hultgren HN, Takaro T: Veterans Administration cooperative study of surgery for coronary arterial occlusive disease. III. Methods and baseline characteristics, including experience with medical treatment. Am J Cardiol **40:** 212–224, 1977.
4. Braunwald E: Editorial. Coronary-artery surgery at the crossroads. N Engl J Med **297:** 661–663, 1977.
5. Proudfit WL, Bruschke AVG, Sones FM Jr: Natural history of obstructive coronary artery disease; ten year study of 601 nonsurgical cases. Prog Cardiovasc Dis (in press).
6. Hultgren HN: VA cooperative study. Presented at the 50th Scientific Session, American Heart Association, Miami, December 1, 1977.
7. Cleveland Clinic Cardiovascular Information Registry. Unpublished data.
8. Hultgren HN, Detre KM, Takaro T, et al: The VA cooperative study of coronary arterial surgery; baseline characteristics of study population and survival in subgroups with medical versus surgical treatment. Prog Cardiol **6:** 67–81, 1977.
9. Detre K, Murphy ML, Hultgren HN: Effect of coronary bypass surgery on longevity in high and low risk patients. Lancet **2:** 1243–1245, 1977.
10. Read RC, Murphy ML, Hultgren HN, et al: Survival of men treated for chronic stable angina pectoris. J Thorac Cardiovasc Surg **75:** 1–16, 1978.
11. Murphy ML, Takaro T, Hultgren HN, et al: Surgical versus medical therapy for coronary artery disease. Survival data. A preliminary report of the randomized VA cooperative study. Presented at 26th Scientific Session, The American College of Cardiology, Las Vegas, March 8, 1977.
12. Gensini G: Personal communication, 1977.
13. Sheldon WC, Rincon G, Effler DB, et al: Vein graft surgery for coronary artery disease; survival and angiographic results in 1000 patients. Circulation **48** (Suppl III): 184–189, 1973.
14. Takaro T, Hultgren HN, Lipton MJ, et al: The VA cooperative randomized study of surgery for coronary arterial occlusive disease. II. Subgroup with significant left main lesions. Circulation **54** (Suppl III): 107–117, 1976.
15. Mustard RA: Major cardiac surgery; are the benefits worth the cost? Ann Thorac Surg **24:** 400–402, 1977.
16. Mathur VS, Guinn GA: Sustained benefit from aorto-coronary bypass surgery demonstrated for 5 years; a prospective randomized study (Abstr). Circulation **55** and **56** (Suppl III): 190, 1977.

17. Collins JJ Jr, Tucker WY, Kopf G, et al: The impact of revascularization surgery upon hospital costs in patients with angina pectoris (Abstr). Am J Cardiol **41:** 44–47, 1978.

18. Sheldon WC, Rincon G, Pichard AD, et al: Surgical treatment of coronary artery disease; pure graft operations with a study of 741 patients followed 3–7 yr. Prog Cardiovasc Dis **18:** 237–253, 1975.