CHAPTER ONE

PROTOCOL SUMMARY

I. INTRODUCTION

Type 2 diabetes mellitus, which is becoming more prevalent in our society as the population ages, is one of the strongest risk factors for coronary artery disease (CAD) and consequent mortality. In addition to generating an enormous toll in human suffering, diabetes places an economic burden approaching 100 billion dollars annually on the U.S. health care system. Despite the well known dismal prognosis of diabetes complicated by angiographically documented CAD, the optimal treatment paradigm for this large group of patients has not been studied. Coronary revascularization, while increasingly used, has not been directly shown to be of additional benefit to simultaneous intensive medical management of CAD along with management of hyperglycemia, hypertension, dyslipidemia, and other risk factors. Moreover, while intensive efforts to lower HbA1c have been demonstrated to favorably affect the clinical course of Type 2 diabetes mellitus in terms of microvascular complications, the optimal hyperglycemia management strategy with regard to macrovascular outcome is not known.

These critical treatment dilemmas have motivated the development of BARI 2D, a multicenter randomized trial designed to determine in patients with Type 2 diabetes and stable CAD: 1) the efficacy of initial elective coronary revascularization combined with aggressive medical therapy, compared to an initial strategy of aggressive medical therapy alone; and 2) the efficacy of a strategy of providing more insulin (endogenous or exogenous), versus a strategy of increasing sensitivity to insulin (reducing insulin resistance), in the management of hyperglycemia, with a target HbA1c level of < 7.0% for each strategy.

II. SPECIFIC AIMS

A. Primary Aim

The primary aim of the BARI 2D trial is to test the following two hypotheses of treatment efficacy in 2400 patients with Type 2 diabetes mellitus and documented stable CAD, in the setting of uniform glycemic control and intensive management of all other risk factors including dyslipidemia, hypertension, smoking, and obesity:

1. Coronary Revascularization Hypothesis: a strategy of initial elective **revascularization** of choice (surgical or catheter-based) combined with aggressive medical therapy results in lower 5-year mortality compared to a strategy of aggressive **medical therapy** alone;

2. Method of Glycemic Control Hypothesis: with a target HbA1c level of <7.0%, a strategy of hyperglycemia management directed at **insulin sensitization** results in lower 5-year mortality compared to a strategy of **insulin provision**.

B. Secondary Aims

The secondary aims of the BARI 2D trial include: a) comparing the death, myocardial infarction or stroke combined endpoint event rate between the revascularization versus medical therapy groups and between the insulin sensitization versus insulin provision groups; b) comparing rates of myocardial infarction, other

ischemic events, angina and quality of life associated with each revascularization and hyperglycemia management strategy; c) evaluating the relative economic costs associated with the trial treatment strategies; d) exploring the effect of glycemic control strategy on the progression and mechanism of vasculopathy including changes in PAI-1 gene expression.

III. RESEARCH DESIGN AND METHODS

A. Patient Eligibility Criteria

The pool of potential trial participants will consist of all patients with a known diagnosis of Type 2 diabetes mellitus who undergo coronary angiography at participating BARI 2D institutions. Inclusion and exclusion criteria for BARI 2D participants are summarized below:

Inclusion Criteria for BARI 2D
1. Diagnosis of Type 2 diabetes mellitus. 2. Coronary arteriogram showing one or more vessels amenable to revascularization (≥50% stenosis). 3. Objective documentation of ischemia **OR** subjectively documented typical angina with ≥70% stenosis in at least one artery. 4. Suitability for coronary revascularization by at least one of the available methods (does not require the ability to achieve complete revascularization). 5. Ability to perform all tasks related to glycemic control and risk factor management. 6. Age 25 or older. 7. Informed written consent.

Exclusion Criteria for BARI 2D
1. Definite need for invasive intervention as determined by the attending cardiologist. 2. Prior bypass surgery (CABG) or prior catheter-based intervention within the past 12 months. 3. Planned intervention for disease in bypass graft(s) if the patient is randomized to a strategy of initial revascularization. 4. Class III or IV CHF. 5. Creatinine > 2.0 mg/dl. 6. HbA1c > 13%. 7. Need for major vascular surgery concomitant with revascularization (*e.g.*, carotid endarterectomy). 8. Left main stenosis ≥ 50%. 9. Non-cardiac illness expected to limit survival. 10. Hepatic disease (ALT> 2 times the ULN). 11. Fasting triglycerides > 1000 mg/dl in the presence of moderate glycemic control (HbA1c <9.0%). 12. Current alcohol abuse. 13. Chronic steroid use judged to interfere with the control of diabetes, exceeding 10 mg. of Prednisone per day or the equivalent. 14. Pregnancy, known, suspected, or planned in next 5 years. 15. Geographically inaccessible or unable to return for follow-up. 16. Enrolled in a competing randomized trial or clinical study. 17. Unable to understand or cooperate with protocol requirements.

Patients with Type 2 diabetes mellitus and CAD documented by coronary arteriography will be eligible for the trial if revascularization is not required for prompt control of severe or unstable angina. Diabetic patients who are being treated with insulin or oral hypoglycemic drugs will be eligible as well as diabetic patients treated with diet and exercise alone provided that a diagnosis of diabetes can be confirmed by record review or that a fasting plasma glucose (FPG)>125/mg/dl (7.0 mmol/l) can be obtained. The determination of suitability for BARI 2D will be made by a physician-investigator at each participating institution on clinical grounds at the time of coronary angiography.

Significant CAD will be defined as at least one stenosis ≥50%. Angina and ischemia will be assessed by use of patient self-report, physician examination, and appropriate diagnostic measures including exercise myocardial perfusion imaging, exercise echocardiography, exercise electrocardiography, and IV dipyridamole or adenosine myocardial perfusion imaging or invasively by doppler or pressure wire. Objective documentation of myocardial ischemia includes any of the following:

1. Exercise or pharmacologically-induced:

    a. ≥1 mm of horizontal or downsloping ST depression or elevation for ≥60-80 milliseconds after the end of the QRS complex;
    b. myocardial perfusion defect;
    c. myocardial wall motion abnormality.

2. Stabilized, prior acute coronary syndrome with CK-MB or troponin elevation or with new, ≥0.5 mm ST depression or elevation, or T wave inversion of ≥3 mm in 2 contiguous ECG leads.

3. Doppler or pressure wire showing coronary flow reserve (CFR) <2.0 or fractional flow reserve (FFR) <0.75.

Among patients without documented ischemia, only patients with stenosis ≥ 70% presenting with classic anginal symptoms will be eligible for randomization.

B. Study Treatment Protocol

The BARI 2D trial will use a 2x2 factorial design, with 2400 patients being assigned at random to initial elective revascularization with aggressive medical therapy or aggressive medical therapy alone with equal probability, and simultaneously being assigned at random to an insulin providing or insulin sensitizing strategy of glycemic control (with a target value for HbA1c of <7.0% for all patients). Following confirmation of patient eligibility and provision of written consent, patients will be randomized as shown below:

Number of Patients Per Treatment Assignment		Revascularization Strategy	
		Revascularization	Medical
Glycemic Control Strategy	Insulin Providing (IP)	600	600
	Insulin Sensitizing (IS)	600	600

C. Revascularization Strategy

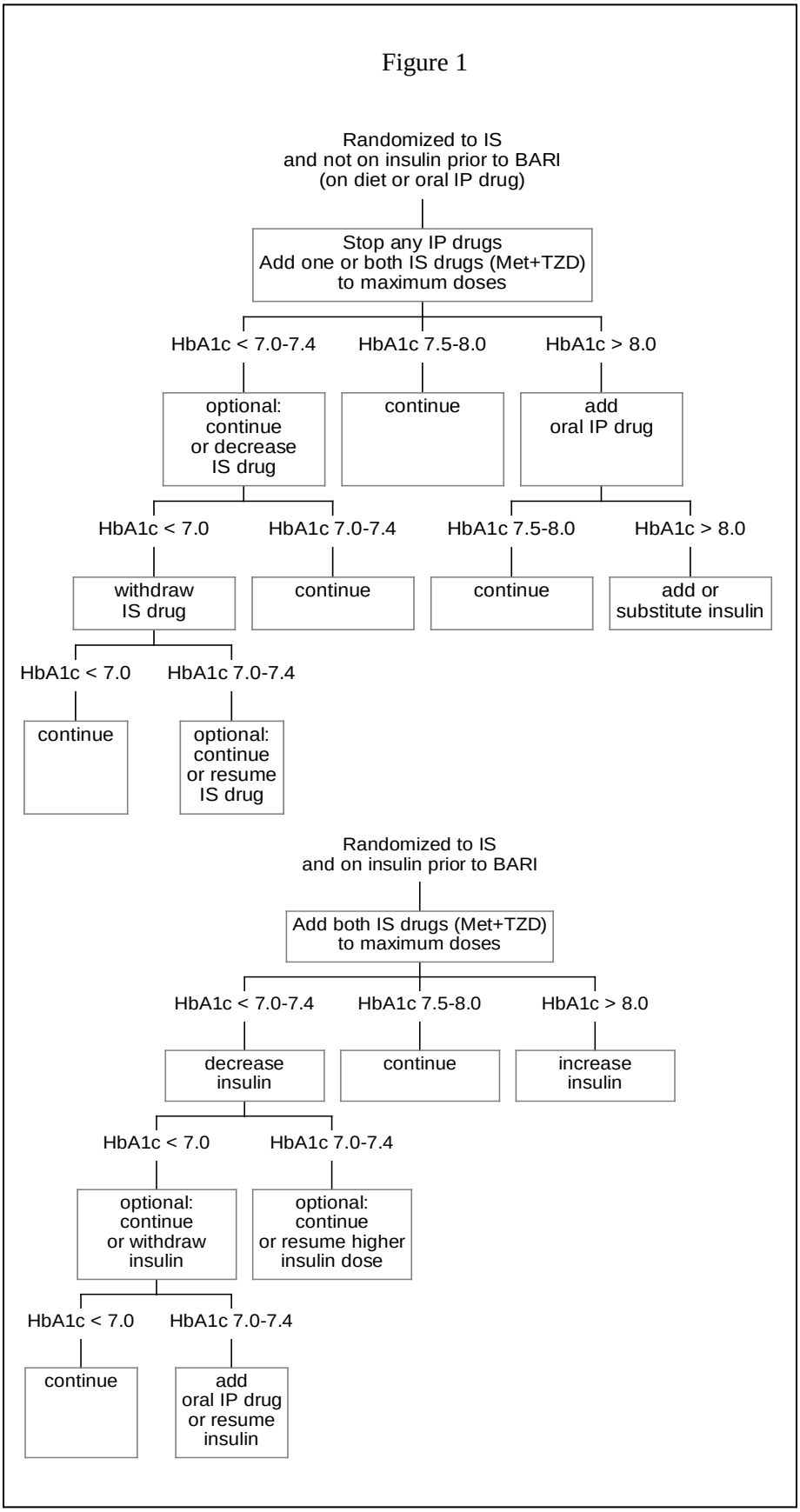
The choice of revascularization procedure will be determined by the responsible physicians, based upon full discussion with interventional cardiologists and cardiac surgeons as deemed appropriate for the individual patient. This choice will be made prior to randomization since randomization is stratified by revascularization procedure chosen. The target goals of both revascularization treatment arms will be the minimization or elimination of CAD symptoms and ischemia. Patients assigned to initial revascularization of choice will undergo the treatment judged to be optimal for their particular angiographic and clinical profile. This may include coronary artery bypass graft (CABG) surgery, percutaneous transluminal coronary angioplasty (PTCA)/other catheter-based intervention, or a combination of these approaches. For patients assigned to revascularization of choice, the initial revascularization is to be performed within 4 weeks of the date of randomization. To ensure the integrity of the invasive intervention arm, participating interventionalists (operators and surgeons) are required to be BARI 2D certified.

D. Glycemic Control Strategy

BARI 2D was designed to test the hypothesis that a treatment strategy which lowers insulin resistance/plasma insulin with insulin-sensitizing (IS) drugs will lead to decreased five-year mortality and CVD events, when compared to the same level of glycemic control (meeting standard of care) achieved by insulin-providing (IP) drugs. There are two classes of insulin sensitizers: 1) biguanides (metformin), which primarily lower hepatic glucose production; and 2) thiazolidinediones (TZD), which primarily reduce insulin resistance in skeletal muscle and adipocytes. IP agents will be sulfonylurea drugs, repaglinide and other approved meglitinides and insulin itself. Since prior to entering the trial the participant's diabetic management could range from diet/exercise alone to insulin treatment, the goal will be to transfer each patient to only those interventions specified by the randomized treatment allocation of the BARI 2D protocol. The algorithms for these are summarized for each glycemic strategy and stratified by prior insulin use as shown in Figures 1 and 2. The alpha-glucosidase inhibitors (acarbose and miglitol) may be used as adjunctive drugs in either arm. The general HbA1c goal will be <7.0%. For elderly patients without evidence of diabetic retinopathy, nephropathy and neuropathy, HbA1c may be maintained between 7.0 and 7.4%, at the investigator's discretion. Moreover, the algorithms outlined in Figures 1 and 2 reflect a recognition that, for patients who enter the study with a relatively high HbA1c on combination therapy, it may be more realistic to expect to achieve a HbA1c level in the range of 7.5-8.0%.

Sustained HbA1c levels above 8.0% will mandate the use of drugs from the opposite arm of the study, but these crossover drugs will be provided at the lowest doses needed to bring HbA1c below 8.0%. If HbA1c levels fail to improve after 1-2 months (or 2-3 months

Figure 1

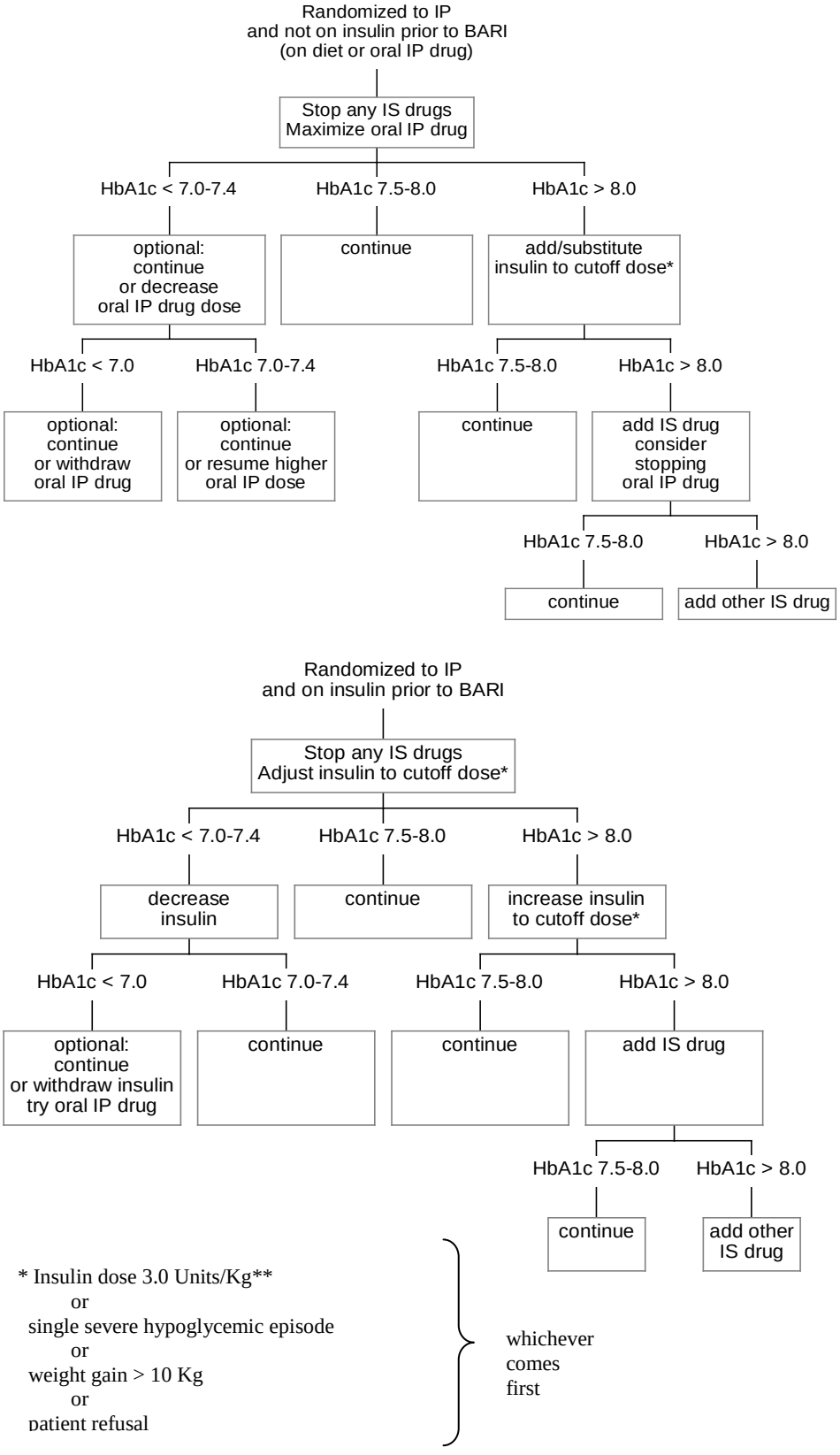


under a TZD regimen), then dosages should be increased and/or the next step in the pertinent algorithm (IS or IP) should be adopted. A comprehensive program of diabetes education will be provided. This will include nutritional counseling to promote weight loss in the obese patients, training in the use of home blood glucose testing, and instruction of patient and family to recognize and deal with episodes of hypoglycemia. In addition, patients will be monitored regularly during the study for home blood glucose results and HbA1c levels, and liver and kidney function will be measured to detect drug toxicity.

E. Endpoints

The primary endpoint of BARI 2D will be all cause mortality, and the principal secondary endpoint will be the combination of death, myocardial infarction or stroke. The classification of MIs will be based on the BARI 2D central laboratory evaluation of enzymes, symptoms and ECG results. Other secondary study endpoints to be evaluated include cardiac-only mortality, myocardial infarction, composite clinical endpoints (most notably death or MI), angina, LV function, the extent of ischemia, subsequent revascularization procedures (CABG and PCI), PAI-1 activity, and quality of life. In addition to clinical endpoints, cumulative medical costs will be analyzed. "Diabetes-specific" complications including retinopathy, nephropathy, neuropathy, and peripheral vascular disease will be monitored regularly.

Figure 2



** Note: This is the lowest dose that should trigger consideration of adding an IS drug. The diabetologist can continue increasing insulin if he/she prefers, so long as it can be done safely and without antagonizing the patient.

IV. FOLLOW-UP

A. Clinic Visits and Patient Follow-up

Following patient randomization, the clinic cardiology investigator will prescribe and discuss the CAD medical therapy regimen and target risk factor goals to be pursued, and will refer the patient to the clinic diabetology investigator within 1 week of study entry. The diabetologist, with the aid of a study diabetes nurse specialist, will discuss the assigned treatment strategies with the patient and will provide comprehensive diabetes care education, including emphasis on seeking medical care for intercurrent illness. In addition, the diabetologist, with the help of a study dietician, will outline a dietary program designed to promote the nutritional needs and ideal body weight of the patient, and emphasize the importance of proper diet and prescribed exercise in achieving optimum glucose control.

The schedule depicting 5-year follow-up is summarized in Table 1. Thus, patients on diet therapy alone will typically require less clinical monitoring (*e.g,*. no risk of hypo-glycemia) and need for consultation, compared to patients on oral agents and insulin. However, after the first 6 monthly visits, a minimum of 3-month visits at the diabetology clinic will be mandated for all randomized patients in order to:

1. Obtain a patient history of symptoms of glycosuria and hyperglycemia, measure body weight and blood pressure, collect a fasting blood sample for lipids, glucose and HbA1c, fibrinolytic and hemostatic factors, and assess liver function.
2. Screen for microalbuminuria by measurement of the albumin to creatinine ratio.
3. Document diabetes mellitus medications being taken by the patient (*e.g.,* oral agents, insulin, etc.).
4. Document medication for hypertension and dyslipidemia.
5. Collect compliance data for evaluation of adherence to target risk factor goals.

Table 1. Data Collection by Follow-up Visit

	Baseline	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo	9 mo	1 yr	Years 2-6 Quarterly	Years 2-6 Semi-Annual	Years 2-6 Annual
Clinic Visit (Diabetology and Cardiology assessments): hx of symptoms of glycosuria and hyperglycemia; body weight; BP; ascertain DM medications, screen for microalbuminuria, assess adherence to risk factor modification goals, HbA1c (local), ascertainment of events (death, MI, repeat revascularization, complications), monitor angina	Diab and Card (within 1 week)	D	D	D	D	D	D C	D	D C	D	C	
Baseline and Annual Clinic Assessment: QOL, cardiac medications, neuropathy	X								X			X
Core Fibrinolysis Lab: PAI-1, t-PA, insulin NMR Lipids	X X	X		X			X		X X		X	
Biochemistry Core Lab: HbA1c	X	X		X			X		X		X	
Biochemistry Core Lab: Lipids	X						X		X			X
Biochemistry Core Lab: Urine (albumin/creatinine)	X								X			X
ECG Core Lab: Resting ECG	X			X					X			X
Pharmacological Nuclear Stress Study									X			X*
Angiogram for Core Lab	X											

*This test is not required at years two and four, but should be done and sent to the NCL if possible

The cardiologist, in addition to the diabetologist, will be expected to see patients at follow-up visits to ascertain control of symptoms of angina, and to review stress tests and any other relevant data obtained as part of each patient's continuing clinical care. These cardiology visits should be done at least every six months, but can be more frequent at the physician's discretion. One potential conflict in motivating patients to pursue the recommended diabetes care and glycemic control goals may arise in patients whose primary care physicians may disagree with the BARI 2D glycemic control target and/or treatment. Therefore, for each patient enrolled in BARI 2D, a written description of the study protocol and treatment aims will be forwarded to the patient's primary care physician. A joint letter from the attending cardiologist and diabetologist will accompany the protocol and will emphasize the desire for a collaborative relationship with the primary care physician in treating the patient, in terms of aggressive control of CAD and diabetes risk factors. This letter should, when appropriate, make clear that the primary care physician will continue managing all other medical problems, *e.g.*, peptic ulcer, arthritis, etc.

B. Blood and Urine Laboratory Studies

Blood draws will be done at baseline and sent to the blood core labs to assay HbA1c, fibrinolytic factors, and insulin. These samples will then be drawn again at 1 month, 3 months, 6 months, 1 year and then semi-annually for the next 4 years. Blood draws for lipid assays will be done at baseline, 6 months, 1 year and then annually for the next 4 years. In addition, cells from the baseline HbA1c specimen will be collected and stored, appropriately frozen, with the future goal of identifying possible new risk factors or underlying mechanisms involved in atherogenesis and the occurrence of macrovascular events.

Urine specimens will be collected at baseline and then annually. They will be assayed at the Biochemistry Laboratory for albumin and creatinine. An A/C ratio will be constructed.

C. Post-Treatment Follow-up Phase

At the conclusion of the treatment and follow-up phase of BARI 2D, participants will be asked to continue in a long-term follow-up phase. This will consist of annual contact to ask a few questions about the patient's current health status and recent clinical events. This annual contact will be carried out by a group at the University of Pittsburgh separate from the Coordinating Center.

V. UNIFORM MEDICAL THERAPY GUIDELINES

An important aspect of BARI 2D will be the uniform, intensive management of all coronary risk factors in all randomized patients, thus enabling an assessment of the efficacy of revascularization and glycemic management strategy over and above maximal management of other factors, and without confounding due to variable management of such factors. Intensive medical therapy for CAD will be prescribed for all patients in the trial, although patients randomized to initial revascularization will not receive routine anti-anginal therapy unless symptoms occur. The basic strategy is to manage according to symptoms, without attempting to achieve abolition of all objective evidence of ischemia, which would require frequent stress testing of asymptomatic patients. Overall, the major components of medical therapy will include, as required on a patient-to-patient basis, antianginal and anti-ischemic therapy, management of hypertension, anti-thrombotic therapy, lipid-lowering therapy, dietary therapy, smoking cessation, exercise, aspirin and other therapy/interventions as indicated.

VI. ORGANIZATIONAL STRUCTURE

A. Clinical Centers: Under the joint direction of a cardiologist and diabetologist, each clinical center will be responsible for the screening and recruitment of eligible patients, treatment assignment,

performance of revascularization for those patients so assigned, intensive diabetes treatment and concomitant medical care for ischemic symptoms and CAD risk factor intervention, and for the collection and timely submission of all clinical and laboratory data required by protocol.

B. Study Chair: Dr. Robert Frye will have ultimate responsibility for the successful conduct and integrity of BARI 2D. He will oversee all aspects of study operation and administration, chair the Steering and Operations Committees, and represent BARI 2D at Program Office and Safety and Data Monitoring Board (DSMB) meetings.

C. Coordinating Center (CC): The CC at the University of Pittsburgh has primary responsibility for the BARI 2D study design, data collection and management, and analysis of BARI 2D data.

D. Diabetes Management Center (DMC): (*Case Western Reserve University, Dr. Saul Genuth, PI)* In contrast to traditional study designs employed in interventional cardiology studies, the success of BARI 2D will depend on the continuous reinforcement of medical guidelines prescribed for each patient from study entry to study end. To ensure this degree of medical involvement at the individual patient level, the DMC, under the direction of Dr. Saul Genuth, will be responsible for overseeing protocol compliance by monitoring and assuring adherence to the glycemic control targets and medical treatment strategies previously specified.

E. Lipid Management Center (LMC): (*University of Pittsburgh, Dr. Trevor Orchard, PI)* Using methods similar to those described for the DMC, lipid values will be reviewed by Dr. Trevor Orchard on a frequent basis, and consultation given to clinical sites where lipid goals have not been achieved overall and for specific patients.

F. Hypertension Management Center (HMC): (*Lahey Clinic Medical Center, Dr. Richard Nesto, PI)* Blood pressure and hypertension treatment will be reviewed by Dr. Richard Nesto on a regular basis and consultation provided to sites where blood pressure goals have not been met.

G. Lifestyle Intervention Management Center (LIMC): *(Dr. Jeanine Albu and Dr. Sheldon H. Gottlieb, Co-Chairs):* Smoking cessation, nutrition, weight loss and exercise will be reviewed by Drs. Albu and Gottlieb on a regular basis, and consultation will be provided for clinical sites which are outliers above the study mean.

H. Core ECG Laboratory (CEL): *(St. Louis University, Dr. Bernard Chaitman, PI)* The CEL will uniformly interpret rest electrocardiograms using validated Novacode criteria, blinded to patient therapy.

I. Economics Core Laboratory: *(Stanford University, Dr. Mark Hlatky, PI)* This laboratory will collect and analyze data on medical care costs and employment. To ascertain economic data, patients will be contacted every 3 months by an interviewer at Stanford.

I. Fibrinolysis Core Laboratory: *(University of Vermont, Dr. Burton Sobel, PI)* A Fibrinolysis and Coagulation Core Laboratory will assess t-PA and PAI-1 antigens and activity, and insulin.

J. Biochemistry Laboratory: *(University of Minnesota, Dr. Michael Steffes, PI)* Blood samples will be sent from the clinical sites to Minnesota for analysis of HbA1c. In addition, frozen blood and urine samples from the Fibrinolysis and Coagulation Core laboratory will be sent for analysis of lipid values and A/C ratio. Cells from baseline HbA1c will be stored for future research.

K. Angiographic Core Laboratory: (*Stanford University, Dr. Edwin Alderman, PI*) Baseline and index post procedure angiograms for patients randomized to immediate revascularization will be interpreted by the Angiographic Core Laboratory for lesion and procedure information.

L. Nuclear Cardiology Core Laboratory: (*University of Alabama, Dr. Ami Iskandrian, PI*) This laboratory will interpret the nuclear studies submitted by the clinical sites.

M. Steering Committee: The primary governing body of the study will be the Steering Committee, which will consist of the Principal Investigators of each clinical site and each core lab; the Study Chair; the Principal Investigator and Co-Investigators of the Coordinating Center; the Principal Investigators of the Diabetes Management Center, the Lipid Management Center and the Hypertension Management Center; and an NIH representative. This group will meet twice during the start-up phase and then twice per year. The group will outline broad study goals, review protocol implementation and decide major issues.

N. Data and Safety Monitoring Board (DSMB) *(Dr. C. Noel Bairey-Merz, Chair)*: A DSMB will be appointed by the NHLBI to protect the scientific integrity of the trial. The Board will review interim trial results and advise NHLBI on all policy matters.

O. Mortality and Morbidity Classification Committee (MMCC) *(Dr. Thomas Ryan, Chari; Dr. Harold Lebovitz, Co-Chair)*: An MMCC has been established to classify cause of death and adjudicate whether a suspected stroke meets criteria to be classified as a stroke.

VII. STATISTICAL ANALYSIS

The two primary objectives of BARI 2D are to compare initial elective revascularization with aggressive medical therapy versus aggressive medical therapy alone, and to compare management of hyperglycemia with a strategy of insulin sensitization versus insulin providing. Although the hypotheses are worded in terms of one strategy being superior to another, two-sided confidence intervals will be reported. All treatment comparisons will be made according to treatment assigned (*i.e.*, the intention-to-treat principle) rather than treatment received, and the primary endpoint is all-cause mortality. The two main effect tests, one for each primary hypothesis, in this 2x2 factorial study will be performed separately with a two sided α-level=0.05. We assume an equal number of patients assigned to each treatment arm, 3 years of recruitment and an additional 4.5 years of follow-up. If 2350 patients are enrolled in the trial, the power to detect a 30% reduction in mortality will be 73% assuming an 11.9% overall mortality rate for the reference group. The power to detect a 30% reduction in the principal secondary enpoint of death, MI or stroke is 95% assuming an overall event rate of 21%. A Data and Safety Monitoring Board (DSMB) will meet every 6 months during the trial to review safety, efficacy, and adherence to protocol.

VIII. DATA MANAGEMENT AND COMPUTING

Data will be collected and entered remotely at the clinical centers utilizing MATRIX, software developed by the BARI 2D Coordinating Center. Database management and data entry systems will monitor accuracy, quality, and completeness of the data, and timeliness of both data collection and data entry. Data entry systems will not allow incomplete data to be transmitted to the CC. Records received by the CC will have passed a comprehensive set of entry point edit checks. Data appended to the central database will be subjected to more extensive intraform and interform editing and monitoring procedures on a routine basis. The CC will provide various monitoring reports such as recruitment, scheduling, and delinquency reports to the clinical coordinators on a regular basis.

The core of the BARI 2D information management system and communications will be the BARI 2D web site. This web site has been designed to ensure accurate and efficient distribution of all study communications. It is the central location for retrieving and disseminating all study information including operation memos, news bulletins, the study directory, and data integrity and compliance reports. A Help Desk system is accessible and managed through the web site along with a summary of frequently asked questions. The BARI 2D web site is divided into a public domain and a private domain. Anyone can access the Public domain and obtain information on the study. Only users with a Coordinating Center assigned password can access the Researchers private domain. The address for the BARI 2D web site is:

http://www.bari2d.org