Unstable Angina
Quality of Life

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Coronary artery disease continues to be the leading cause of death in the United States despite an encouraging 48% reduction in age-adjusted mortality since the epidemic peaked in 1963. Coronary artery disease results in approximately 500,000 deaths each year with about 750,000 hospital admissions for acute myocardial infarction and probably an equal number of admissions for unstable angina. Unstable angina can be the harbinger of acute myocardial infarction and sudden death. It likely has a similar coronary pathophysiology of plaque rupture and coronary thrombus formation. Interrupting the process and stabilizing the lesion may be possible with medication alone in many patients. Angioplasty and bypass surgery are important additional therapies should medical therapy fail to control symptoms.

This issue of Circulation includes a paper by Booth et al comparing various indexes of quality of life in patients with unstable angina randomized to a strategy of coronary artery bypass graft surgery with those of a group assigned to a nonsurgical strategy and followed for 5 years. The Veterans Cooperative Studies Program has supported randomized trials of coronary bypass surgery in both chronic stable angina and in unstable angina; these studies have made major contributions to the development of indications for the use of bypass surgery. The European Coronary Surgery Study and two studies supported by the National Heart, Lung, and Blood Institute have also made contributions to this effort.

The Veterans Administration Cooperative Study carried out by Booth et al includes 468 patients with either progressive/new onset angina (Type I, 374 patients) or prolonged angina at rest (Type II, 94 patients) equivalent to class IB and class IIB/IIIB, respectively, in Braunwald's recently proposed classification scheme. Randomization created groups well balanced for recognized prognostically important baseline characteristics (and presumably for unrecognized factors as well). Operative mortality in those assigned to surgery was 4.1%. Analysis of 1-year graft patency determined on 67% of surgically assigned patients revealed that approximately 55% of these patients had all grafts patent and approximately 90% had at least one patent graft. By 60 months 43% of patients assigned to the nonsurgical strategy had undergone bypass; three fourths of these patients had undergone bypass during the first 18 months. Five-year mortality follow-up is complete and reveals no survival difference overall. A survival advantage in surgically assigned patients with three-vessel disease and in surgically assigned patients with impaired ventricular function compared with patients assigned to the nonsurgical strategy has been reported.

Coronary artery bypass graft surgery palliates coronary disease by reducing the frequency and severity of anginal episodes in both stable and unstable angina patients. The observation that at 3 months of follow-up approximately 80% of surgically assigned patients noted improvement in symptoms compared with less than 60% of patients assigned to the nonsurgical strategy is not a surprise. The advantage persisted; at 5 years 55% of the patients assigned to the surgical strategy were free of pain compared with 33% of those assigned to the nonsurgical strategy. Moreover, this improvement in symptoms is reflected in improved treadmill performance, reduced medication requirement, and a trend toward reduced recurrence of unstable angina.

Clinical trial protocols include design compromises which in turn require care in interpretation of trial results. The Veterans Administration study reported in this issue is no exception. The study was designed to detect a 50% reduction in mortality in patients assigned to the surgical strategy in 400 Type I patients and 200 Type II patients, assuming a 5-year mortality in those assigned to the nonsurgical strategy of 30% and 50%, respectively. The group of patients assigned to the nonsurgical therapy had a mortality rate about half that assumed in the sample size calculation, and recruitment of Type II patients resulted in a sample half of that anticipated. Thus, the investigators might have missed a clinically important effect because of the play of chance, in a study with smaller than planned sample size, an unanticipated low annual mortality rate of 4% in the nonsurgically assigned patients with unstable angina, and a substantial "crossover" or lack of compliance with treatment assignment.
Sample size below optimum and crossovers are characteristics shared by all the major bypass surgery clinical trials.\textsuperscript{4,8,9,11} Small sample size is made worse by crossover, which is driven by an ethical requirement. In the event of progression of symptoms all trial protocols permit the use of surgery in nonsurgically assigned patients, and some patients initially assigned to the surgical strategy decline, after reconsideration, to undergo surgery. Prohibition of crossover is impossible in experiments involving patients; anticipated lack of compliance with treatment assignment can be overcome by increasing sample size.

All bypass surgery trials test for differences arising from an initial strategy rather than for differences between surgery now or never, a question that may be interesting in the abstract but unlikely to be as clinically useful as the question of surgery now or later. The primary analysis in randomized trials must be by intention to treat rather than by treatment received, even though small sample size, diluted further by crossover, limits the sensitivity of the experiment to detect an effect.\textsuperscript{16} Evaluation of quality of life is notoriously difficult, particularly in patients who undergo major surgical procedures in trials in which treatment assignment is not easy to mask. Recognition of this problem led to coronary bypass surgery trials designed with concurrent randomized controls and hard primary endpoints of death or death and myocardial infarction. In the study by Booth et al.,\textsuperscript{1} quality of life assessments were carried out as secondary endpoints. Investigators have sought to limit bias in quality of life assessments by using a variety of endpoints with varying degrees of subjectivity, ranging from quite subjective (pain frequency and severity) to more objective endpoints (treadmill time, hospitalization rates, and medication use).

Another problem in assessing quality of life endpoints is incomplete ascertainment of outcome. For example, in the unstable angina study by Booth et al.,\textsuperscript{2} 20–30\% of randomized patients were not seen in clinic follow-up and/or did not have treadmill tests, while, in contrast, mortality follow-up was complete. It is unlikely that patients appearing for follow-up are a random sample of all trial patients, so the risk of bias is raised with no easy way to assess its extent or direction. The investigators concluded that bypass results in an immediate, lasting improvement of quality of life as measured by pain relief. The conclusion would be more certain quantitatively if the findings were based on complete follow-up and insulated from bias by masking of treatment assignment. The quality of life findings of the study\textsuperscript{2} are congruent with other randomized studies in patients with angina and have a plausible biological mechanism, improved coronary blood flow.\textsuperscript{8,14,15}

A major problem with clinical trial design and interpretation is that improved understanding of underlying pathophysiology and other clinical studies has a way of rapidly rendering trials obsolete. This has been particularly true in cardiovascular medicine over the past two decades. When the Veterans Administration Cooperative Study of unstable angina by Booth et al.\textsuperscript{2} began recruitment in 1976, the key ingredients of nonsurgical treatment included long-acting nitrates and propranolol with bed rest and sedation. Anticoagulation was not used routinely; calcium antagonists were not available, and angioplasty had not been attempted in human coronary disease. There have been major advances in both nonsurgical and surgical treatment of patients with unstable angina in the last decade including, perhaps most importantly, the recognition of the pathophysiological importance of plaque rupture and local thrombus formation.\textsuperscript{17,18} Clinical trials have established the efficacy of aspirin in reducing subsequent death and myocardial infarction in patients with unstable angina.\textsuperscript{19,20} It appears that heparin is at least as effective as aspirin in reducing the rates of death and infarction.\textsuperscript{21} Trials are now underway to test the usefulness of thrombolytic therapy and/or percutaneous transluminal coronary angioplasty (PTCA) in patients with unstable ischemic states.

Changes have also occurred in coronary artery bypass graft technique, with emphasis on the use of the internal mammary artery as a more durable conduit, and in the technical aspects of angioplasty, permitting application of PTCA to many patients whose coronary ananomies heretofore made it technically difficult or impossible.\textsuperscript{22,23} Several major trials comparing coronary artery bypass or PTCA in patients with unstable ischemic states are underway. There are major research efforts into new angioplasty methods, including the use of new mechanical devices and of lasers, which may substantially expand the technical range of angioplasty in the future.

Major changes have also occurred in the management of patients with coronary disease after their discharge from the hospital. It is clear, based on research from trials completed in the last decade\textsuperscript{24,25} and on other observations, that reduction of blood cholesterol, blood pressure control, and smoking cessation reduce cardiovascular endpoints in patients with vascular disease. Although risk factor control is mentioned as part of the medical regimen, there are no data reported regarding risk factor modification in the study by Booth et al.\textsuperscript{2} Risk factor modification in the Coronary Artery Surgery Study conducted during the same interval was modest.\textsuperscript{15} Recent studies using angiographic endpoints emphasize the importance of plasma cholesterol level reduction in patients with coronary disease, particularly those who have undergone coronary bypass graft surgery.\textsuperscript{26,27} A number of ongoing studies will further define the extent to which plasma cholesterol level reduction is helpful in patients with coronary disease.

The investigators involved in the cooperative study\textsuperscript{2} continue to follow these patients. Data from the 10-year follow-up will be very valuable in assessing the durability of bypass in these patients. Aging of grafts fashioned 10 years ago and the continued crossover of patients to bypass may lead to convergence of mortal-
ity and quality of life variables. For the moment, after 5 years of follow-up, the study has demonstrated improved pain control and improved exercise performance with reduced medication requirement in those assigned to the strategy of bypass surgery. Surgery may improve survival in selected subsets, particularly in those with impaired ventricular function and possibly those with three-vessel disease.

Cardiologists, cardiovascular surgeons, and their patients with unstable angina have available an effective series of interventions of increasing complexity and cost, beginning with risk factor modification: aspirin and/or heparin; nitrates, \( \beta \)-adrenergic blocking agents and calcium antagonists; thrombolytic therapy; and if need be, PTCA and/or coronary bypass graft surgery. Patients with unstable angina vary widely in characteristics and prognosis. The challenge for physicians is to choose therapy in a proper sequence which results in optimum survival and quality of life for the individual. The study by Booth et al has produced important data that will assist patients and their physicians in making these selections.

References


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