# Protocol for the Bypass Angioplasty Revascularization Investigation

**In this supplement we present the design of the Bypass Angioplasty Revascularization Investigation (BARI). The BARI team of investigators, data coordinators, staff, and support committees are committed to providing the highest quality data to scientifically test the proposed hypotheses. Considerable controversy exists about the extension of percutaneous transluminal coronary angioplasty (PTCA) into the arena of therapy for multivessel coronary artery disease. Although coronary artery bypass surgery has been thoroughly compared with medical therapy in randomized trials, studies of PTCA to date have been observational in nature. The presumption that the results of trials of coronary bypass surgery can be applied to the use of PTCA is not established; this creates a dilemma that requires resolution in the most objective and scientific manner. In the Wangensteens's book (*The Rise of Surgery,* 1978), there is an excellent discussion of the controversy that surrounded the work of Semmellweiss. In one of the earliest efforts to bring science to the bedside and to influence medical practice, he investigated childbirth outcome in terms of whether the physician's hands were washed before delivery. Those times were filled with extreme reluctance on the part of the medical establishment to accept the observations of Semmellweiss. As the Wangensteens suggest, "Trial, not debate, is the proper manner in which to resolve a question of this kind." It is in this spirit that the BARI investigators are conducting the BARI trial. To the best of our ability, we will provide information that will benefit patients and physicians in making decisions on revascularization procedures. (*Circulation* 1991;84[suppl V]:V-1–V-27)**

The application of invasive therapy to the treatment of severe coronary artery disease (CAD) has progressively increased during the past decade. In the United States in 1988 approximately 250,000 patients with CAD were treated with percutaneous transluminal coronary angioplasty (PTCA), and nearly as many patients received coronary artery bypass graft (CABG) surgery (National Center for Health Statistics, 1988; personal communication). These numbers represent dramatic increases in the use of invasive procedures compared with those of 1980, when 6,000 PTCAs and 137,000 CABG operations were performed.[1] Therefore, coronary revascularization is an important component of health care costs in the United States, with current direct costs easily exceeding the prior estimate of over $5 billion for CABG alone in 1984.[2]

At the present time, the choice between PTCA and CABG for patients with multivessel CAD who need revascularization and who are suitable for either procedure represents a clinical dilemma because the relative indications for PTCA and CABG in these patients are not yet clearly defined.

Before informed therapeutic choices between the two procedures can be made, controlled studies are needed to objectively compare the benefits and risks of an initial strategy of PTCA versus CABG in appropriately selected patients. The Bypass Angioplasty Revascularization Investigation (BARI) has been designed to accomplish this through random assignment of revascularization strategy and systematic follow-up over 5 years. Although the primary clinical indication for revascularization varies among BARI patients (symptom relief or treatment of profound ischemia), all patients are judged to be at relatively high risk for subsequent cardiac events.

In addition to the clinical trial component, all patients who are eligible but refuse random assignment are asked to participate in the BARI Registry. The registry also contains a 5–10% random sample of those who are deemed ineligible for random assignment because they are considered angiographically unsuitable for PTCA and/or CABG.

Evidence from this clinical trial will provide a scientific basis for choosing PTCA or CABG as the initial revascularization treatment of severe multivessel coronary disease.

## Specific Aims

BARI is a comparative study of PTCA and CABG, the two most prevalent revascularization methods used to treat advanced CAD. The study focuses on the treatment of patients who have multivessel disease and severe angina or ischemia, those who require revascularization, and those who are suitable for either procedure. The primary aim of BARI is to test the hypothesis that an initial strategy of PTCA in these eligible patients compared with CABG does

not compromise clinical outcome during a 5-year follow-up period.

*Aims of the Randomized Clinical Trial*

Because CABG is of established benefit for patients with severely symptomatic multivessel disease, the use of an alternate treatment strategy, regardless of its potential efficacy, must not impose a greater risk of mortality than CABG. For this reason, and to provide a reliable end point for calculation of sample size, mortality is the primary end point of the trial. The sample size was selected to enable BARI to rule out with high probability that the 5-year mortality rate with PTCA exceeds the 5-year mortality rate with CABG by more than 2.5%. (For a discussion of sample size calculations, see Appendix 3.) Although mortality is essential in assessing the safety of the PTCA strategy in patients with multivessel CAD, other end points of clinical outcome are of critical importance, particularly if there is no difference in mortality between the two treatment strategies. Because the acceptable difference in mortality is small, a large sample size is required. This large sample size also provides sufficient power to examine treatment differences in rates of myocardial infarction (MI), repeat revascularization, and recurrent severe angina or ischemia. Distribution of exercise capacity, ventricular function, and need for medication will also be compared by treatment assignment at selected follow-up points.

In addition, BARI will provide much-needed answers to questions concerning the economic and psychosocial aspects of myocardial revascularization. The economic and quality-of-life consequences of PTCA and CABG strategies over a 5-year follow-up period will be compared. BARI will provide estimates of initial and continuing indirect and direct costs of the two procedures and provide measures on quality of life. These critical data are collected in-depth at seven participating BARI centers in an ancillary study of economics and quality of life (SEQOL). This study is funded by the Robert Wood Johnson Foundation, having had initial funding from Advanced Catheter Systems. In addition to SEQOL, data on the number of significant cardiac hospitalizations, employment status, and limitations of activities are collected for all BARI patients. (Also see resource use and quality of life [p V-8].)

Although BARI is designed for the overall comparison of PTCA versus CABG as the initial strategy, it will also provide comparative data for predetermined subgroups, which are defined by the various clinical and angiographic presentations. Clinical subgroups of special interest are those with unstable angina, stable Canadian Cardiovascular Society Classification functional class III or IV angina, or class I or II angina in the presence of either documented ischemia or recent Q wave MI. Angiographic subgroups will be defined by the number of significantly stenosed vessels, the number and proportion of myocardial territories with a jeopardized coronary supply, the complexity of the lesion and vessel anatomy, and the degree of left ventricular function.

*Aims of the Bypass Angioplasty Revascularization Investigation Registry*

The BARI Registry will include eligible patients who refuse random assignment as well as a 5–10% sample of patients who are excluded from the trial based on angiographic criteria. The group of eligible patients who refused random assignment will lend itself to the investigation of selection factors involved in the choice of PTCA versus CABG. In addition, we will be able to compare the results of treatment selected by choice with that selected by random allocation. The Registry patients who are ineligible for random assignment because of angiographic criteria will be used to assess how angiographic exclusion practices differ across sites, which treatment such patients actually receive, and the long-term outcome with the given treatment.

## Patient Selection

*Inclusion Criteria*

Patients included in BARI must be representative of those who have ***multivessel coronary disease*** and are treated for severe angina or myocardial ischemia in current clinical practice. Specifically, eligible patients must meet the following criteria: ***clinically severe angina or objective evidence of ischemia*** that requires the need for a revascularization procedure, angiographically documented multivessel coronary disease, suitability for both PTCA and CABG, and informed consent for random assignment.

*Patient Screening for Exclusion Criteria*

The population that is considered for BARI consists of those patients who undergo diagnostic coronary arteriography in a BARI institution and may include patients with off-site angiograms.

*Exclusions from screening.* Patients are first evaluated for entry on the screening log. A patient is considered eligible for screening and is placed on the screening log, allowing the patient to be tracked through the remainder of the screening system if the patient has none of the following exclusions: absence of significant coronary disease, primary congenital heart disease, primary valvular heart disease, primary myocardial heart disease (including patients with a ventricular aneurysm, which requires surgery), prior PTCA or CABG, single-vessel CAD, and/or an age ≥80 years.

*Clinical and major angiographic exclusions.* Patients placed on the screening log are evaluated for clinical and major angiographic exclusions. If none of the following exclusions are present, the patient is considered clinically eligible: age <17 years, geographically inaccessible or unable to return for follow-up,

Definitions for terms printed in bold italics may be found in the Glossary; see Appendix 2.

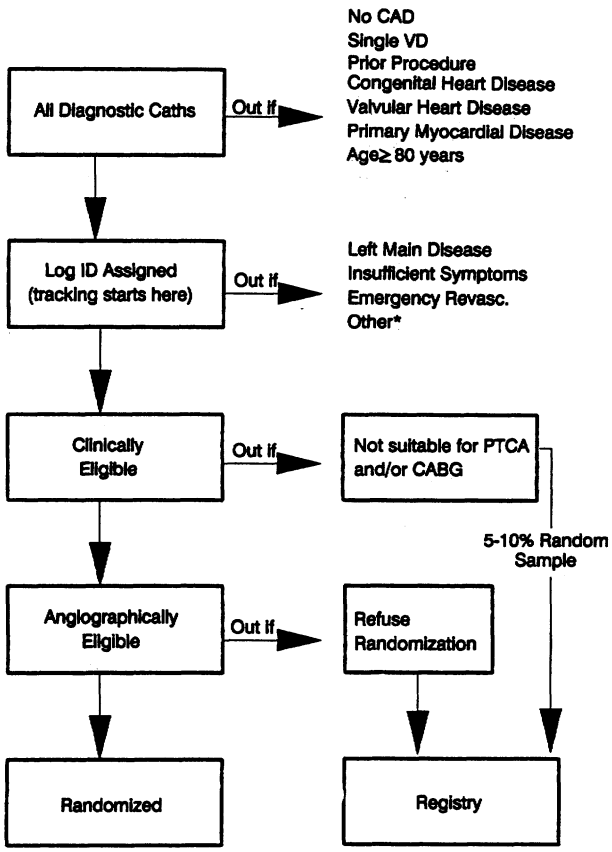


FIGURE 1. *Flowchart showing patient screening mechanism. A full list of exclusion criteria appears within the text of the Protocol (see pp V-2–V-3, Patient Selection). *Other screening log exclusions include noncardiac illness expected to limit survival, age <17, geographic inaccessibility, clinical contraindications to PTCA or CABG, inability to understand or cooperate with protocol, enrolled in competing study, technically unsatisfactory angiogram, extensive ascending aortic calcification, primary coronary spasm, concomitant major surgery required, and pregnancy.*

insufficient angina or objective evidence of ischemia, unstable angina or acute MI, which requires emergency revascularization, left main stenosis ≥50% or of a character that precludes angioplasty, noncardiac illness that is expected to limit survival, extensive ascending aortic calcification, primary coronary spasm, inability to understand or cooperate with protocol requirements, coronary angiogram that is technically unsatisfactory, suspected or known pregnancy, enrollment in a competing clinical trial, contraindication to CABG or PTCA because of a coexisting clinical condition, and/or concomitant major surgery that is required (e.g., aortic and/or mitral valve surgery, carotid endarterectomy, and/or resection of left ventricular or abdominal aortic aneurysm).

*Final angiographic exclusion.* Clinically eligible patients are evaluated for final angiographic eligibility. The surgeon and angioplasty operator assess the patient's suitability for each procedure according to their technical expertise and considerations of patient safety. On the basis of angiographic findings, patients are excluded at this point if the patient is judged to be unsuitable for PTCA and/or CABG. (The criteria for this decision are described on pp V-3–V-6, PTCA and CABG guidelines, respectively.)

Because the BARI investigators recognize the limitations of trying to prospectively describe all the features that define suitability for PTCA and CABG, the final evaluation for eligibility involves the subjective judgment of both the surgeon and the angioplasty operator. This results in a certain degree of diversity across centers, an additional strength of the trial that allows the results to be applicable to the broad group of patients considered for angioplasty. Baseline data collected on all patients will allow BARI to characterize in detail angiographic findings of patients considered clinically eligible for the trial. The population excluded at the final angiographic level will be studied by using a 5–10% random sample that is selected for inclusion in the registry.

*Informed consent.* Eligible patients who sign an informed consent for random assignment are entered in the clinical trial. Those who refuse random assignment but sign an informed consent for follow-up are entered in the registry. Those who refuse follow-up are recorded, but no further data are collected.

Prototype consent forms for randomly assigned and registry patients are shown in Appendix 8. Local institutional review boards may prefer a modification of the consent forms to provide additional information. Any local change in the consent forms must meet Public Health Service requirements.

*Random assignment of patients.* The Coordinating Center (CC) prepared the sequence of random assignment of patients to the treatment groups before their enrollment. Random assignment was stratified by clinical site, and within each clinical stratum, blocks of varying length were used. The sequence of random assignment was verified and incorporated into the BARI computer system for each clinical site. Details of the design and implementation of random assignment are presented in Appendix 4.

*Participation in other trials.* Randomly assigned BARI patients may not participate in any other clinical trial while they are participating in BARI. However, registry patients are free to participate in other studies. BARI clinical sites may participate in other studies for which BARI-eligible patients are also eligible, but they must continue to meet their commitment to randomly assign an adequate number of BARI patients.

## Angioplasty Guidelines

### *Criteria for Acceptable Candidacy to Percutaneous Transluminal Coronary Angioplasty*

To be suitable for PTCA, a patient must have anatomic characteristics associated with a reasonable probability of successful balloon dilatation. The arteries that are patent but significantly narrowed

should be able to sustain prolonged occlusion without the development of cardiogenic shock. Although the potential for complete revascularization is not a requirement for entry of patients in BARI, there must be a reasonable probability for successful relief of the major stenoses presumed to be contributing to active myocardial ischemia. These criteria are judged by a BARI-certified angioplasty operator before random assignment. Reasons for excluding patients are documented on the Angiographic Exclusion form and include the following: PTCA of (a) vessel(s) responsible for ischemia is unlikely to be successful because of excessive tortuosity of vessels proximal to the lesion, excessive angulation within the lesion, excessive lesion length, total chronic occlusion, or inability to dilate because of excessive calcification; and PTCA would be excessively dangerous because abrupt closure is likely and would result in cardiogenic shock, or a major side branch cannot be adequately protected.

*Guidelines for Strategy in Percutaneous Transluminal Coronary Angioplasty*

Once a patient has been randomly assigned to PTCA, the procedure must be performed within 2 weeks. Clinical information derived from the medical history, physical examination, ECG, and noninvasive stress testing, coupled with the results of coronary and left ventricular cine angiography, determine the strategy to be used for each patient assigned to PTCA. The aim of the procedure is to maximize the effectiveness of PTCA in relieving ischemia and minimizing the risk of procedure-related untoward events. A lesion may be targeted for PTCA if all of the following conditions are met: a stenosis represents a 50% or greater diameter reduction by caliper measurement, the normal vessel diameter adjacent to the site of stenosis is >1.5 mm, and the vessel supplies a sizable region of viable myocardium. Nonsignificant lesions, lesions located distally or in small arteries, and lesions in arteries that supply areas of infarction are not routinely dilated. For each patient a hierarchy of lesion priority is set in such a way that PTCA is attempted first in lesions that are most likely to be responsible for the patient's ischemia. Before revascularization of a patient in the study, the clinical importance and suitability of each lesion for PTCA is categorized, and a treatment plan is specified by a BARI-certified operator. These data will be used to define patient subsets for analysis of PTCA outcome and to assess operator performance.

*Guidelines for the Percutaneous Transluminal Coronary Angioplasty Procedure*

For randomly assigned patients, all PTCAs should be performed by a certified BARI angioplasty operator, and the initial PTCA must be performed by a certified BARI operator. An experienced catheterization laboratory staff should assist, and backup cardiac surgical support must be immediately available. Preprocedure medication should include aspirin (unless contraindicated) and other medication deemed appropriate for the clinical status of the patient. Each patient should be fully heparinized during the procedure.

PTCA should be performed in a cardiac catheterization laboratory that is capable of providing high-quality video images with immediate replay (including 4- or 5-in. image-intensifier modes), biplane imaging or rapidly available orthogonal single-plane images, compound angulated projections, hemodynamic monitoring, and high-quality film processing. A full range of commercially available guiding and dilating catheters and guide wires should be available. PTCA may be performed by either the brachial or femoral approach.

Each procedure begins with a coronary cine angiogram of the vessels to be dilated. At least two scout projections of each vessel are obtained. For each targeted lesion, PTCA is attempted with the goal of achieving <50% residual stenosis and normal ***TIMI*** (grade 3) distal flow*.[2] A PTCA procedure is considered completed when the patient is removed from the cath lab table.

Considerations of patient safety or logistics may require that the initial PTCA procedure be performed over more than one session. If this approach is used the decision to do so must be made by the end of the first procedure, and all subsequent procedures should be performed within 2 weeks after the first. After PTCA cine angiography of treated arteries should be repeated in the same projections as initially used. Additional projections may be acquired as needed.

Heparin should be continued for 24–48 hours after the procedure in patients whose PTCA was performed for total occlusion or was associated with lesion dissection, thrombosis, transient occlusion, or in whom distal embolization was observed. Oral calcium antagonist therapy should be continued for 4 weeks, and a regimen of one aspirin tablet per day should be indefinitely continued.

In the case of abrupt closure, every effort should be made to reestablish patency and flow and avoid MI. This effort may include emergency CABG or the use of ***new technology devices.***

*Complications*

Patients are monitored for adverse events throughout the hospitalization. These complications and their definitions are listed in Appendix 5. The need for additional revascularization procedures, including emergency CABG and repeat PTCA for abrupt reclosure, are also recorded. Each lesion that is subjected to PTCA is assessed for the occurrence of dissection and acute closure.

*Guidelines for Repeat Percutaneous Transluminal Coronary Angioplasty*

Patients who have an initially successful PTCA may undergo repeat PTCA when anatomic and clin-

*TIMI flow criteria are given in the Glossary; see Appendix 2.

ical circumstances are judged suitable. This may occur under two circumstances: restenosis of a successfully dilated coronary artery that is associated with clinical manifestations, either by recurrent angina or significant ischemia documented by objective measures (see p V-8); and recurrent ischemia for which repeat angiography indicates the development of new significant CAD that is responsible for the ischemia and amenable to PTCA.

When PTCA is repeated, the procedure should be performed by a BARI operator according to protocol guidelines. Indications for repeat PTCA will be monitored carefully, particularly for patients participating in a study of the 1-year follow-up angiography. Repeat PTCA must be performed in accordance with BARI indications for such procedures. Deviations are considered protocol violations and require defense and justification by the responsible BARI investigators.

Patients that are randomly assigned to CABG who have recurrent ischemia that is associated with bypass conduit or native artery stenosis or occlusion for which PTCA is deemed desirable should have PTCA performed by a certified BARI operator in accordance with the BARI protocol.

*Guidelines for Subsequent Coronary Artery Bypass Graft Surgery*

It is possible that patients who are randomly assigned to PTCA will have CABG before, during, or after their initial PTCA procedure. To ensure the appropriate use of CABG in such patients, the following guidelines are recommended. 1) Once the patient is randomly assigned, PTCA must be performed within 2 weeks to minimize the time during which pre-PTCA crossover could occur. 2) During the initial PTCA procedure, patients who experience closure of an artery that was previously patent but narrowed may require emergency CABG for relief of ischemia or infarction if they are refractory to repeat angioplasty or medical therapy. The decision to proceed with emergency CABG under this circumstance should be strictly based on the need to provide appropriate patient care. 3) After an initially successful PTCA, indications for subsequent elective CABG are either recurrence or persistence of disabling symptoms that are accompanied by evidence of myocardial ischemia resulting from inadequate or unsatisfactory PTCA and anatomy that is judged to be unsuitable for repeat PTCA. 4) Subsequent CABG may be necessary for the recurrence of symptoms and ischemia after a period of symptomatic relief with evidence of restenosis of a previously successfully dilated coronary artery, as described in the previous section. Patients who require revascularization after initial PTCA should first be considered candidates for repeat PTCA. PTCA may be repeated more than once if there is a repetitive recurrence of symptoms or severe ischemia as defined. The decision to proceed with CABG in such patients should be based on the presence of angina or ischemia of sufficient severity to warrant surgery in the presence of evidence that the initial or repeat PTCA has been unsuccessful. If PTCA would be particularly difficult or associated with an increased risk of untoward events, CABG may be considered without repeat PTCA. 5) Subsequent CABG may be necessary for the recurrence of symptoms or ischemia resulting from the development of new CAD. Consideration should be given first to repeat PTCA. If repeat PTCA is judged to be inappropriate or not feasible, then CABG should be considered if the symptoms are disabling despite optimal medical therapy or if severe ischemia is documented.

*Angioplasty Operator Certification*

Criteria for certification include participation as an independent operator in more than 300 elective PTCA procedures, of which at least 100 were multivessel disease cases; demonstration of a success rate per lesion of 85% or greater for subtotal lesions among the last 100 cases; overall incidence per patient of PTCA-related acute myocardial infarction or emergency CABG of 5% or less; and an overall mortality rate of 2% or less for elective PTCA patients.

To complete certification requirements, each BARI angioplasty operator submits to the Central Radiographic Laboratory (CRL) preprocedure and postprocedure films of five consecutive PTCA procedures performed on patients with multivessel disease. The Central Radiographic Laboratory evaluates the films and determines the quality of the procedures, requesting additional films as needed. In-depth information about the CRL may be found in Appendix F. The current BARI certified angioplasty operators at each participating clinical site are listed in Appendix 8.

*Classification of Outcome of Percutaneous Transluminal Coronary Angioplasty*

To define what constitutes a successful PTCA procedure is complex. One approach will be to assess lesion improvement. The following are requirements for complete lesion improvement: TIMI grade 3 flow, luminal diameter reduced by $\geq$20%, and residual stenosis of <50% diameter narrowing. If partial, the lesion that is subjected to PTCA has all of the following features: TIMI grade 3 flow and luminal diameter reduced by $\geq$20% but residual stenosis of not <50% diameter narrowing. If there is no lesion improvement, neither of the above definitions for this improvement has been met.

Patients who undergo a PTCA procedure in which each diseased vessel is not dilated but all targeted vessels are improved is classified as "incompletely revascularized by intent." Patients in whom PTCA results are partially satisfactory (that is, not all targeted vessels are improved) are classified as "incompletely revascularized but not by intent."

*Lesion Classification*

In the analysis of PTCA outcome, it will be important to describe the characteristics of the lesions that

are targeted for treatment. The lesion classification system developed for use in BARI is described below.

1) BARI class A–A lesion is considered to be class A if it exhibits all of the following characteristics and has no class B or C characteristics: discreteness with critical narrowing of <10 mm in length, vessel diameter adjacent to the site of stenosis of >1.5 mm, lesion accessible and not excessively tortuous, subtotal occlusion, and concentricity with smooth borders.

2) BARI class B–A lesion is considered to be class B if it exhibits at least one of the following characteristics but none of those of class C: discreteness with critical narrowing 10–20 mm in length, recent (within 3 months) total occlusion, moderate vessel tortuosity proximal to the lesion, irregular borders, ostial location, significant calcification, lesion in bifurcation, moderate vessel angulation within lesion, thrombus, ulceration, and/or eccentricity.

3) BARI class C–A lesion is considered to be class C if it exhibits any of the following characteristics: excessive vessel tortuosity proximal to the lesion or excessive vessel angulation at its site, chronic (>3 months) total occlusion ***(TIMI grade 0)*** or an unknown period of total occlusion, critical narrowing of >20 mm in length, and/or inability to protect major side branches.

*New Technology Devices*

The New Technology Committee monitors the development of new techniques and devices such as stents, cardiopulmonary support system, atherectomy, and laser and recommends if and under what circumstances they can be used in BARI. No new devices, neither those of Investigative Device Exemption (IDE) nor those of new technology that are federally approved, are to be used as an initial strategy in randomly assigned patients. The devices can be used in clinical situations such as abrupt closure with hemodynamic compromise in which, based on local experience and judgment, the technique is in the best interest of the patient. This restriction does not apply to registry patients. After completion of the initial single or planned staged PTCA procedure, new technology devices may be used if additional coronary interventions are required.

## Surgical Guidelines

*Criteria for Acceptable Candidacy for Surgery*

Before random assignment, a BARI-certified surgeon must deem the patient suitable for CABG. Specifically, patients must have the following characteristics: target vessels of an adequate size for insertion of a bypass graft (i.e., luminal diameter of >1 mm in all arteries to be bypassed); satisfactory distal runoff; no severe diffuse atherosclerotic involvement of distal coronary arteries including the absence of multiple discrete severe lesions throughout the course of the artery to be bypassed; absence of extreme aortic calcification; and disease severe enough to warrant surgery.

Although the patient must meet the entry angiographic criteria for multivessel disease, the bypass of additional arteries with only 50–60% luminal diameter narrowing by visual assessment in a patient randomly assigned to CABG is permissible.

*Guidelines for Operative Management*

Once the patient is randomly assigned to CABG, the procedure must be performed within 2 weeks. Rigid control of all aspects of the management of the patient during and after surgery is not possible, but the surgery form documents the techniques and methods used in the surgical management of these patients. Anesthetic techniques are not standardized. Cold potassium cardioplegia (either crystalloid or blood) is the protection of choice; however, cold ischemic arrest may be routinely preferred by some surgeons or in special situations, and this decision is left to the individual surgeon's judgment.

The internal mammary artery should be used for revascularization of the left anterior descending coronary artery whenever feasible. The choice of conduit for revascularization of other arteries depends on the experience and judgment of the surgeon. Details of the cannulation technique, methods of myocardial preservation, grafts used, aortic cross clamping, duration of cardiopulmonary bypass, perioperative medications, and patient status are recorded.

Preoperative and postoperative use of antiplatelet drugs is recommended. For elective procedures 100 mg dipyridamole four times daily for the 2 days preceding CABG may be used, with daily aspirin intake after operation when deemed reasonable. In the absence of evidence that long-term dipyridamole therapy is essential after CABG, aspirin not exceeding 325 mg/day will be acceptable unless there are contraindications to the use of antiplatelet drugs.

*Complications*

Patients are monitored for adverse events throughout their hospitalization. These complications and their definitions are listed in Appendix 5.

*Guidelines for Repeat Coronary Artery Bypass Graft Surgery or Subsequent Percutaneous Transluminal Coronary Angioplasty*

Repeat CABG should be considered on either the recurrence of significant clinical manifestations that suggest a need for further invasive therapy to relieve myocardial ischemia or on discovery of evidence of profound ischemia with exercise testing (see Inclusion Criteria, p V-2). Final decisions regarding the appropriateness of CABG or subsequent PTCA in patients who have had prior CABG are based on angiographic evidence of graft narrowing or progressive and severe atherosclerosis in ungrafted vessels to a narrowing of the luminal diameter of ≥50% by caliper measurement. Patients who have severe lesions in ungrafted coronary arteries or bypass grafts may be considered for

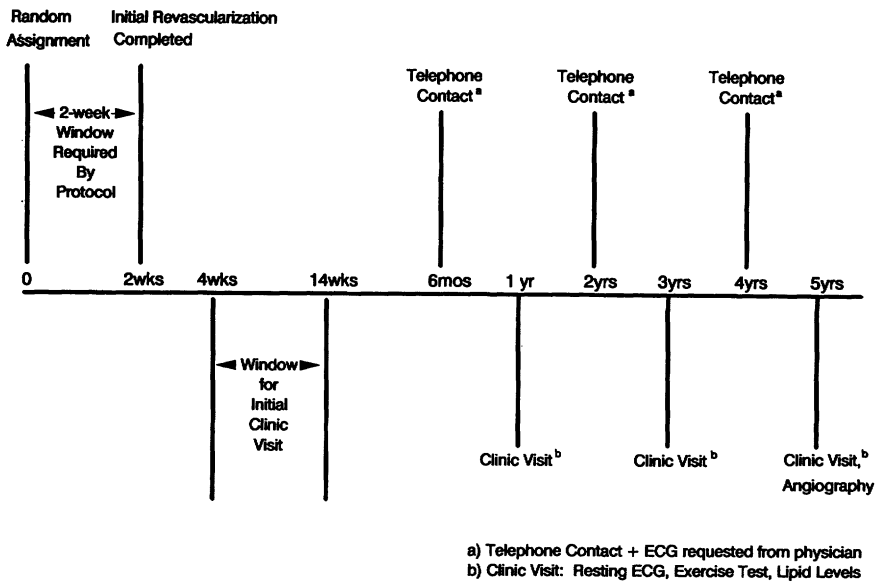


FIGURE 2. *Follow-up chart for randomly assigned patients. Patient follow-up is described more fully on p V-7. Follow-up for registry patients occurs at identical intervals except that the 4–14-week contact is omitted, and all follow-up is done by telephone contact.*

PTCA if recurrent symptoms or signs of profound ischemia are thought to be related to lesions in vessels that are amenable to PTCA.

*Surgeon Certification*

Each surgeon who performs CABG on patients who are randomly assigned in the BARI trial will require initial certification that is based on the following criteria: practice as an attending staff surgeon for 3 years or more, majority of practice devoted to coronary artery surgery, most recent 100 consecutive primary, elective, isolated CABG operations with a mortality rate of no more than 2% (death within 30 days of procedure) and an MI rate of no more than 4% (new Q waves within 30 days of procedure), performance as principal surgeon of 100 or more CABGs with internal mammary artery grafts, and the principal BARI cardiac surgeon at the participating BARI Clinical Unit is satisfied that the judgment, technical performance, results, and care after the procedure meet current standards of the institution's Department of Surgery.

*Surgeon Participation*

BARI surgeons are an integral part of the study. They serve as representatives on all working committees and share responsibility with the cardiologists for adherence to protocol and policy decisions. The surgeons who are currently participating in the BARI trial are listed in Appendix 8.

**Patient Follow-up and End Point Ascertainment**

Effective follow-up depends on the relationship developed by the BARI staff with referring physicians and patients. All BARI centers make an effort to actively involve referring physicians in the study. This helps to ensure that therapy guidelines are followed and that subsequent revascularization is performed at BARI institutions according to the guidelines.

Patients in BARI are followed for a minimum of 5 years from the time of entry into the randomly assigned trial or registry. During this follow-up period nine major end points are ascertained: these are mortality, MI, angina/chest pain, myocardial ischemia, subsequent revascularization, resource use, quality of life, angiographic characteristics at 5 years, and left ventricular function at 5 years.

*Scheduled Follow-up*

Scheduled follow-up points are at 4–14 weeks (randomly assigned patients only); at 6 months; and at 1, 2, 3, 4, and 5 years after study entry. Randomly assigned patients alternate between clinic visits (4–14 weeks and 1, 3, and 5 years) and telephone contact (6 months and 2 and 4 years), and registry patients have telephone contacts only (see Figure 2). During the clinic visit, randomly assigned patients undergo ECG and exercise treadmill tests, and blood is drawn for fasting-state serum lipid levels. When the follow-up is by telephone, an ECG is requested from the primary physician. Data collected for the randomly assigned and registry patients are identical with the exception of the early follow-up, lipid levels, and exercise treadmill tests.

Information that is collected at each contact includes symptomatic status, health behavior (diet, exercise, etc.), and quality of life. If a follow-up contact is not possible within the specified time window, the evaluation takes place thereafter as soon as possible. During each scheduled follow-up, events that require data collection to document end points are identified.

*Ascertainment of End Points*

At each follow-up contact all hospitalizations that occurred since the last contact are identified. A

Hospital Course form is required for the following conditions: cardiac hospitalization for 3 days or longer, cardiac procedure (coronary angiography, PTCA, CABG), hospitalization of any length for cardiac arrest, and hospitalization of any length for a condition thought to be a complication of a revascularization procedure.

Data from the Follow-up and Hospital Course forms are used to identify study end points. For each end point additional data are collected as outlined below.

1) Mortality—when a patient is identified as deceased, the CC must be notified within 3 days by means of a Notification of Major Event form. In addition, the following information must be sent to the CC: a mortality data form, a narrative report from the Principal Investigator that describes the events surrounding the death and that is signed by the BARI surgeon and/or PTCA operator involved with the case, a death certificate, a coroner's report (if autopsy is done), a cath lab report (if the patient died within 30 days of PTCA), a surgical report (if the patient died within 30 days of CABG), any ECGs performed within 24 hours of death, and any cardiac enzymes drawn within 24 hours of death. This information is used by the ***Morbidity and Mortality Classification Committee (MMCC)*** to categorize each death.

2) MI—when MI is suspected, all ECGs that are recorded within 3 days after the event are sent to the Central ECG Laboratory (in-depth information about the Central Electrocardiographic Laboratory [CEL] may be found in Appendix 7), and a Suspected MI report form is required. These data are used to determine whether the event was an MI. When data are missing or inconsistent, the MMCC reviews all available data to determine whether an MI occurred. MIs that do not result in hospitalization will be identified through the yearly scheduled ECGs.

3) Angina—angina, which is classified as stable or unstable, is assessed at scheduled follow-up points and during hospitalization. Stable angina is classified according to the ***Canadian Cardiovascular Society Classification (CCSC)***. Unstable angina is classified according to the presence or absence of acceleration (increased frequency, severity, duration), pain that lasts 20 minutes or longer and is associated with negative cardiac enzymes, pain that continues within 14 days after infarction, transient ECG changes, and pain at rest.

4) Myocardial ischemia—exercise treadmill testing will be used to assess ECG evidence of myocardial ischemia in randomly assigned patients only. An exercise ECG is performed at 4–14 weeks and 1, 3, and 5 years. Additional exercise ECGs are required when myocardial ischemia is a reason for subsequent revascularization. All exercise ECGs are evaluated by the CEL for a ***myocardial ischemic response***.

5) Subsequent revascularization—all revascularization procedures subsequent to the initial revascularization require data collection forms, including Repeat Revascularization, PTCA or CABG Procedure, and Hospital Course forms, and preprocedure and postprocedure ECGs. Angiography in asymptomatic patients is discouraged except for the scheduled angiogram at 5 years and the 1-year angiogram in patients enrolled in the 1-year angiographic study. No patient should undergo repeat revascularization on the basis of anatomic findings alone. To be eligible for angiography during follow-up, a BARI patient must have clinically severe angina, ischemia, or infarction as described by at least one of the following criteria: unstable angina, CCSC III or IV angina, CCSC I or II angina and an ejection fraction of <50%, MI (Q wave or non–Q wave) after the initial procedure, and/or ***severe ischemia on noninvasive testing*** after initial revascularization. After angiography, the decision to perform a repeat revascularization procedure is left to the discretion of the investigator and the referring physician; however, the guidelines for subsequent revascularization (given in detail on pp V-3–V-7) must be followed in randomly assigned patients, and revascularization should be performed by a BARI surgeon or angioplasty operator.

6) Resource use—resource use is calculated by using the mean number of significant cardiac hospitalizations. SEQOL is collecting bills from initial and follow-up hospitalizations as well as data concerning follow-up outpatient visits, tests, procedures, and medications. Data are also being collected concerning the wider economic impact of the two procedures, particularly on employment. These data will be analyzed to compare the profile of long-term costs and benefits of PTCA and CABG.

7) Quality of life—at baseline and at each follow-up point, quality of life is assessed by using a brief questionnaire. Data on employment, self-care, social life, home life, sex life, and leisure activities are included. The SEQOL ancillary study collects data on an array of quality-of-life measures at baseline and during follow-up, including functional status, emotional health, health concerns, and social functioning.

8) Angiographic assessment—the extent of revascularization will be angiographically assessed at the 5-year follow-up. The following criteria will be evaluated: the condition of CABG revascularization conduits (stenosis, disease, patency); condition of dilated segments; revascularization status (e.g., global left ventricular coronary perfusion and regional perfusion in relation to baseline stenoses of a >50% reduction in luminal diameter); progression of preexisting lesions or development of new lesions in native vessels that affects revascularization status; and adequacy of revascularization, as indicated by integration of regional coronary distribution with regional wall motion.

9) Left ventricular function—left ventricular ejection fraction will be angiographically obtained at baseline and at 5 years. In the event that a contrast left ventriculogram is not obtained or is technically inadequate, a radionuclide angiogram will be required as a surrogate measurement.

## Concomitant Therapy Guidelines

*Introduction*

Patients who are enrolled in BARI must receive careful attention to concomitant medical therapy, regardless of assignment to PTCA or CABG. It is important to maintain comparability of concomitant therapy for the two treatment strategies to avoid bias in the comparison between the strategies. Although most patients are followed primarily by their local physicians, the BARI investigator must establish an appropriate relationship with the patient and referring physician to ensure careful attention to concomitant medical therapy according to the guidelines outlined below.

*Risk Factor Modification*

Risk factor modification will be initiated for all patients after enrollment in the study. Because all randomly assigned patients will be seen at the 4–14 week follow-up, it is the responsibility of the BARI investigators to initiate risk factor modification if it has not already been undertaken at the time of revascularization.

*Behavior modification.* Instruction for behavior modification in the areas of smoking, exercise, and diet is initiated for all patients after enrollment in the study and is reinforced at each follow-up clinic visit and telephone contact.

*Treatment of specific medical problems.* Hypertension—treatment may include common medications that are used after PTCA and CABG (calcium channel blockers, β-blockers) as a first-line therapy in an attempt to simplify medical therapy. Angiotensin converting enzyme (ACE) inhibitors, which are used as a first-line antihypertensive therapy in clinical practice, may also be used as indicated. The criterion for treatment is a resting systolic blood pressure of >160 mm Hg or a diastolic blood pressure of >90 mm Hg on two measurements. The goal of therapy is to maintain a blood pressure of <140/90 mm Hg. Diabetes—this will be treated with diet, oral hypoglycemic agents, and insulin, as clinically indicated. When control is poor, consultation with a diabetologist should be obtained. Lipid abnormalities—total cholesterol, HDL, LDL, and triglycerides are obtained at baseline, 4–14 weeks, and annually thereafter. Baseline diet histories are encouraged though not recorded for BARI. Patients are instructed in an appropriate diet program based on individual patient profile. Diet therapy remains an integral part of the approach to lipid disorders and must be maintained regardless of drug regimens. Every reasonable effort should be made to achieve the following target lipid levels: total cholesterol less than 180 mg/dl, HDL cholesterol greater than 45 mg/dl, LDL cholesterol less than 110 mg/dl, triglycerides less than 120 mg/dl, and a total cholesterol/HDL ratio of less than 4.5.

Patients who do not sufficiently respond to diet and exercise programs should begin lipid-lowering drug therapy, following the algorithm proposed by the National Cholesterol Education Program.[8] Surgery or a recent MI may temporarily lower the serum cholesterol value, and this must be taken into account when evaluating lipid values.

*Additional Concomitant Therapy*

All patients should be indefinitely maintained on antiplatelet therapy with one aspirin per day unless the drug is contraindicated or not well tolerated. In the latter case, alternative therapy with other antiplatelet drugs may be considered. Recurrent myocardial ischemia should be treated with nitrates, calcium channel blockers, and β-blockers according to usual clinical practice.

## Data Analysis

*Introduction*

BARI compares the safety and efficacy of the PTCA and CABG treatment strategies rather than the treatments themselves. All primary analyses will be conducted by intention to treat regardless of what treatment or treatments patients received. Comparisons of treatment strategy will be made not only for the entire randomly assigned trial population but also within relevant subgroups.

*End Points*

To compare end points, 5-year incidence rates and confidence limits will be calculated for the difference in rates between the initial CABG and initial PTCA strategies. The primary study end point is mortality at 5 years. Other major end points include MI, angina/chest pain, myocardial ischemic response, subsequent revascularization, resource use, quality of life, and measures of angiographic characteristics and left ventricular function at 5 years.

*Composite End Points*

To simultaneously analyze several outcomes, composite end points will be created. For example, angina-free and event-free survival are best viewed in a hierarchical manner, which has been used to express outcome in the National Heart, Lung, and Blood Institute PTCA Registry. When assessing long-term symptomatic relief, subsequent procedures and pharmacological intervention must be taken into account. This will be done in a cross-sectional analysis. When given sufficient intervention, it is expected that most patients will end up either asymptomatic or mildly symptomatic at follow-up. The comparison of the two treatments will be based on the number and types of procedures and the amount of medication that is required to achieve asymptomatic status. The distribution of the most severe form of intervention is expected to be inherently different between the two treatment strategies. The CABG group undergoes a more extensive and invasive technique initially, whereas the PTCA strategy group is expected to have a greater number of subsequent procedures during follow-up.

*Subgroups*

As much as possible, we will limit formal analyses to those subgroups that have been specified a priori. It should be noted that because of the smaller sample sizes, these subgroup analyses will have limited power. Multivariate models that include treatment by covariate interaction will be used to see whether the treatments differentially affect outcome in various clinical subgroups. Important baseline factors that define subgroups include the following: symptomatic status (angina/ischemia pattern), left ventricular function, extent of myocardial ischemia, and angiographic risk (e.g., the presence of a class III lesion or the amount of myocardium at risk). Some subgroups might also be created on the basis of exploratory statistical analyses. Analysis of a multitude of such subgroups creates a multiple-comparison problem that will be acknowledged.

*Methods of Analysis*

Methods of analysis can be classified by whether data are collected cross sectionally (e.g., 5-year ventriculography), longitudinally (e.g., angina status at each follow-up point), or the time to event (e.g., time from baseline to death).

*Analysis of baseline data.* Comparability of the two treatment groups is expected because of the process of random assignment; nevertheless, distributions of baseline characteristics within the two groups will be examined. The following set of key baseline characteristics will be defined: known risk factors for cardiac mortality (e.g., history of congestive heart failure, previous MI, history of diabetes, and history of hypertension); usual coronary risk factors (lipid levels, smoking status, and blood pressure levels); angiographic risk factors (severity of coronary artery disease, impaired left ventricular function); duration and nature of symptoms, functional capacity, medication use, and results of baseline ECG; and demographic factors (age, sex, race, education, and socioeconomic status).

Suitable techniques will be used to test for comparability of the distribution of these variables between the two treatment groups. Results of these analyses will be used to describe the study population and to determine any imbalance for which adjustment must be made in the final analysis of treatment comparisons.

*Time-to-event analyses.* Standard life table techniques will be used to analyze mortality and MI. All-cause mortality and cardiac mortality will be separately assessed. Cumulative event rates for survival and MI-free survival will be compared between the two treatment groups.

*Cross-sectional and longitudinal analyses.* Some important BARI end points, such as the status of angina and myocardial ischemic response, will be measured and analyzed cross sectionally.

Some patients originally present with angina and others are asymptomatic with ischemic manifestation at entry. Patients with angina can be analyzed for the recurrence of angina, whereas ischemic patients can be separately analyzed for ischemia at follow-up. This analysis (in effect two subgroup analyses) would describe the relative efficacy of the two treatments for relief of the specific symptoms that the original strategy was intended to relieve. Alternatively, the subgroups can be combined and analyzed for the recurrence of any symptom.

Observations at multiple time points will be handled by various approaches. One method will simply be to assess the outcome at final follow-up. Another approach is to average the severity of response over multiple observations during follow-up. Profile analysis, generalized linear models, and survival models that allow inclusion of time-dependent covariates (e.g., events, medications) may be appropriate to examine differences between treatments over time in an exploratory manner.

Further cross-sectional analyses include the following examples. Exercise testing—exercise test results will be compared at each time point by treatment. The association of exercise test results and subsequent revascularization procedures will be examined. Return to work—employment status before and after treatment will be cross tabulated. The interpretation of such data will take into account the fact that a large portion of the BARI population will be men and women near retirement age who will not remain in the active labor force, regardless of the success of the procedure. Cost analysis—a major ancillary study will be devoted to the thorough evaluation of cost data generated from BARI by seven clinical centers. Analysis of cost data in the main study will be limited to the comparison of the number of significant cardiac hospitalizations for each of the two initial strategies. Follow-up angiographic analyses—the angiographic follow-up data, collected at 1 year at selected centers and at 5 years at all centers—will provide information in the following areas: graft patency, patency of dilated segments, and progression/regression of the atherosclerotic process in both treated and untreated segments. The distribution of changes in these areas between baseline and follow-up angiography will be compared by treatment group. A myocardial jeopardy index, which is computed by the CRL from the angiography readings, will allow overall assessment of revascularization results.

*Interim Data Analysis*

End point data are not revealed to clinical investigators during the course of the study but are presented at semiannual meetings of the Safety and Data Monitoring Board (SDMB). First and foremost, mortality and MI rates by treatment group are presented. These rates are expected to be relatively low and similar in the two treatment groups. Procedural complications are reported for each treatment group, as are rates of subsequent procedures during follow-up. Should one of the treatment groups experience significantly higher rates of mortality or MI, the SDMB would consider either early termination of the trial or modification of the protocol to exclude patients in certain subgroups.

*Registry Analyses*

*Eligible but not randomly assigned patients.* It is assumed that the BARI clinical trial results would hold true in a larger population of patients whose disease characteristics are similar to those of the BARI patients. To test this assumption, outcomes from the randomly assigned trial will also be studied in BARI-eligible patients who do not consent to random assignment. If after adjustments for differences between the randomly assigned and the eligible but not randomly assigned groups the long-term outcome by treatment is similar, then the trial results can be generalized to patients who meet BARI criteria.

In spite of careful statistical adjustments to maximize comparability, the investigation of end points among eligible but not randomly assigned patients will only have the status of a good observational study and will not be suitable for providing primary estimates for treatment comparisons. In particular, in the registry population treatment is recommended based on a variety of selection factors, many of which are subtle and cannot be measured. An additional problem to be solved in analyses of such data will be the definition and time of treatment assignment.

As is typical for observational studies, registry analyses will also explore and generate hypotheses regarding the relation of various patient characteristics to outcome (predictors of events). The characteristics to be considered will be the key baseline variables of the randomly assigned study. Periprocedural outcomes such as mortality, myocardial infarction, and other complications will serve as end points in these analyses; procedure-related complications and outcomes will in turn also serve as risk factors for long-term events.

Statistical methods such as linear regression, logistic regression, and Cox regression will be used to obtain adjusted estimates of the effect of prognostic variables on outcome. As in the trial, testing for qualitative interaction between treatments and risk may be appropriate.

*Patients clinically but not angiographically eligible.* A 5–10% random sample of patients who meet clinical criteria for the randomly assigned trial but are excluded on angiographic grounds will be used to assess the appropriateness of angiographic exclusion for BARI.

In this sample baseline characteristics as well as in-hospital outcome and major follow-up events will be analyzed by the given treatment. Results of these analyses will lend insight into the prognostic importance of those vessel/lesion characteristics that are not otherwise present in BARI-eligible patients.

*Determination of time 0.* For the randomly assigned patients, the clear choice for time 0 is the time of random assignment. For registry patients, the time of assignment of the BARI identification number is used. Random assignment determines the treatment group in the clinical trial, but a clear-cut treatment assignment does not apply to registry patients. Here, treatment can be defined by the management received within 2 weeks of BARI ID assignment, or alternatively within 3 months. The 2-week rule is based on the requirement that the assigned treatment be delivered within 2 weeks in the trial.

*Quality Control/Reproducibility of Measurements*

To establish the reproducibility of key measurements in BARI, replicate blinded assessments will be performed on randomly selected samples. Measures in this category include angiographic baseline characteristics, measure of PTCA outcome, occurrence of MI, cause of death, and functional test outcome. (Details for some of these analyses are described in the Central Laboratory sections located in Appendixes 6 and 7).

Reliability will be assessed by appropriate statistical techniques that are applicable to the replication of measurement design.

*Exploratory Methods of End Point Analysis*

*Completeness of revascularization.* With respect to CABG, it has been claimed that the more complete the revascularization the better the results. This clinically appealing statement has never been adequately tested because no one would randomly assign patients to complete versus incomplete revascularization. The BARI trial will indirectly test this hypothesis because the PTCA strategy does not necessarily aim for or achieve the completeness of revascularization that CABG does.

*Percutaneous transluminal coronary angioplasty as a delay for coronary artery bypass graft surgery.* An additional goal of BARI is to learn the rate and timing of the crossover from PTCA to CABG. A PTCA patient is a crossover case if he or she undergoes CABG at any time after random assignment either before or after PTCA. The percentage of patients who cross over, as well as the length of delay to CABG, will be analyzed.

*Repeat revascularization.* The attribution of events in the presence of subsequent revascularization by a treatment other than the one randomly assigned is of particular concern in BARI. Although the literature has described many avenues of analysis in such situations, none of these analyses can be interpreted in a classical statistical sense. However, to assess the impact of crossover two ancillary methods of analysis are proposed, with the clear understanding that the results obtained must be interpreted in the same manner as any other observational study results.

The first exploratory method is to censor follow-up at the time of the different method of revascularization. This approach looks at patients only during the continuation of their originally assigned treatment and does not count events after initiation of the other treatment. This method of analysis has less power to detect differences between the treatment groups because many patients may be lost because of a subsequent procedure. More importantly, this method could also lead to biased results if subse-

quent procedures occur frequently and in a highly selective manner, removing individuals who are either at more or less risk than others for the end point of interest. This possibility must be examined before such analysis, and great care should be exercised in drawing inferences.

A second auxiliary method is the transitional life table analysis, in which patients are considered to be members of their original treatment group until the different revascularization procedures and members of the other group thereafter. This approach allows all follow-up data to be used in the analysis, although there may again be bias because patients who subsequently receive the other treatment may be different from those who remain with their treatment assignment.[4]

These two methods have been useful in previous studies.[4]

## Organizational Structure

### *Introduction*

Investigators in the BARI study collaborate through an organizational structure designed to maintain the continuity of study operations and to facilitate effective communication and cooperation among components.

### *Operational Components*

*Clinical centers.* Fourteen primary clinical centers with one or more hospitals are participating in BARI. All are located at major medical centers in the United States and Canada. The clinical centers are responsible for the screening and recruitment of eligible patients, performance of PTCA and CABG, coordination of patient care and follow-up, and collection of all clinical information and test data that are required by the BARI protocol. Individual clinical sites may also consider interaction with other institutions to enhance recruitment; such relationships consist of the following specific categories.

*Coinvestigational sites.* Each one of these functions as a satellite of an original BARI clinical center and uses resources of the parent site. At these sites the same protocol activities as at the associated parent site are performed; however, computer and data management resources are shared with the parent site. Investigators at these sites become voting members of the Steering Committee if requirements for protocol and performance criteria (certification of surgeons, angioplasty operators, and coordinators) and minimum recruitment levels (3 patients/mo) are achieved.

*European parallel study.* The Institute for Clinical and Experimental Medicine in Prague, Czechoslovakia, participates in the BARI study through a United States–Czechoslovakian scientific agreement. Random assignment in this parallel study began in February of 1989. All data that are collected will be analyzed as an ancillary study to BARI.

*Coordinating center.* The CC at the University of Pittsburgh has primary responsibility for the BARI study design, data collection and management, and analysis of BARI results. The CC staff maintain the protocol and operations manual, design and support the data entry and management system, and implement certification and procedures of random assignment. CC staff are responsible for preparing and distributing regular BARI progress reports and minutes, preparing reports for the SDMB, monitoring end point results, preparing data analyses, and ensuring the quality and accuracy of data collection. CC investigators will ultimately play a key role in the preparation of reports for publication.

*Central radiographic laboratory.* The BARI CRL is located at Stanford University, Palo Alto, Calif. The laboratory is responsible for the receipt, review, and analysis of all BARI radiographic test data, including the assessment of PTCA performance and success, on all randomly assigned patients from each of the BARI clinical sites and for transmission of the results to the CC in a timely fashion. In addition, this laboratory is responsible for monitoring the quality, completeness, and timeliness of BARI radiographic procedures that are performed at the clinical sites. The CRL will also be responsible for reviewing the angiograms of the patients who are excluded from BARI eligibility based on angiography criteria and who are subsequently selected for the registry. (The functions of the CRL are discussed further in Appendix 6.)

*Central ECG laboratory.* The BARI CEL is located at St. Louis University. It is responsible for quality control and interpretation of all resting and exercise ECGs required by the BARI protocol. (The functions of the CEL are discussed further in Appendix 7.)

*Coordinating Center for the Study of Economics and Quality of Life.* The SEQOL coordinating center is currently located at Stanford University, which moved from Duke University in January of 1990, and is responsible for the coordination and quality control of data collection at the seven BARI clinical sites that are participating in the SEQOL study (Boston University, Cleveland Clinic Foundation, Duke University, Mayo Clinic, St. Louis University, University of Alabama, and University of Michigan). The ancillary study activities are supported by a grant from the Robert Wood Johnson Foundation.

### *Administrative Components*

*Study Chair.* The Study Chair, which is appointed by the National Heart, Lung, and Blood Institute director, has major responsibility for the scientific direction of the BARI trial. The Study Chair has been appointed to serve for the duration of the study unless other arrangements are made by mutual agreement between the Chair and the National Heart, Lung, and Blood Institute director. In the event that the Study Chair is vacated because of death, resignation, or inability to serve because of serious illness, the National Heart, Lung, and Blood Institute director will appoint a new Chair.

*National Heart, Lung, and Blood Institute Program Office.* The National Heart, Lung, and Blood Institute Program Office is in the Cardiac Diseases Branch of the Division of Heart and Vascular Diseases and is responsible for the overall direction and monitoring of BARI. The Program Office participates in the general organizational and scientific guidance of the study and monitors the study progress for the institute. Statistical guidance is provided by the National Heart, Lung, and Blood Institute.

*Steering Committee.* The Steering Committee is composed of the Study Chair and the Principal Investigators from each BARI Clinical Site, the Central Laboratories, the Coordinating Center, and the National Heart, Lung, and Blood Institute Program Office. This committee provides the scientific direction for the study and periodically meets to assess progress. The Steering Committee developed the BARI protocol and is responsible for its execution.

The following technical subcommittees have been appointed: Angiography, PTCA, CABG, Design and Analysis, End Points, Forms, Entry Criteria, Concomitant Therapy, Economic, and New Technology. These subcommittees are charged with overseeing specific areas of the BARI protocol.

*Operations Committee.* The Operations Committee is responsible for the daily conduct of BARI as an extension of the Steering Committee. Weekly conference calls are conducted to ensure that important issues are appropriately addressed and problems resolved. It is composed of the Study Chair, the Principal Investigator of the Coordinating Center, representatives from the National Heart, Lung, and Blood Institute Program Office, Principal Investigators of the Central Laboratories, and other BARI participants on an ad hoc basis as required.

*Policy and Publication Committee.* The Policy and Publication Committee (PPC) has the responsibility of approving ancillary studies and analyses of the BARI data base beyond the primary baseline and outcome papers. Principal Investigators as well as associate investigators at all BARI clinical and central sites are encouraged to develop protocols and publish research papers with BARI study data. The PPC will ensure that these protocols are methodologically sound and that the publication of high-quality manuscripts progresses efficiently.

*Independent Components*

*Safety and Data Monitoring Board.* The SDMB is an external review committee appointed by the National Heart, Lung, and Blood Institute that has the responsibility of protecting the scientific integrity of the BARI trial. The Board reviews interim trial results and advises the National Heart, Lung, and Blood Institute on all policy matters. The SDMB includes senior scientists, cardiologists, surgeons, a biostatistician, and an ethicist. The Study Chair, the Principal Investigator from the Coordinating Center, and representatives from the National Heart, Lung, and Blood Institute Program Office also participate as nonvoting members.

The group meets semiannually; in addition, at monthly intervals the CC provides data to the Chair of the SDMB to ensure early identification of potential adverse outcomes of therapy during the recruitment phase.

*Morbidity and Mortality Classification Committee.* The MMCC is an external National Heart, Lung, and Blood Institute–appointed group responsible for the review and classification of MI and death among study patients. Classification is based on case summaries provided by the CC. The Committee serves independent of BARI and clinical and central laboratory investigators.

## Data Management/Computing

*Overview*

The CC has implemented a distributed data entry system for BARI. Each clinical site has been provided with an IBM PS/2® (a registered trademark of International Business Machines Corp.) microcomputer system that is equipped with the hardware and software necessary for data collection and management at the clinical site. Data are transferred weekly from each site to the CC, where they are maintained in an aggregate database on the CC's Digital Equipment Corporation VAX 6310 computer system (Digital Equipment Corporation, Maynard, Mass.).

*Distributed Data Entry and Management*

The BARI distributed data entry system consists of six phases. At the site level, the forms* are entered into the microcomputer and intraform edits performed. Data are then transmitted to the data center by means of a telecommunications link and uploaded into data sets on the VAX computer. At this point interform edits are done, and then finally the data are appended to the aggregate BARI data base. These phases are discussed in greater detail below and are also described in the Data Management Manual.

*Form entry.* The Epidemiology Data Center at the University of Pittsburgh has designed and implemented a screen-oriented data entry program for the IBM microcomputer called the PoP data entry system. In this system the pages of study forms appear on the microcomputer screen in much the same way as they appear on paper. Data are transcribed from paper forms to the corresponding data fields that are displayed on the microcomputer. During data entry each field is interactively subjected to data type verification and range checks. Data are further verified by using a double entry system. All data must be entered twice before subsequent system processing can occur. Each discrepancy that requires resolution during this process is recorded in an audit file that contains a full account of all changes made to the study data records, the date of each change, and the ID number of the operator who makes the changes.

*Data Entry Form sets may be ordered at a cost of $50.00 from the BARI Data Coordinating Center, University of Pittsburgh, 127 Parran Hall/130 DeSoto Street, Pittsburgh, PA 15261.

*Intraform edits.* After entry and verification, each data record undergoes defined intraform logic and consistency checks. A report that lists the nature of each error is generated for resolution by the clinical site staff. Corrections to the data are then made through the PoP update module.

*Data transmission.* Data records that are free of errors are flagged for transmission to the CC. An automated data file transfer system retrieves data records from each clinical center once a week by means of modem and telephone lines. This occurs at night while the centers' microcomputers are not in use. The CC host computer dials the telephone number of the clinical center's modem. As a security measure, the center's modem, on recognition of the incoming call, disconnects the line and then redials the CC to proceed with file transfer. The entire transaction is recorded in an audit file that is reviewed the next morning. Unsuccessful transfers are identified and resolved during that day.

Data that are contained in files transmitted to the CC can no longer be accessed by the clinical center. Any subsequent changes to the data must be made through the submission of data base update requests, which is discussed below.

*Load data.* At the CC data records are transferred to the VAX 6310 computer and loaded into System 1032 Data Base Management System (DBMS) data sets. (System 1032 is a product of CompuServe Data Technologies, Boston.)

*Interform edits.* At the VAX level each data set is processed through extensive interform edits to ensure consistency and validity across all forms. Error reports are generated and sent to the clinical centers for resolution. Data changes that are required to resolve errors at this level are made by submitting a data base update record by means of the PoP system. These records are retrieved during the weekly data file transfer and are loaded into the VAX system, where a program accesses the data base and performs the requested change. This system generates an audit trail of all changes made to the BARI data base at the VAX level.

*Appending data.* The data transmitted weekly to the CC from the clinical sites are loaded into the aggregate data base on the VAX. An append audit trail is generated that shows all records loaded into S1032 data sets and any records that are rejected. All data analyses originate from this final, clean, aggregate data base.

### *Form Inventory*

PoP provides an automatic form inventory system. Information from each entered form is automatically extracted from the data record and recorded in a separate inventory data base. The inventory data base is used to monitor data management progress at the site level. In addition, this data base generates scheduling reports that inform the clinical staff of patients who are due for a protocol visit during the next month.

### *Coordinating Center Statistical Computing*

The aggregate study data base is maintained in the System 1032 DBMS. Files for analysis that use statistical programs such as SAS, SPSS, BMDP, and MINITAB (SAS Institute Inc., Cary, N.C.; SPSS Inc., Chicago, Ill.; BMDP Statistical Software, Los Angeles; and Minitab, Inc., State College, Pa; respectively) are easily generated. The 1032 DBMS includes a powerful programming language that allows new variables to be created from existing information. All study analyses are completed on the VAX computer by using standard statistical packages whenever possible.

### *Data Security*

*Clinical site microcomputer.* Each clinical site is responsible for confidentiality by appropriately restricting physical access to the BARI microcomputer, which is placed in a locked room after working hours.

Data backup is forced daily and can also be performed more often if desired. The clinical site data manager is responsible for placing backup diskettes in a safe storage area in a location remote from the microcomputer. Damage to the hard disk results in the loss of no more than 1 day's work. All microcomputer drives are backed up once each month.

To gain access to the PoP data entry system, users must go through a log-in procedure. Each user has a unique identification name. Audit trail files associate all PoP data system activities with the user's identification name. The clinical site data manager is responsible for maintaining a confidential list of system users and passwords.

*Treatment assignment file.* The treatment assignment file on each site computer contains the treatment assignment schedule for that site. When a patient is randomly assigned, the PoP module selects the next treatment assignment in the list and associates it with the randomly assigned patient's name and BARI identification name number. The BARI identification and the treatment assigned are then stored in a random assignment file.

Because of its highly sensitive nature, the random assignment file is encrypted. This ensures that the next available random assignment cannot be determined by any method other than that of the PoP random assignment module. The random assignment file is protected from accidental deletion and cannot be modified.

In an effort to prevent improper assignment to randomly assigned treatment, the PoP random assignment module requires that patient data that pertain to exclusion criteria be entered. Treatment will be assigned only after data corresponding to appropriate criteria have been entered. Once a patient receives a treatment assignment, there is no way of removing the patient from the random assignment file.

*Coordinating Center VAX Computer.* The CC ensures patient confidentiality by using alphanumeric

identification names to identify forms. This identification name is easily linked to the patient name at the site level only.

Study data files at the CC are protected against inadvertent change or access by nonproject personnel. The VAX computer system provides protection at the individual file level by means of passwords and file protection codes that are controlled by the project manager. File protection codes can permit certain users to have "read only" access to data without the ability to make changes.

Backup of VAX files is performed daily. In addition, a special tape backup is made weekly for the entire VAX computer system. These tapes are stored in a room and location that are separate from the daily backup medium. Therefore, a computer system failure will at worst result in the loss of 1 day's work. In a worst-case disaster (fire, explosion, etc.), no more than 1 week's work would be lost.

## Appendix 1: Acronyms

AAP, Angiographic Assessment Program; ACE, angiotensin converting enzyme; BARI, Bypass Angioplasty Revascularization Investigation; BMDP, BioMedical Data Program; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CASS, Coronary Artery Surgery Study; CC, Coordinating Center; CCSC, Canadian Cardiovascular Society classification; CEL, Central Electrocardiographic Laboratory; CRL, Central Radiographic Laboratory; DBMS, Data Base Management System; ECG, electrocardiogram; EF, ejection fraction; ETT, exercise treadmill testing; IMA, internal mammary artery; LAO, left anterior oblique; LV, left ventricle; MC, Minnesota Code; MI, myocardial infarction; MMCC, Morbidity and Mortality Classification Committee; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; PI, Principal Investigator; PTCA, percutaneous transluminal coronary angioplasty; RAO, right anterior oblique; SAS, Statistical Analysis System; SDMB, Safety and Data Monitoring Board; SEQOL, Study of Economics and Quality of Life; SPSS, Statistical Package for the Social Sciences; TIMI, Thrombolysis in Myocardial Infarction.

## Appendix 2: Bypass Angioplasty Revascularization Investigation Glossary of Definitions

### *Canadian Cardiovascular Society Classification of Angina*

Class I: Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina occurs with strenuous or rapid prolonged exertion at work or recreation.

Class II: Slight limitation of ordinary activity, such as walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals; the limitation of ordinary activity in cold or windy weather, while under emotional stress, or during the few hours after awakening; walking more than two blocks on a level surface; or climbing more than one flight of ordinary stairs at a normal pace and under normal conditions.

Class III: Marked limitation of ordinary physical activity, such as walking one to two blocks on a level surface or climbing one flight of stairs under normal conditions and at a normal pace; comfortable at rest.

Class IV: Inability to carry on any physical activity without discomfort. Anginal syndrome may be present at rest.

### *Clinically Severe Angina or Ischemia*

Clinically severe angina or ischemia involves any of the following conditions: 1) non–Q wave myocardial infarction stabilized 4 hours to 6 weeks; 2) unstable angina stabilized 4 hours to 6 weeks; 3) stable CCSC III or IV angina; 4) stable CCSC I or II angina and one or more of the following: a) ***severe ischemia on noninvasive testing,*** b) Q wave MI (stabilized for 24 hours, revascularization clinically indicated, and ability to randomly assign patients within 30 days after MI), c) resting ejection fraction <50%, d) a history of stable class III or IV angina and current intensive medical therapy (with exercise testing waived); 5) no angina but ***severe ischemia on noninvasive testing*** and prior Q wave MI; 6) no angina within 6 weeks of study entry but a history of prior angina, with current ***severe ischemia on noninvasive testing.***

### *Definite Q Wave Myocardial Infarction*

A definite Q wave MI involves the two-step worsening of Minnesota code Q waves, as determined by the CEL.

### *Multivessel Coronary Disease*

The BARI definition of multivessel coronary disease requires that two or more myocardial territories (anterior, lateral, inferior/posterior) be jeopardized. Therefore, the following definition could also be termed multiterritory disease. To be eligible for BARI a patient must have a 50% or greater diameter reduction by caliper measurement in arteries that supply at least two of the three major myocardial territories (Table 1, Figure 3). These arteries must be >1.5 mm in diameter adjacent to the site of the stenoses. Assignment of coronary segments to a specific myocardial territory (anterior, lateral, inferior/posterior) includes consideration of coronary artery dominance (Table 1).

**TABLE 1. Coronary Segments***

| Myocardial territory | Right dominant | Left dominant | Balanced |
|---|---|---|---|
| Anterior | 12–17, 29 | 12–17, 29 | 12–17, 29 |
| Lateral | 18–22, 28 | 18–22, 28 | 18–22, 28 |
| Inferior/ posterior | 1–9 | 23–27 | 1–5, 23–26 |

*See Figure 3.

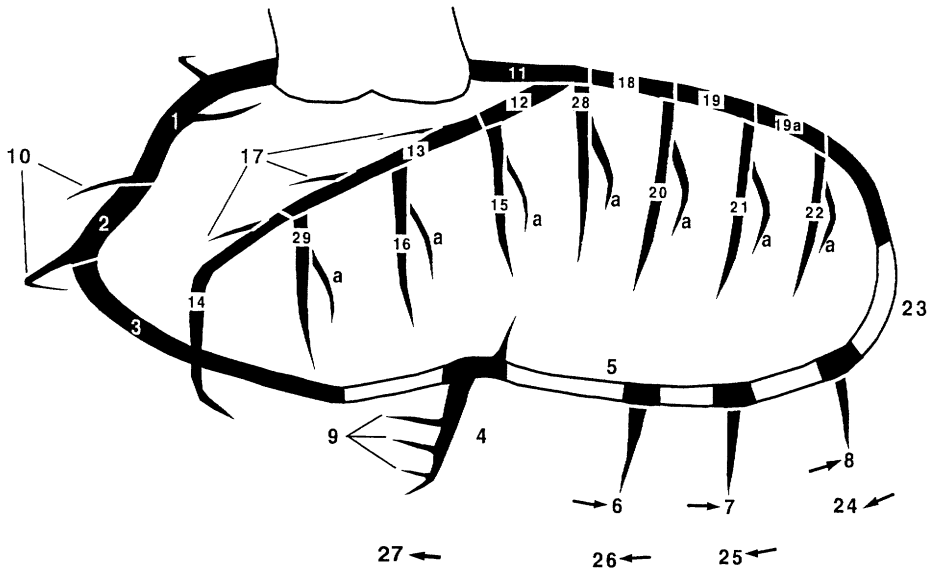


FIGURE 3. *Coronary artery map. Right coronary artery: 1, proximal; 2, middle; 3, distal; 4, posterior descending; 5, right posteroatrioventricular; 6, first posterolateral; 7, second posterolateral; 8, third posterolateral; 9, inferior septal artery; 10, acute marginal artery. Left coronary artery: 11, left main; 12, proximal left anterior descending; 13, middle left anterior descending; 14, distal left anterior descending; 15, first diagonal; 15a, first diagonal branch; 16, second diagonal; 16a, second diagonal branch; 17, anterior septals; 18, proximal circumflex; 19, middle circumflex; 19a, distal circumflex; 20, 21, 22, first, second, and third obtuse marginal; 20a, 21a, 22a, first, second, and third obtuse marginal branches; 23, left atrioventricular; 24, 25, 26, first, second, and third posterolaterals; 27, left posterior descending; 28, ramus; 28a, ramus branch; 29, third diagonal; 29a, third diagonal branch.*

*Myocardial Ischemic Response (End Point Definition)*

A myocardial ischemic response is indicated by any of the following exercise-induced ECG responses: 1) horizontal or downsloping ST segment depression ≥1 mm 80 msec after the J-point; 2) a slow upsloping ST segment depressed ≥1.5 mm 80 msec after the J-point; and/or 3) ST segment elevation ≥1 mm 80 msec after the J-point in a non–Q wave lead, each as compared with the rest tracing.

*New Technology Devices*

New technology devices include those currently holding Investigational Device Exemption status and any one deemed "new technology" by the New Technology Committee. Some examples are stents, atherectomy, and laser catheters. (See pp V-3–V-6, Angioplasty Guidelines.)

*Severe Ischemia on Noninvasive Testing (Entry Criteria Definition)*

Severe ischemia on noninvasive testing is defined as the results of testing as listed herein: 1) Exercise treadmill testing: exercise-limiting definite angina, with final exercise stage less than Bruce stage 3; and exercise-induced ***severe ST segment response,*** with a final exercise stage less than Bruce stage 3. In addition, patients who do exercise in Bruce stage 3 may also be considered for random assignment if the ischemic changes occur within the first 6 minutes and the patient is judged to be a candidate for revascularization. 2) Exercise $^{201}$Tl: multiple reversible defects, increased lung uptake and a single reversible or fixed defect, and one fixed defect and one reversible defect remote from the fixed defect. 3) Persantine $^{201}$Tl: multiple reversible defects and one reversible and one fixed defect. 4) Exercise radionuclide ventriculography: resting ejection fraction ≥0.50 and exercise ejection fraction <0.50, with a decline in ejection fraction of at least 5% in the absence of left bundle branch block or significant arrhythmia; and resting ejection fraction ≥0.50, with a severe ST segment response and work load <450 kpm.

*Severe ST Segment Response*

A severe ST segment response may be indicated by any of the following exercise-induced ECG responses: 1) horizontal or downsloping ST segment depression ≥1.5 mm 80 msec after the J-point; 2) slow upsloping ST segment depression ≥2.0 mm 80 msec after the J-point; and/or 3) ST segment elevation ≥1 mm 80 msec after the J-point in a non–Q wave lead, each as compared with the rest tracing.

*Suspected Myocardial Infarction*

MI is suspected if any episode of chest pain lasts 20 minutes or longer or if there is the occurrence of new Q waves in the ECG or if there is elevation of cardiac enzymes, as well as any other reason to suspect an MI.

*Flow Classification (Thrombolysis in Myocardial Infarction): A Randomized Clinical Trial of Tissue-Type Plasminogen Activator (t-PA) in Patients With Acute Myocardial Infarction*

Four specific grades of coronary flow rate, as developed in the TIMI study, are given below.

*Grade 3 flow.* Antegrade flow into the terminal coronary artery segment distal to a stenosis occurs as promptly as anterograde flow into a terminal coronary artery segment proximal to the stenosis. The clearance of contrast material from the distal coronary artery terminal segment is as rapid as clearance from an uninvolved, more proximally located coronary artery segment.

*Grade 2 flow.* Contrast material opacifies the terminal coronary artery segment distal to the stenosis. However, the entry of contrast material into the terminal coronary artery segment is perceptibly slower than it is into a more proximally located terminal coronary artery segment. Alternatively, the clearance of contrast material from a terminal coronary artery segment distal to a stenosis is noticeably slower than that from a comparable segment that is not preceded by a significant stenosis.

*Grades 1 and 0 flow.* There is no obvious flow of contrast material beyond the stenosis in question. A small amount of contrast material may penetrate the occlusion (grade 1); however, the contrast material fails to fully opacify the coronary artery beyond the occlusion.

*Flow of contrast material not assessable.* In this situation there may be competitive flow to a terminal coronary artery segment. For instance, total occlusion in the proximal right coronary artery may be associated with both anterograde (ipsilateral) and retrograde (contralateral) collateral flow to the distal right coronary artery bed. There may be relatively faint visualization of the distal right coronary bed by the anterograde collateral flow and also by retrograde collateral flow. In this situation it is not possible to accurately assess the flow rates of contrast material in the terminal right coronary artery bed because of the competitive nature of flow. It may also be impossible to judge relative flow in a proximal total occlusion in which collateral flow to the terminal coronary segments is poor. If the terminal coronary segments in this situation are poorly visualized, the correct judgment concerning perfusion may be unclear, and this choice should be indicated.

## Appendix 3: Sample Size

Mortality was used as the basis for selecting the sample size for the trial. For PTCA (a procedure less invasive than CABG) to be recommended as an initial revascularization strategy, it is of primary importance to know that the long-term results with PTCA are not appreciably worse than with CABG in terms of mortality. With this in mind, the basis of the BARI sample size calculation was to choose a sample size large enough so that, with a high probability, the upper confidence limit for the absolute difference between PTCA and CABG mortality rates would not exceed a specified value.[5] This specified value represents the maximum acceptable absolute difference between the CABG and PTCA event rates. In BARI the specified value was taken to be 2.5%, in light of the estimated 5% mortality rate discussed below. In other words, the sample size was chosen in such a way that if the two strategies were in fact identical in terms of mortality, the study would have a high probability of ruling out excess mortality of 2.5% or more in the PTCA group relative to the CABG group.

Review of the data from the National Heart, Lung, and Blood Institute PTCA Registry and the CASS Trial and Registry indicates that for patients with multivessel CAD, a 5-year mortality rate of 5% after either therapy was a reasonable estimate. For the purpose of calculating sample size, we assume this to be the true common mortality for both PTCA and CABG patients in BARI. Under this assumption, a sample size of 2,400 patients (1,200 assigned to each treatment) yields a probability of 88% that the upper 95% confidence limit for the true difference between the 5-year mortality rates of PTCA and CABG will not exceed 2.5%. Note that if the upper confidence limit of the true difference is 2.5%, then the observed difference must be appreciably less than 2.5%. For example, if the observed 5-year mortality rates were 5.9% for PTCA and 5% for CABG, the observed difference would be 0.9% and the upper 95% confidence limit for the true difference would be 2.4%.

## Appendix 4: Random Assignment

### *Stratification*

The sequence of random assignment is stratified by clinical center. This allows for approximately equal allocation of the two treatments within each center as well as preservation of the overall balance between the two treatment groups.

Because of the large number of patients anticipated (1,200 for each treatment), the probability of serious imbalance in the distribution of risk factors is unlikely. In case of such an occurrence, adjustment can be accomplished during the analysis. This can be done without a significant loss of efficiency, and it is preferable to the administratively more complex process of stratifying during random assignment. Therefore, the sequence of random assignment is stratified by clinical center only, and other clinically important factors will be adjusted for (if necessary) in analyses after random assignment.

### *Design of Random Assignment*

The BARI clinical trial requires a scheme of random assignment that will provide a balance in the total number of patients assigned to each treatment group both early and late in the trial. Early balance is necessary to maximize the power to detect differences for safety-monitoring purposes and to adjust for any early learning curve effects in the trial. To achieve this balance, a blocked scheme of random assignment has been implemented, with generation of a separate sequence for each clinical center as described below.

Block lengths were selected at random. After this number was chosen, a permutation of this number of

treatment assignments, with half being PTCA and half CABG, were selected at random from all possible permutations. This permutation then became part of the assignment sequence. The process was repeated until the assignment sequence was of a length of 500 or more. (Each center is expected to recruit an average of 175 patients for a trial size of 2,400 patients, but assignment schemes are longer to allow some clinics to recruit more patients in case other clinics fall behind the projected recruitment rates or have to stop recruitment.)

*Treatment Assignments*

By using the blocked random assignment scheme indicated above, the CC has generated the treatment assignment schemes for all centers. The file with the random assignment sequence for each center is encoded and stored on the same microcomputer that is used for data entry. Because a high level of security is essential for this file, it is encrypted on each microcomputer to ensure that there is no unauthorized access to these blinded data. Security issues are discussed further on p V-13 (Data Management).

When a patient is to be randomly assigned, the clinic coordinator uses the software developed for random assignment. The coordinator is prompted with a list of questions that reflect BARI trial inclusion and exclusion criteria. Answers to these questions must match the entry criteria (i.e., BARI eligibility must be verified) before the program will indicate that the patient is indeed eligible and provide the patient's treatment assignment. The CC closely monitors the use of the random assignment program.

A contract is maintained at all centers to guarantee service within 4 hours of notification of computer breakdown. The CC is available to assign treatments by telephone in the event that computer repair is delayed. Copies of each random assignment sequence are stored at the CC in secured computer files.

## Appendix 5: Complications

*Abrupt Closure (Regardless of Previous Dilatation)*

There is clinical evidence of one or more coronary arteries abruptly closing.

*Arterial Embolus of Extremity or Permanent Loss of Pulse*

Acute occlusion of a main or distal arterial trunk supply in a limb assessed by the lack of detectable distal arterial pulsations (by pulsation or Doppler examination) that had previously been observable. The loss of pulse may or may not be associated with ischemia of the affected limb.

*Cardiogenic Shock*

Hypotension (systolic blood pressure of less than 80 mm Hg) that is associated with reduced urine output, decreased mental acuity, and compensatory vasoconstriction.

*Cardiac Tamponade*

Hemodynamic compromise, with hypotension and low cardiac output secondary to increased pericardial pressure.

*Cerebrovascular Accident (CVA)*

A focal neurological deficit that is still at least partially evident more than 24 hours after its onset.

*Chest Tubes for More Than 5 Days After Surgery (Self-Explanatory)*

*Coma*

Profound depression in the level of consciousness, reflected by the loss of contact with the environment and loss of spontaneous movement. Brain stem activity (respiration and response to deep pain) may or may not be preserved.

*Congestive Heart Failure (CHF)*

Manifested by one or more of the following features: dyspnea on exertion, edema, fatigue, orthopnea, and/or paroxysmal nocturnal dyspnea. Other findings that support the clinical diagnosis include the presence of an S3 gallop, elevated jugular venous pressure, and radiographic evidence of pulmonary congestion. Verification by a physician's statement in the medical record is required.

*Deep Wound Infection*

Positive culture from the mediastinal tissues beneath the sternum.

*Dementia*

Broad-based loss in higher intellectual function (including cognitive, perceptual, calculational, and/or recall functions) that is evident to family members and close associates or demonstrated on serial functional testing.

*Hemorrhage*

Severe bleeding sufficient to require transfusion of packed red blood cells.

*Hypersensitivity Reaction*

An allergic reaction to iodine-containing radiographic contrast media or protamine, which is marked by the development of urticaria, wheezing, prolonged hypotension, or laryngospasm.

*Hypotension*

Reduction in systolic blood pressure to $<90$ mm Hg or reduction by $\geq 30$ mm Hg compared with the baseline value, which persists for more than 1 minute and requires treatment.

*Nonfatal Cardiac Arrest That Requires CPR or Countershock (Self-Explanatory)*

*Postthoracotomy Syndrome*

Clinical syndrome of pleuro/pericarditis manifested by chest pain and fever.

*Pulmonary Edema (Cardiac)*

Acute congestive heart failure resulting in the accumulation of pulmonary interstitial and alveolar fluid, manifested by profound dyspnea, orthopnea, rales, and evidence of pulmonary congestion on chest X-ray.

*Pulmonary Embolus*

Acute occlusion of one or more branches of the pulmonary arteries with thrombotic material, usually originating from the iliofemoral or pelvic veins, manifested by the abrupt onset of pleuritic chest pain, worsened gas exchange, increased pulmonary artery pressure, or frank hemodynamic collapse.

*Renal Failure*

Progressively deteriorating renal function requiring dialysis.

*Reoperation for Bleeding*

Reoperation performed to remedy excessive bleeding after initial surgery.

*Respiratory Failure That Includes Noncardiac Pulmonary Edema and Adult Respiratory Distress Syndrome (ARDS)*

Inability of the patient to maintain adequate gas exchange during spontaneous ventilation, even with the assistance of supplemental oxygen. In cases where a patient is receiving mechanical ventilatory assistance after surgery, respiratory failure shall be considered the inability to wean the patient from mechanical ventilation within 48 hours of completion of the surgical procedure.

In noncardiac pulmonary edema the same clinical and radiographic appearances that are in cardiac pulmonary edema are present. However, the pulmonary capillary wedge pressure is $\leq$15 mm Hg.

ARDS is the increased interstitial and alveolar lung water resulting from lung injury from any of a variety of causes in the absence of a cardiac etiology.

*Superficial Wound Infection*

Positive culture from the surgical or PTCA wound site.

*Transient Ischemic Attack (TIA)*

A focal neurological defect (usually corresponding to a single vascular territory) that spontaneously resolves so that no residual evidence exists within 24 hours.

*Wound Dehiscence*

The splitting or bursting open of a procedural wound.

## Appendix 6: Angiography and Functions of the Central Radiographic Laboratory

*Purpose of the Central Radiographic Laboratory*

The CRL is responsible for processing all BARI data that relate to angiograms. Through the development and implementation of the AAP, the CRL ensures that angiographic data regarding coronary anatomy and lesion morphology are collected in a standard format across all sites. Angiographic data for all BARI patients are entered into the AAP at each site. In addition, the CRL performs central angiographic readings for all randomly assigned patients. The central readings performed by the CRL will be used in the primary analysis of BARI.

*Angiographic Procedural Requirements*

Nitroglycerin is usually administered immediately before coronary arteriography. Notations of catheter size, nitroglycerin administration, and projections used are documented on a Procedure Report Form. Multiple standard views are obtained by using caudal RAO and cranial LAO projections of the left coronary artery and paired LAO/RAO projections of the right coronary artery when possible. Six-inch or 7-in. image-intensifier modes are used for standard views. Before PTCA two views are obtained of each lesion, and these views are replicated after PTCA. A left ventricular angiogram in which a 30° RAO view is used is required, and a cranially angulated steep LAO view is also obtained when possible.

*Required Angiograms*

All angiograms that are performed on BARI patients must be entered into the AAP at the clinical site. Angiograms are assigned to the following categories.

*Baseline.* The angiogram that is used to document angiographic eligibility for BARI is considered the baseline angiogram. This angiogram must be entered into the AAP within 5 working days of random assignment.

*Before and after initial PTCA.* For patients that are randomly assigned to PTCA, data must be entered within 5 working days of completion of the procedure.

*Intercurrent angiograms.* All angiograms that are performed during follow-up, whether they are part of a subsequent revascularization procedure or not, are considered intercurrent angiograms. These must be entered within 5 working days of the angiogram for randomly assigned patients.

*Angiographic Data Entry, Management, and Interpretation*

The acquisition of angiographic data is performed by using the AAP, a microcomputer and software system that was developed specifically for use in BARI. The AAP provides a uniform format for the

entry and storage of coronary and left ventricular angiographic data at the clinical sites and provides tools (calipers, tables, reports) for clinicians and angiographers at each institution. Electronic calipers are used to measure catheter diameter (as a calibration), lesion diameter, and the diameter of normal reference segments of the vessel proximal and distal to the lesion. The microcomputer system facilitates the electronic transfer of data from the clinical sites to the CRL. The same AAP system is used at the CRL for angiographic interpretation and data analysis. The microcomputer hardware was provided to the original 14 clinical centers and to the CRL by a gift from Hewlett-Packard Co., Palo Alto, Calif.

All baseline, PTCA, and intercurrent films for randomly assigned patients are sent to the CRL by commercial delivery service as soon as possible after patient discharge. Films are read at the CRL and returned within 20 working days whenever possible. Site angiographic readings that entered into the AAP are transmitted to the CRL by way of telephone connections on a weekly basis.

At the CRL evaluation of baseline and intercurrent angiograms is done by a senior angiographer, who reviews coronary vessel distribution, branching, and myocardial territory supplied. Lesions are assessed for location, severity (calipers), and morphology. LV angiography is evaluated by using quantitative methods for the measurement of ejection fraction and regional wall motion. These evaluations are compared with the initial site reading, and if there are no major differences the CRL reading is final. In the case of major differences, the film is read by a second CRL reader and adjudication is performed. Evaluation of PTCA films is performed by a senior angioplasty operator, who reviews the studies for lesion severity and morphology before and after PTCA. The same adjudication procedures that were outlined above are performed during this evaluation.

### *Quality Control*

*Angiograms.* The CRL reviews all randomly assigned studies for image quality and protocol compliance. Feedback is provided to the site, the angiographer, and the Operations Committee.

*PTCA procedures.* Films that document PTCA procedures are reviewed to assess PTCA outcome. Films are graded with respect to protocol compliance as well as angiographic findings.

*CRL angiographic readings.* The CC randomly designates angiographic studies to be reread at the CRL. This rereading is performed in a blind manner to compare the initial CRL reading with the rereading of the same angiogram to determine the amount of variability in the CRL interpretation of specific angiographic variables.

## Appendix 7: Electrocardiography and Functions of the Central Electrocardiographic Laboratory

### *Purpose of the Central Electrocardiographic Laboratory (CEL)*

The CEL analyzes all rest and exercise ECGs that are collected in BARI. Rest ECGs are evaluated for evidence of QRS, ST, and T wave items by using the standard Minnesota code and supplemental criteria.[7] Exercise ECGs are evaluated for ischemia based on the BARI definitions for severe ischemia on noninvasive testing (entry criteria definition) and myocardial ischemic response (end point definition).

### *Resting ECG Acquisition by Using Marquette MAC-12 Units*

Through an educational grant from Marquette Electronics (Milwaukee, Wis.), the CEL has provided Marquette MAC-12 units to the original 14 clinical centers that did not have Marquette equipment. Baseline, preprocedure, postprocedure, and scheduled follow-up ECGs are acquired on Marquette equipment. This standard recording apparatus facilitates ECG transmission to the CEL and the system provides a repository for digitized ECGs, allowing easy retrieval for subsequent coding.

### *ECG Coding*

Rest ECGs are evaluated by using the Minnesota Code. To more accurately describe the patient population in BARI, additional data are collected as part of an extension of the Minnesota Code. The actual height or depth of the ST segment shift is recorded, and codes have been added to describe the depth and extent of T wave inversion in the anterior precordial leads. Finally, Q wave codes have been added to identify characteristics that, along with ST segment and T wave changes, are associated with a high probability of myocardial infarction.

ECGs are received and logged in at the CEL. When multiple ECGs are sent to document the postprocedure period or evaluate a suspected myocardial infarction, the ECGs that have the best representation of Q waves and ST segment changes are chosen for analysis. ECGs are first evaluated for technical quality, including the presence of missing leads, excess artifacts, excess baseline wandering, switched leads, and invalid calibration. ECGs are logged into an inventory system, and a coding clerk measures Q wave depth and width, R wave amplitude, ST segment displacement, and T wave amplitude by using an eight-power magnified loupe calibrated in increments of 0.1 mm. These measurements are verified by the coding supervisor and then entered into a MicroVAX computer. Logical edits are then performed to verify the codes, and any discrepancies are resolved. The codes are then reviewed by a physician, who has the option to make changes to the data. All digitized ECGs are transmitted to Dalhousie University, where electronic determination of the Minnesota Code is performed. Any discrepancies between the Dalhousie and CEL readings are adjudicated, with the CEL making the final code determination. The final data are used to create summary files that are transmitted weekly to the CC.

### *Quality Control of ECG Coding*

Coding clerks and physician electrocardiographers must pass a comprehensive coding test before the

actual coding of project tracings. Within the CEL, ECGs are periodically recirculated to detect coding deficiencies. A staff member who is identified as having inadequate performance undergoes remedial training until performance improves. Kappa statistics are calculated biannually for the physicians and laboratory supervisors.

In addition, the CC is recirculating a blinded sample of 200 baseline ECGs for Q wave interpretation. A 25% sample of ECGs that indicate Q waves during follow-up and an additional 0.5% of ECGs without Q waves are also being recirculated. This serves to document the reliability of the central diagnosis of this major BARI end point. Interreader variability of binary data will be assessed by using the Kappa statistics.

*Exercise Test Acquisition*

Exercise tests are performed by using a motor-driven treadmill and following the Bruce protocol[8] with no or at least one half of a warmup stage if necessary. A physician is in attendance throughout the test, and the patient and ECG tracings are carefully observed. All patients undergo a pretest evaluation, during which ongoing drug therapy and indications for stopping the exercise are ascertained.

The Mason-Likar 12-lead torso ECG is the lead set used. Four specific tracings are required: upright immediately before exercise; peak exercise; immediate postexercise; recovery period (3–5 minutes after exercise); or an ECG showing maximum postexercise change.

*Exercise Test Digitization*

Exercise ECGs are first examined for the presence of excess artifacts, baseline wandering, and missing leads or ECGs. Each test is reviewed by the laboratory supervisor or associate to determine the presence of exclusion codes such as left bundle branch block, left ventricular hypertrophy, etc. The maximum depth of ST segment depression, maximum height of ST elevation in a non–Q wave lead, maximum number of abnormal leads, and maximum height of ST elevation in a Q wave lead are calculated. A Q wave lead is one in which the Q wave width exceeds 0.03 seconds. This is determined from the resting ECG that undergoes Minnesota Coding. These exercise ECG data are transmitted weekly to the CC.

*Quality Control of Exercise ECG Data*

A 2% sample of scheduled and unscheduled exercise ECGs are submitted for reproducibility studies. The sample is enriched with 25% of all exercise tests that indicate a myocardial ischemic response. Variables to be analyzed for reproducibility include the maximum number of abnormalities in any lead group, the total number of abnormal leads, and the maximum depth of ST segment depression.

*Serial Comparison*

For both rest and exercise ECGs, serial comparisons are performed by using the most recent rest ECG or exercise test and the ECG or test that preceded it. Both ECGs or sets of ECGs are available to the laboratory supervisor and physician at the time of overreading. The standard Minnesota and supplemental codes are used to determine significant change in Q, ST, and T wave items.

## Appendix 8
### Form A

*Consent for Participation in the Research Study Entitled Bypass Angioplasty Revascularization Investigation (BARI), a Randomized Trial Comparing Coronary Bypass Surgery to Coronary Angioplasty*

Study Investigators: _____

Office of Human Research: _____

*General Description and Purpose of Research*

You are invited to participate in a trial sponsored by the National Heart, Lung, and Blood Institute which involves comparison of two treatments for patients with severe myocardial ischemia and coronary artery disease. You have coronary artery disease involving at least two of the major coronary arteries that supply blood to your heart muscle. Your doctors have determined that you are a candidate for either percutaneous transluminal coronary angioplasty (PTCA), a procedure in which a balloon catheter will be passed across the narrowing in your coronary artery to open the narrowing, or coronary artery bypass graft (CABG) surgery, an operation in which the narrowing in the coronary artery will be bypassed by using a vein from your leg or an artery from your chest. One of the potential complications of using the balloon catheter (PTCA) is that the narrowing may return at the site of dilation. This renarrowing has been found in as many as 30% of patients undergoing this procedure at various medical centers. Narrowing generally occurs within the first 6 months, and a second balloon angioplasty procedure usually can be performed. When the narrowing does not recur within the initial 6 months, it is not likely to occur in the subsequent 3–5 years.

I understand that the risks of CABG and PTCA are considered to be similar and that it is possible for death to occur in approximately 1–2% of patients undergoing these procedures. The likelihood of sustaining a heart attack (myocardial infarction) during either of these procedures is approximately 5%. During the study, 2,400 patients will be assigned by chance to either form of therapy during a period of 2 years in 14 hospitals.

If I agree to participate in the randomized clinical research study, one of these two revascularization procedures will be chosen randomly (by chance) as the method to correct the narrowings of my coronary arteries. If I am selected to receive CABG, this procedure will be carried out within 2 weeks after my coronary angiogram was made, at a time that is

mutually agreeable to me and the physicians caring for me.

If I am selected to receive PTCA, I agree to undergo a repeat heart catheterization and to have balloon angioplasty performed on one or more of the narrowings in my coronary arteries. The PTCA procedure is successfully performed in approximately 80% of patients. Should this procedure fail because of complications resulting from the procedure, I understand that it may be necessary to proceed immediately with CABG.

After the treatment, whether it is PTCA or CABG, I will be carefully followed for 5 years and will be seen, or contacted by telephone, throughout my hospital stay, at 4–12 weeks after hospital discharge, at 6 and 12 months after the procedure, and every year thereafter. An exercise test will be performed at 4–14 weeks and at 1, 3, and 5 years after the procedure to determine maximal exercise capacity; this test may provide diagnostic information concerning my state of health. I understand that certain complications may occur during or after an exercise test, such as abnormal blood pressure response, dizziness, irregular heart beat, or, very rarely, a heart attack or death. However, the risk of a complication during exercise testing is infrequent, and the risk is further decreased by the presence of appropriate medical facilities and an experienced medical team.

At 5 years, I will be admitted to the hospital for a repeat coronary angiogram. Coronary angiography defines the presence, location, and extent of coronary disease and associated heart muscle function. The test will assess the results of the PTCA or CABG. Complications from a coronary angiogram are infrequent (less than 1%) and include a blood clot where the catheter is introduced and the possibility of a stroke, heart attack, or death (less than 5%). The risk is no greater than that incurred during the initial coronary angiography.

*Risks and Benefits*

I understand that there are possible risks to me if I agree to participate in this study. The risks are those of the PTCA procedure, CABG, exercise tests, and coronary angiography as stated above. I understand that my doctor has recommended that I have a revascularization procedure (PTCA or CABG) and that the test procedures described above are routinely used in the assessment and follow-up of patients with coronary artery disease. With participation in this study there is a risk that I may receive the less effective of the treatments being studied. However, the potential benefits include the possibility that I may receive the more effective therapy. The best medical knowledge at this time does not permit a scientific recommendation to me as to which option is better.

*Voluntary Consent, Right to Withdraw*

If I agree to participate in this study, I understand that my care will in no way be compromised. My participation in this study is voluntary. My refusal to participate will involve no penalty or compromise in my medical care or loss of benefits to which I am otherwise entitled. I may discontinue participation at any time without penalty or loss of the benefits to which I am entitled.

*Alternative Treatments*

Possible alternatives to my participation in this study include medical therapy with standard approved drug regimens, coronary angioplasty, or coronary bypass surgery. Each of these three options is standard in the management of patients with coronary artery disease.

*Investigational Sponsorship and Cost Considerations*

The physician investigators listed on this form; research personnel associated with this study at _____; and the National Heart, Lung, and Blood Institute (the sponsor of the study) may inspect and copy my medical records relating to this study. The results of the study will be reported to a coordinating center selected for data analysis. Confidentiality of my medical record will be maintained by the use of a numerical or alphabetical code. In the event of any publications regarding this study, my identity will not be disclosed. I will be informed of any significant new findings developed during the course of the research which may relate to my willingness to continue in the study. These findings may also be published in the medical literature.

The choice of PTCA or CABG may affect the number of days I will be hospitalized. In general, CABG requires a longer hospitalization than PTCA does. However, PTCA may require repeat admissions in the initial year after the procedure because of recurrent narrowings, which may require a second angioplasty procedure. One of the purposes of this study is to determine whether there are differences in the total number of days of hospitalization, over the long term, depending on the initial revascularization procedure chosen. My physician has recommended that I would best be treated by having PTCA or CABG. Therefore, the costs of the PTCA and of the CABG, the direct hospital expenses, and the direct physician fees that are considered clinically indicated for my care will not be paid for by the sponsor of this study. The use of exercise studies with or without a radionuclide is considered routine clinical care in the follow-up of patients with coronary artery disease and will not be paid for by the sponsor. The cost of the coronary angiogram performed 5 years after CABG will be paid for by the sponsor of the study if this test is not required as part of usual care.

(Medical Center Title), in fulfilling its public responsibility, accepts professional liability and responsibility for physical injury if it is caused by negligence of the Center and its employees or agents. No person shall have any authority, orally or in writing, to change the terms of the foregoing. Any questions that I have concerning the research study or my partici-

pation in it, before or after my consent, will be answered by _____.

In the event I believe that I have suffered any injury as a result of participation in the research project, I am to contact _____, who will be able to refer me to an individual who will review the matter with me, identify other resources that may be available to me, and provide information concerning additional inquiries. If I am a woman, I am not pregnant, to the best of my knowledge. I am not participating in any other medical research study. I have read the above statement and have been able to express concerns which have been satisfactorily responded to by the investigator.

I believe I understand the purpose of this study, as well as the potential benefits and risks that are involved. I hereby give my informed and free consent to be a participant in this study.

_____ _____
Patient's Signature Date

_____ _____
Witness's Signature Date

I certify that I have explained to the above individual the nature, purpose, potential benefits, and possible risks associated with participating in this research study. I have answered any questions that have been raised and have witnessed the above signature. These elements of informed consent conform to the assurance given by _____ Department of Health and Human Services, to protect the rights of human subjects. I provided the patient a copy of this signed consent document.

_____
Investigator's Signature Date

## Appendix 8
### Form B

*Patient Consent to Participate in the Bypass Angioplasty Revascularization Investigation Registry*

Principal Investigator _____

Approved by Institutional Review Board _____

Date_____

Some patients at the _____ Medical Center undergoing percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) surgery are being enrolled in a Registry of scientific data as part of a national collaborative clinical study comparing the outcome of these procedures. The purpose of this Registry is to provide scientific information about the merits of PTCA compared with CABG, another procedure for restoring the flow of blood to heart muscle. You are invited to participate in this Registry. If you decide to participate, you will be interviewed each year for the next 5 years or more by mail or telephone. Should you move from your present address, a private agency may be used to determine your new home or place of work. These interviews will take approximately one-half hour of your time. The questions asked will be about your symptoms of angina or other heart problems. You will also be asked whether or not you have undergone any hospitalizations because of your heart problems or whether you have undergone a repeat PTCA or CABG or have been hospitalized for treatment of a heart attack. The questions are not considered to have psychological stress. No standard treatment will be required by your treating physicians nor will any standard treatment be withheld from you. You will receive no payment or other compensation for participating in this Registry. There may be no immediate benefit to you, but the combined information from this Registry may help your physician and other physicians in the future to better understand the effects of the treatment you have received on ischemic heart disease and its course.

I understand that, upon my request, a BARI research investigator will answer questions about the study. I may refuse to participate or discontinue participating in the study at any time without penalty or loss of benefits available to me as a patient at this medical center.

I understand that no commitment is made to provide complimentary medical care or compensation for any adverse results of my participation in this study. Further information concerning institutional policies in this regard or information about the conduct of this study or the rights of research subjects may be obtained from _____.

Confidentiality of information concerning participants will be maintained. Names of participants or material identifying participants will not be released without written permission, except as such release is required by law. Medical records related to this study may be made available to the Food and Drug Administration, as provided for in federal regulations.

_____ _____
Date Signature of Participant

_____ _____
Date Signature of BARI Investigator Obtaining Consent

## Appendix 9
### BARI
### List of Participants
### Clinical Centers

**University of Alabama**

| | |
|---|---|
| Principal Investigator: | William J. Rogers, MD |
| PTCA Operators: | William A. Baxley, MD |
| | Larry S. Dean, MD |
| | Gary S. Roubin, MD |
| Surgeons: | James K. Kirklin, MD |

| | |
|---|---|
| | John W. Kirklin, MD |
| | Albert Pacifico, MD |
| | George L. Zorn, MD |
| Associate Investigators: | Edgar Charles, PhD |
| | Thomas D. Paine, MD |
| Coordinators: | Larry E. Maske, RN |
| | Terri E. Morgan, RN |
| | Leah C. Carr (SEQOL) |
| Data Manager: | John A. Trobaugh, RA |
| Staff: | Karen W. Anderson |
| | Fredericka Harris |
| Former Participants: | Thomas Bulle, MD |
| | J. Bradley Cavender, MD |
| | Paul J. Garrahy, MD |

**Brown University: Rhode Island Hospital**

| | |
|---|---|
| Principal Investigator: | David O. Williams |
| PTCA Operators: | Thomas M. Drew, MD |
| | David O. Williams |
| Surgeon: | Arun K. Singh, MD |
| Associate Investigators: | George N. Cooper, MD |
| | Barry L. Sharaf, MD |
| Coordinators: | Mark Macedo, RN |
| | Janice L. Wheeler, RN |
| Former Participants: | John Moran, MD |
| | Edward S. Thomas, MD |
| | Harvey White, MD |

**Bellevue Hospital (Satellite to Brown)**

| | |
|---|---|
| Principal Investigator: | Frederick Feit, MD |
| PTCA Operators: | Michael J. Attubato, MD |
| | Frederick Feit, MD |
| Surgeons: | Stephen B. Colvin, MD |
| | Aubrey C. Galloway, MD |
| Associate Investigator: | Peter F. Pasternack, MD |
| Coordinator: | Sonja Shapiro, RN |

**Boston University**

| | |
|---|---|
| Principal Investigator: | David P. Faxon, MD |
| PTCA Operators: | John E. Brush, MD |
| | David P. Faxon, MD |
| | Gary R. Garber, MD |
| | Alice K. Jacobs, MD |
| | Nicholas A. Ruocco, MD |
| Surgeons: | James D. Fonger, MD |
| | Richard S. Shemin, MD |
| Associate Investigators: | Michael A. Bettmann, MD |
| | Jesse W. Currier, MD |
| | James A. Rothendler, MD |
| | Thomas J. Ryan, MD |
| | Donald A. Weiner, MD |
| Coordinators: | Beth R. Hankin, RN |
| | Mary E. Mazur, RN |
| Former Participants: | Roger M. Mills, MD |
| | Gaetano Paone, MD |

**Cleveland Clinic Foundation**

| | |
|---|---|
| Principal Investigator: | Patrick L. Whitlow, MD |
| PTCA Operators: | Irving Franco, MD |
| | Patrick L. Whitlow, MD |
| Surgeons: | Delos Cosgrove, MD |
| | Floyd Loop, MD |
| | Bruce Lytle, MD |
| | Robert Stewart, MD |
| | Paul C. Taylor, MD |
| Associate Investigators: | Alexios P. Dimas, MD |
| | William Proudfit, MD |
| | Benjamin Robalino, MD |
| | Eric Topol, MD |
| | Kevin Vaska, MD |
| | George Williams, PhD |
| Coordinator: | Amy Rogers, RN |
| Data Manager: | Sharon Senick |
| Staff: | Kathy Comella, RN |
| | Marsha Lowrie, RN |
| | Joyce Tedrick, RN |
| Former Participants: | John Frierson, MD |
| | Jay Hollman, MD |

**Duke University**

| | |
|---|---|
| Principal Investigator: | Robert M. Califf, MD |
| PTCA Operators: | Robert P. Bauman, MD |
| | Victor S. Behar, MD |
| | Yihong Kong, MD |
| | Mitchell W. Krucoff, MD |
| | Kenneth G. Morris, MD |
| | Robert H. Peter, MD |
| | Harry R. Phillips, MD |
| | Richard Stack, MD |
| | James E. Tcheng, MD |
| Surgeons: | Robert H. Jones, MD |
| | H. Newland Oldham, MD |
| | Peter Van Trigt, MD |
| Associate Investigators: | Thomas Bashore, MD |
| | Donald F. Fortin, MD |
| | David J. Frid, MD |
| | Kerry Lee, PhD |
| | Michael J. Miller, MD |
| | E. Magnus Ohman, MD |
| | David B. Pryor, MD |
| | Alan N. Tenaglia, MD |
| Coordinators: | Mary Ann Sellers, RN |
| | Ellen T. Hampton, RN |
| Data Manager: | Terri Daniels |
| Staff: | Leonard Santoro |
| Former Participants: | Sandra G. Burks, RN |
| | Stephanie Caminiti, RN |
| | Peter J. Quigley, MD |
| | J. Scott Rankin, MD |
| | Joan Richard, RN |

**Harvard University: Beth Israel Hospital**

| | |
|---|---|
| Principal Investigator: | Donald S. Baim, MD |
| Coprincipal Investigator: | Robert Safian, MD |
| PTCA Operators: | Julian Aroesty, MD |
| | Donald S. Baim, MD |
| | Daniel Diver, MD |
| | Beverly Lorell, MD |
| Surgeons: | Robert Johnson, MD |
| | Robert Thurer, MD |
| | Ronald Weintraub, MD |
| Coordinator: | Mary Cunnion |
| Former Participants: | Raymond McKay, MD |
| | Tia DeFeo-Fraulini, MS |
| | Carolyn McCabe |

**Maine Medical Center (Satellite to Harvard)**

| | |
|---|---|
| Principal Investigator: | Mirle A. Kellett Jr., MD |
| PTCA Operators: | Warren D. Alpern, MD |
| | Richard A. Anderson, MD |
| | D. Joshua Cutler, MD |
| | Mirle A. Kellett Jr., MD |
| | Paul W. Sweeney, MD |
| Surgeons: | Desmond J. Donegan, MD |
| | Saul Katz, MD |
| | Robert S. Kramer, MD |
| | Chris A. Lutes, MD |
| | Jeremy R. Morton, MD |
| | Edward R. Nowicki, MD |
| | Joan F. Tryzelaar, MD |
| | Richard L. White, MD |
| Associate Investigator: | Costas T. Lambrew, MD |
| Coordinators: | Pamela Birmingham, RN |
| | Jane Conner Kane, RN |
| | Nancy Tooker, RN |

**University of Massachusetts**

| | |
|---|---|
| Principal Investigator: | Bonnie H. Weiner, MD |
| PTCA Operator: | Bonnie H. Weiner, MD |
| Surgeons: | Dani Bitran, MD |
| | John Moran, MD |
| | Okike N. Okike, MD |
| | Thomas Pezzella, MD |

| | |
|---|---|
| | Thomas J. VanderSalm, MD |
| Coordinators: | Marie Borbone, RN |
| | Paul Wanta, RN |
| Data Manager: | Theresa Wisnewski |
| Former Participants: | Joseph Benotti, MD |
| | James Dalen, MD |
| | John Gaca, MD |
| | Jeffrey Leppo, MD |
| | Michael Pasque, MD |
| | Marilyn Shay, RN |

**Mayo Clinic**

| | |
|---|---|
| Principal Investigator: | Michael Mock, MD |
| PTCA Operators: | John Bresnahan, MD |
| | David Holmes, MD |
| | Guy S. Reeder, MD |
| Surgeons: | Charles Mullany, MD |
| | Thomas A. Orszulak, MD |
| | Hartzell Schaff, MD |
| Associate Investigators: | Peter B. Berger, MD |
| | Bernard Gersh, MD |
| | Raymond Gibbons, MD |
| | Stephen L. Kopecky, MD |
| | Fred Nobrega, MD |
| | Robert S. Schwartz, MD |
| | Hugh C. Smith, MD |
| Coordinator: | Sylvia Matheson, RN |
| Data Managers: | Lisa Kelly |
| | Mary Peterson |
| | Lou Ann Pierre, RN |
| Former Participants: | Dennis Bresnahan, MD |
| | Ronald Vlietstra, MD |

**Medical College of Virginia**

| | |
|---|---|
| Principal Investigator: | Michael J. Cowley, MD |
| PTCA Operators: | Michael J. Cowley, MD |
| | Germano DiSciascio, MD |
| | George Vetrovec, MD |
| Surgeons: | Albert Guerraty, MD |
| | David Salter, MD |
| | Andrew Wechsler, MD |
| Associate Investigator: | Chauncey W. Crandall, MD |
| Coordinators: | David Debottis, RN |
| | Ann Maziarz, RN |
| Former Participants: | Kim Kelley, RN |
| | R. R. Lower, MD |
| | Amar Nath, MD |
| | Bonnie Sechrist, RN |
| | S. Szentpetery, MD |

**University of Michigan**

| | |
|---|---|
| Principal Investigator: | Bertram Pitt, MD |
| PTCA Operators: | Eric Bates, MD |
| | Stephen Ellis, MD |
| | Linda Lee, MD |
| | Eric J. Topol, MD |
| | Joseph Walton, MD |
| Surgeons: | Steven Bolling, MD |
| | Michael Deeb, MD |
| | Marvin Kirsh, MD |
| Coordinator: | Karen Burek, RN |
| Staff: | Linda Belzowski, RN |
| | Markus Schwaiger, MD |
| | Hui-lee Shu |
| Former Participants: | Diane Scarpace, RN |
| | Mack Stirling, MD |
| | Peter Thomasma |
| | Eric J. Topol, MD |
| | Steve Werns, MD |

**Montreal Heart Institute**

| | |
|---|---|
| Principal Investigator: | Martial G. Bourassa, MD |
| PTCA Operators: | Raoul Bonan, MD |
| | Gilles Côté, MD |
| | Jacques Crépeau, MD |
| | Pierre DeGuise, MD |
| Surgeons: | Yves Castonguay, MD |
| | Yves Leclerc, MD |
| | Conrad Pelletier, MD |
| Associate Investigators: | André Arseneault, MD |
| | Gilles Hudon, MD |
| | Jacques Lespérance, MD |
| | David D. Waters, MD |
| Coordinator: | Johanne Trudel, RN |
| Data Manager: | Claudette Faille |
| Staff: | Huguette Flageol |
| | Lucette Whittom, RN |

**Toronto Hospital (Satellite to Montreal)**

| | |
|---|---|
| Principal Investigator: | Leonard Schwartz, MD |
| PTCA Operators: | Harold Aldridge, MD |
| | Leonard Schwartz, MD |
| | David Uden, MD |
| Surgeons: | Tirone David, MD |
| | Chris Feindel, MD |
| | Bernard Goldman, MD |
| | Irving Lipton, MD |
| | Lynda Mickleborough, MD |
| | Richard Weisel, MD |
| Associate Investigators: | David Almond, MD |
| | Michael McLoughlin, MD |
| | Leon Zelovitsky, MD |
| Coordinator: | Linda Ganassin, RN |
| Staff: | Karen Mackie, RN |

**New York Medical College**

| | |
|---|---|
| Principal Investigator: | Michael V. Herman, MD |
| PTCA Operator: | Melvin B. Weiss, MD |
| Surgeons: | Richard Moggio, MD |
| | Richard Pooley, MD |
| | George Reed, MD |
| | Mohan Sarabu, MD |
| Coordinator: | Doris Efstathakis, RN, BSN |
| Data Manager: | Yonina Sait, PA |
| Former Participants: | Peter Praeger, MD |
| | Kathleen Ryman, MD |
| | Eric Somberg, MD |
| | Jonathan H. Stein, MD |

**St. Louis University**

| | |
|---|---|
| Principal Investigator: | Bernard R. Chaitman, MD |
| PTCA Operator: | Morton J. Kern, MD |
| Surgeons: | George Kaiser, MD |
| | Vallee Willman, MD |
| Associate Investigator: | Robert Wiens, MD |
| Coordinator: | Katherine Galan, RN |
| Staff: | Jane Fehl, LPN |
| | Barbara Poole |
| Former Participants: | Hendrick Barner, MD |
| | Ubeydullah Deligonul, MD |
| | Michel G. Vandormael, MD |

**Jewish Hospital (Satellite to St. Louis)**

| | |
|---|---|
| Principal Investigator: | Ronald J. Krone, MD |
| Coprincipal Investigator: | Nicholas Kouchoukos, MD |
| PTCA Operators: | Ronald J. Krone, MD |
| | Ali Salimi, MD |
| Surgeons: | Nicholas Kouchoukos, MD |
| | Thomas H. Wareing, MD |
| Associate Investigators: | Patricia Cole, MD |
| | Robert Kleiger, MD |
| | Sandor Kovacs, MD |
| | Michael Rich, MD |
| | Anil Shah, MD |
| Coordinators: | Mary Caruso, RN |
| | Jane Humphrey, RN |
| | Lisa Spinner, RN |
| Staff: | Cynthia Benson |
| | Gail Eisenkramer |
| | Thelma Jones |
| | Ethel Kelly |
| | Jean Moore |
| | Rose Umstead |
| | Juanita Weaver |

**BARI/Parallel Study**
**Institute of Clinical and Experimental Medicine**
**Prague, Czechoslovakia**

| | |
|---|---|
| Principal Investigator: | Vladimír Staněk, MD |
| PTCA Operators: | Alfréd Belán, MD |
| | Josef Kovác, MD |
| Surgeons: | Pavel Firt, MD |
| | Jan Pirk, MD |
| Associate Investigators: | Vladimír Kočandrle, MD |
| | Michael Želízko, MD |
| Coordinator: | Růzena Jandova, MD |
| Data Manager: | Erhard Tchernoster, Ing. |

**Former Site**

**Georgetown University**

| | |
|---|---|
| Principal Investigator: | Kenneth Kent, MD |
| PTCA Operator: | Kenneth Kent, MD |
| Surgeons: | Nevin M. Katz, MD |
| | Robert Wallace, MD |
| Associate Investigators: | Larry Elliott, MD |
| | Curtis Green, MD |
| | James Lavelle, MD |
| | Charles Rackely, MD |
| Coordinator: | Beverly Shriver, RN |

**Central Electrocardiographic Laboratory**

**St. Louis University Medical Center**

| | |
|---|---|
| Principal Investigator: | Bernard R. Chaitman, MD |
| Associate Investigators: | Robert D. Wiens, MD |
| | Preben Bjerregaard, MD |
| | Leonardo Maitas, MD |
| | Bonpei Takase, MD |
| | Liwa T. Younis, MD, PhD |
| Coordinators: | Leslee Shaw, MA |
| | Karen Stocke |
| Programmers: | Li-Yung Lui, MS |
| | Kim Russell |
| Staff: | Steve Cannon |
| | Teresa Cutts |
| | Debbie Kargl |
| | Willie Mathis |
| | Mark Muehl, MA |
| | Barbara Poole |
| | Laura Schaefer |
| | Art Stelken, MA |
| | Jesse Williams |
| Former Participants: | Brian Bilgere |
| | Mary Ellen Hauesen |
| | Jeanine Sabatino |

**Central Radiographic Laboratory**

**Stanford University Medical Center**

| | |
|---|---|
| Principal Investigators: | Edwin L. Alderman, MD |
| | Michael Stadius, MD |
| Associate Investigators: | Byron Brown, PhD |
| | William Sanders, MSEE |
| | Lewis Wexler, MD |
| Coordinator: | Brooke Hollak, RN |
| Staff: | Terri Beam |
| | Gao Shao-Zhou, MD |
| Former Participant: | Robert Moore, MD |

**Ancillary Study**

**SEQOL: Study of Economics and Quality of Life**
**Stanford University School of Medicine**

| | |
|---|---|
| Principal Investigator: | Mark Hlatky, M.D. |
| Coordinator: | Kathryn Cavanaugh, MPH |
| Former Participant: | N. Clapp-Channing, MPH, RN |

**Coordinating Center**

**University of Pittsburgh, Pittsburgh, Pennsylvania**

| | |
|---|---|
| Principal Investigators: | Katherine M. Detre, MD, DrPH |
| | Sheryl F. Kelsey, PhD |
| Coordinator: | Kim Sutton-Tyrrell, RN, DrPH |
| Assistant Coordinator: | Barbara L. Naydeck |
| Statisticians: | Huiman X. Barnhart, MA |
| | Joyce F. Killinger, MS |
| | Joseph E. Melvin |
| | Allan D. Rosen, MS |
| | Ann Rodewald Steenkiste, MS |
| Data Coordinator: | Sharon Weber Crow |
| Data Managers: | Regina M. Hardison |
| | Meg Cooper, MEd |
| | Gail Harger, MSIS |
| System Programmers: | Dave W. Burry |
| | Jeffrey P. Martin |
| | Emil A. Maurer |
| System Support: | William P. Amoroso, MPH |
| | Larry Kamons, MSIS |
| | Timothy E. Kuntz, MSIS |
| | Nancy H. Remaley, MSIS |
| Consultants: | Joel Greenhouse, PhD |
| | Robert L. Hardesty, MD |
| | Barry F. Uretsky, MD |
| Former Participants: | Lynette M. Anderson |
| | Donald Borrebach, MS |
| | Mary Ann Carr, MS |
| | Richard Holubkov, MS |
| | Diane F. Hursh |
| | Jennifer A. Metzler |
| | Angela Spadaro |
| | John Wilson, PhD |

**Program Office**
**Cardiac Diseases Branch**
**Division of Heart and Vascular Diseases**
**National Heart, Lung, and Blood Institute**
**National Institutes of Health**
**Bethesda, Maryland**

| | |
|---|---|
| Program Administrator: | George Sopko, MD, MPH |
| Coinvestigators: | Michael Horan, MD |
| | Rachel Solomon, M.H.S. |
| | David Zucker, PhD |
| Former Participants: | Michael J. Domanski, MD |
| | Louis Offen, MD |
| | Thomas Robertson, MD |
| | Joel Verter, PhD |

**Safety and Data Monitoring Board**

| | |
|---|---|
| Chair: | J. David Bristow, MD, Oregon Health Sciences University |
| Members: | James Childress, PhD, University of Virginia |
| | Timothy Gardner, MD, Johns Hopkins Hospital |
| | Herman Gold, MD, Massachusetts General Hospital |
| | J. Ward Kennedy, MD, University of Washington |
| | Genell Knatterud, PhD, Maryland Medical Research Institute |
| | Robert Roberts, MD, Baylor College of Medicine |
| | John Waldhausen, MD, Hershey Medical Center |
| | Carl White, MD, University of Minnesota Hospital |

**Morbidity and Mortality Classification Committee**

| | |
|---|---|
| Chair: | Ronald Prineas, MD, PhD, University of Miami |
| Members: | Charles Fisch, MD, Krannert Institute of Cardiology |
| | Leon Greene, MD, Harborview Hospital |
| | Robert B. Karp, MD, University of Chicago Medical Center |
| | Spencer B. King III, MD, Emory University Hospital |
| | Jay Mason, MD, University of Utah Medical Center |
| | Jack L. Titus, MD, PhD, United Hospital |

**Office of Study Chair**
**Mayo Clinic Foundation**
**Rochester, Minnesota**

Robert Frye, MD
Professor of Medicine
Chairman of Internal Medicine

## References


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KEY WORDS: • PTCA • multivessel CAD • CABG • revascularization