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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

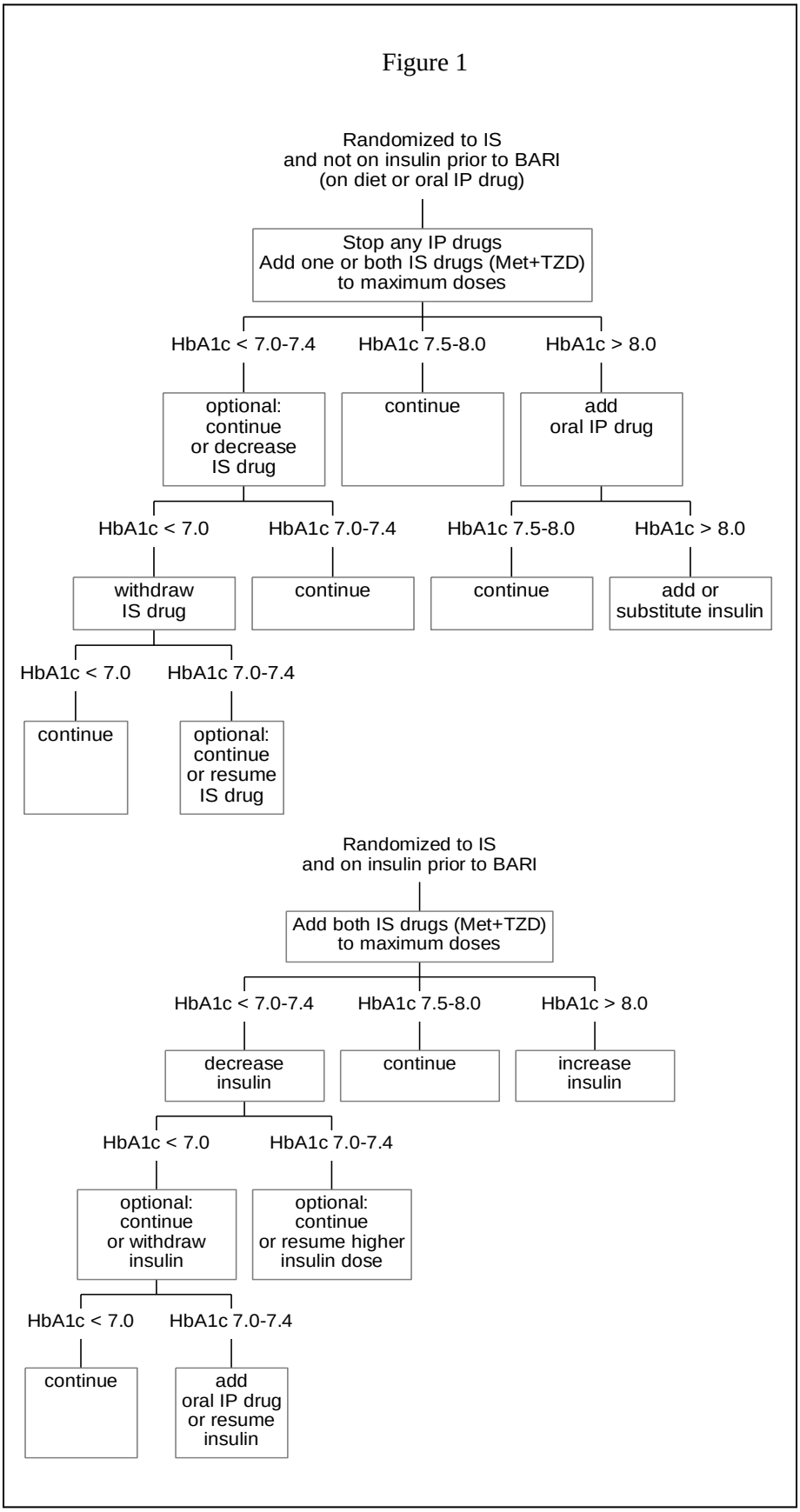
The choice of revascularization procedure will be determined by the responsible physicians, based upon full discussion with interventional cardiologists and cardiac surgeons as deemed appropriate for the individual patient. This choice will be made prior to randomization since randomization is stratified 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

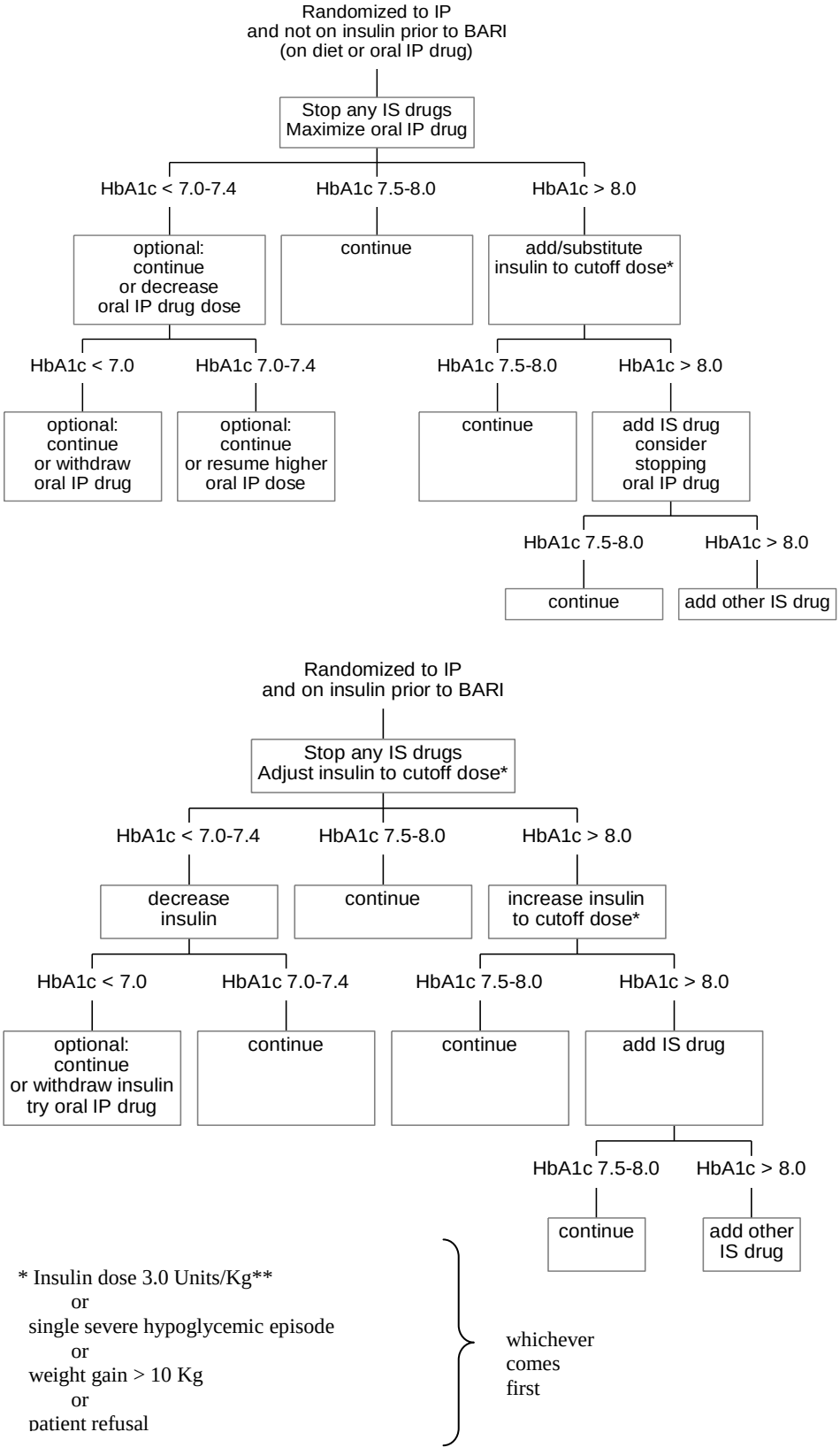


under a TZD regimen), then dosages should be increased and/or the next step in the pertinent algorithm (IS or IP) should be adopted. A comprehensive program of diabetes education will be provided. This will include nutritional counseling to promote weight loss in the obese patients, training in the use 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

CHAPTER TWO

STUDY ORGANIZATION

I. OPERATIONAL UNITS

A. Clinical Sites

Site Name	Site Location	
Alabama, University of (Pilot Site)	Birmingham	AL
Albert Einstein College of Medicine	Bronx	NY
Barnes Jewish Hospital	St.Louis	MO
Baylor College of Medicine	Houston	TX
Boston University	Boston	MA
British Columbia, University of	BC	CAN
Brown University/Rhode Island Hospital	Providence	RI
Chicago, University of	Chicago	IL
Cleveland, University Hospitals of (Pilot Site)	Cleveland	OH
Duke University	Durham	NC
Emory University Hospital	Atlanta	GA
Fletcher Allen Health Care (Pilot Site)	Colchester	VT
Florida, University of	Gainesville	FL
Greater Ft. Lauderdale Heart Group Research	Ft. Lauderdale	FL
Fuqua Heart Center/Piedmont Hospital	Atlanta	GA
Henry Ford Heart & Vascular Institute	Detroit	MI
Houston VA Medical Center	Houston	TX
Johns Hopkins University	Baltimore	MD
Kaiser Pemanente Medical Center	San Jose	CA
Lahey Clinic Medical Center (Pilot Site)	Burlington	MA
Maryland Hospital, University of	Baltimore	MD
Mayo Clinic-Rochester (Pilot Site)	Rochester	MN
Mayo Clinic-Scottsdale	Scottsdale	AZ
Mexican Institute of Social Security	Mexico City	MEXICO
Michigan, University of	Ann Arbor	MI
Mid America Heart Institute	Kansas City	MO
Minnesota, University of	Minneapolis	MN
Montreal Heart Institute (Pilot Site)	Montreal	CAN
Mt. Sinai Medical Center	New York	NY
Na Homolce Hospital	Prague	CZECH REPUBLIC
New York Hospital Queens	Queens	NY

New York Medical College	Valhalla	NY
New York University School of Medicine	New York	NY
Northwestern University	Chicago	IL
Ohio State University	Columbus	OH
Ottawa Heart Institute/Ottawa Hospital Civic Campus	Ottawa	CAN
Pittsburgh Medical Center/VA Hospital (Pilot Site)	Pittsburgh	PA
Quebec Heart Institute	Sainte-Foy	CAN
University of Sao Paulo Heart Institute	Sao Paulo	BRAZIL
St. Louis University	St. Louis	MO
St. Joseph's Hospital/Michigan Heart and Vascular Institute	Ann Arbor	MI
St. Luke's/Roosevelt	New York	NY
Tennessee, University of/Memphis VA Hospital	Memphis	TN
Texas Health Science @ San Antonio	San Antonio	TX
Texas, University of @ Houston	Houston	TX
The Toronto Hospital	Toronto	CAN
Virginia, University of	Charlottesville	VA
Washington Hospital Center	Washington	DC
Wilhelminen Hospital	Vienna	AUSTRIA

Role of the Clinical Site: 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.

Role of the Principal Investigator: The responsibilities of each cardiology and diabetology principal investigator include:

a. Ensuring their clinical site is compliant with all aspects of the study including Institutional Review Board requirements;

b. Collaborating with BARI 2D colleagues at their clinical site as well as outside colleagues to educate and generate support for the study;

c. Ensuring that the nurse coordinators have their support to carry out their responsibilities;

d. Reading all BARI 2D communications distributed by the Coordinating Center via e-mail, web site, fax or mail and responding as appropriate in a timely manner;

e. Conducting weekly meetings with BARI 2D staff at their clinical site to discuss recruitment, patient management according to the BARI 2D protocol and follow-up compliance;

f. Attending BARI 2D investigator meetings;

g. Communicating with the Coordinating Center regarding protocol issues or any general problems.

Role of the Clinical Coordinator: The clinic site coordinator is essential to the overall operational aspects of the trial. Together with the Principal Investigator, the coordinator will contribute to the success of participant enrollment, patient education and compliance with risk factor modification and site compliance with data and specimen collection. The coordinator is

responsible for working closely with each component of the trial at their clinical site. Each coordinator must be certified by the Coordinating Center on the BARI 2D protocol, BARI 2D standard clinical measurements and BARI 2D MATRIX.

B. Coordinating Center (CC): University of Pittsburgh, Pittsburgh, PA
Principal Investigator: Dr. Katherine Detre

Role: The Coordinating Center responsibilities include:

1. Scientific
   a. Design and implementation of study
   b. Protocol development
   c. Monitor protocol compliance
   d. Train Personnel
   e. Collaborate with core laboratories and management centers
   f. Prepare reports for all study components
2. Administrative
   a. Receive and distribute funds to support the study
   b. Oversee Institutional Review Board compliance
   c. Liaison for communications among all components of the study.

C. Management Centers

►**Diabetes Management Center (DMC):** Case Western Reserve University
Principal Investigator: Dr. Saul Genuth Cleveland, OH

Role: The DMC is responsible for overseeing protocol compliance by monitoring and assuring adherence to the glycemic control targets and medical treatment strategies.

►**Lipid Management Center (LMC):** University of Pittsburgh, Pittsburgh, PA
Principal Investigator: Dr. Trevor Orchard

Role: The LMC is responsible for overseeing protocol compliance by monitoring and assuring adherence to lipid control.

►**Hypertension Management Center (HMC)**: Lahey Clinic Medical Center
Principal Investigators: Dr. Richard Nesto Burlington, MA
Dr. Phyllis August New York, NY

Role: The HMC is responsible for overseeing protocol compliance by monitoring hypertension treatment and blood pressure goals.

►**Lifestyle Intervention Management Center (LIMC)**: St. Luke's Roosevelt Hosptial and Johns Hopkins University School of Medicine

Principal Investigators:	Dr. Jeanine Albu	New York, NY
	Dr. Sheldon Gottlieb	Baltimore, MD

Role: The LIMC is responsible for overseeing protocol compliance by monitoring smoking cessation, nutrition, weight loss and exercise goals.

D. Core Laboratories

►**Angiography Core:** Stanford University, Stanford, CA
Principal Investigator: Dr. Edwin Alderman

Role: The Angiography Core Laboratory will provide angiographic data that is objective, reproducible and consistent with the study goal.

►**Biochemistry Core**: University of Minnesota, Minneapolis, MN
Principal Investigator: Dr. Michael Steffes

Role: The Biochemistry Core Laboratory will analyze samples from the clinical sites for HbA1c, lipids and urine albumin/creatinine ratio. This lab will store cells from baseline HbA1c for future genetic research.

►**ECG Core:** St. Louis University Medical Center, St. Louis, MO
Principal Investigator: Dr. Bernard Chaitman

Role: The ECG Core Laboratory will classify myocardial infarction/ischemic events through analysis of resting test electrocardiographic data, cardiac enzyme findings and clinical documentation.

►**Economics Core:** Stanford University, Stanford, CA
Principal Investigator: Dr. Mark Hlatky

Role: The Economics Core Laboratory will collect and analyze data on medical care costs and employment.

►**Fibrinolysis and Coagulation Core:** University of Vermont, Burlington, VT
Principal Investigator: Dr. Burton Sobel

Role: The Fibrinolysis and Coagulation Core Laboratory will measure insulin, t-PA antigen, and PAI-1 antigen and activity.

►**Nuclear Cardiology Core:** University of Alabama, Birmingham, AL
Principal Investigator: Dr. Ami Iskandrian

Role: The Nuclear Cardiology Core Laboratory will detect extent and progression of coronary artery disease, assess left ventricular function, impact of therapy and the prevalence of silent myocardial infarction and ischemia.

II. ADMINISTRATIVE COMPONENTS

A. Study Chair: Mayo Clinic, Rochester, MN
Chair: Dr. Robert Frye

Role: The study chair has responsibility for the successful conduct and integrity of the study. He will oversee all aspects of study operation and administration and chair the Steering and Operations Committees.

B. NHLBI Program Office: National Institutes of Health, Bethesda, MD
Program Officer: Suzanne Goldberg

Role: The NHLBI Program Office will participate in the general organizational and scientific guidance of the study and will collaborate in the overall direction and monitoring of the trial.

C. Steering Committee
Membership: All operational and administrative components

Role: The Steering Committee is the primary governing body of the study.

D. Operations Committee
Membership:

Edwin Alderman, MD	Principal Investigator, Angiography Core Laboratory
Maria Mori Brooks, PhD	Co-Principal Investigator, Coordinating Center
Bernard Chaitman, MD	Principal Investigator, ECG Core Laboratory
Sharon Crow, BS	Project Coordinator, Coordinating Center
Patrice Desvigne-Nickens, MD	Program Associate, NIH/NHLBI
Katherine Detre, MD, DrPH	Principal Investigator, Coordinating Center
Abby Ershow, ScD	Nutrition Program Officer, NIH/NHLBI
Robert Frye, MD	Study Chair, Mayo Clinic
Saul Genuth, MD	Principal Investigator, Diabetes Management Center
Suzanne Goldberg, RN, MSN	Project Officer, NIH/NHLBI
David Gordon, MD	Secretary, BARI 2D DSMB
Regina Hardison, MS	Director of Data Management, Coordinating Center
Mark Hlatky, MD	Principal Investigator, Economics Core Laboratory
Tracey Hoke, MD	Deputy Project Officer, NIH/NHLBI

Ami Iskandrian, MD	Principal Investigator, Nuclear Core Laboratory
Teresa Jones, MD	Program Director for Diabetes Complications, NIH/NIDDK
David Kelley, MD	Diabetology Co-Principal Investigator, Pittsburgh Medical Center/VA Hospital
Sheryl Kelsey, PhD	Co-Investigator, Coordinating Center
Kenneth Kent, MD	Cardiology Principal Investigator,Washington Hospital Center
Charles Mullany, MD	BARI 2D Surgeon
Richard Nesto, MD	Principal Investigator, Hypertension Management Center
Trevor Orchard, MD	Principal Investigator, Lipid Management Center
Edward Sako, MD, PhD	BARI 2D Surgeon
Burton Sobel, MD	Principal Investigator, Fibrinolysis Core Laboratory
George Sopko, MD	Program Associate, NIH/NHLBI
Michael Steffes, MD	Principal Investigator, Biochemistry Core Laboratory

Role: The Operations Committee addresses scientific and administrative issues required for the day-to-day operation of the study. This Committee meets weekly by conference call to discuss concerns of any study component and to monitor study progress.

E. Ancillary Studies Committee

Co-Chairs: Dr. David Faxon, University of Chicago
Dr. Mark Molitch, Northwestern University

Role: This Committee is responsible for reviewing each ancillary study proposal, assigning a priority score and making a final recommendation to the Steering Committee, where all ancillary study proposals must be approved by a majority vote.

III. INDEPENDENT COMPONENTS

A. Data and Safety Monitoring Board (DSMB)

Chair: Dr. J. Ward Kennedy, VA Medical Center, Seattle, WA

Role: This NHLBI-appointed Board is responsible for protecting the scientific integrity of the trial. The DSMB will review interim trial results for patient safety and recommend continuation or termination and will advise the NHLBI on all policy matters.

B. Morbidity and Mortality Classification Committee (MMCC)

Role: This Committee is responsible for the classification of death and stroke among study participants.

C. BARI 2D Safety Officer

Michael Mock, MD

Role: The BARI 2D Safety Officer serves in an advisory capacity to the BARI 2D Coordinating Center. The safety officer reviews all Serious Adverse Event (SAE) forms submitted to the Coordinating Center from the clinical sites and makes a determination regarding whether or not the reported event was a) related to the intervention and b) unexpected. The safety officer also serves as a consultant to the Coordinating Center regarding patient safety issues.

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CHAPTER THREE

DATA COLLECTION OVERVIEW

SECTION ONE: **FORMS SUMMARY**

SECTION TWO: **CORE LAB MEASUREMENT/EVALUATION FOLLOW-UP SCHEDULE**

SECTION THREE: **DATA COLLECTION BY FOLLOW-UP VISIT**

SECTION FOUR: **DATA COLLECTION AND PATIENT MANAGEMENT BY CLINIC VISIT**

SECTION FIVE: **CONVERSION CHARTS**

SECTION SIX: **INSTRUCTIONS FOR ENTERING DATES**

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CHAPTER THREE : SECTION ONE FORMS SUMMARY

STUDY ENTRY

SCREENING LOG (SL)
Log all patients with a signed informed consent.

NOTIFICATION OF PATIENT CONSENT (NPC) FOR IND
Complete after patient has signed an informed consent for use of combined therapy of insulin and rosiglitazone.

NOTIFICATION OF GENETICS CONSENT (NGC)
Complete after patient has signed an informed consent to participate in the genetics component of the trial.

ANGIOGRAPHIC TREATMENT SUMMARY (ATS)
Complete prior to entry of randomization module.

CORONARY ARTERY BYPASS GRAFT STATUS (PB)
Complete as the angiogram is evaluated for entry into BARI 2D, if patient has had prior coronary artery bypass surgery.

RANDOMIZATION WORKSHEET (RW)
Complete as patient is evaluated for eligibility, at the time the intended revascularization is determined, and at the time of randomization.

ANGIOGRAPHIC ACQUISITION (AA)
Complete for angiograms at baseline with or without PCI or for assigned initial PCI.

BASELINE FORM-1 (BF-1): Questionnaire
BASELINE FORM-2 (BF-2): Cardiac History and Status
BASELINE FORM-3 (BF-3): Diabetes History and Status
BASELINE FORM-4 (BF-4): Physical Exam
Complete on date the patient is randomized.

NON-PHARMACOLOGIC INTERVENTION FORM (NP)
Complete at baseline.

CLINIC VISIT MONITORING FORM (CM)
Complete at one week diabetology clinic visit.

RESTING ECG LOG (RL)
Complete at baseline.

SAMPLE ID LOG: URINE, LIPIDS, INSULIN & FIBRINOLYTIC (BLV)
SAMPLE ID LOG: HbA1c AND GENETIC (BLM)
Complete for core lab samples at baseline.

PCI PROCEDURE (PP) OR SURGERY PROCEDURE (SP)
Complete for initial assigned revascularization

FOLLOW-UP: SCHEDULED

CLINIC VISIT MONITORING FORM (CM)
Complete at the scheduled clinic visit monthly for the first six months, then quarterly.

NON-PHARMACOLOGIC INTERVENTION FORM (NP)
Complete at one month, three months, six months then every six months.

SAMPLE ID LOG: URINE, LIPIDS, INSULIN & FIBRINOLYTIC (BLV)
SAMPLE ID LOG: HbA1c AND GENETIC (BLM)
Complete for core lab samples at one month, three months, six months, then every six months.

RESTING ECG LOG (RL)
Complete at three months, one year, then annually.

ANNUAL FOLLOW-UP FORM-1 (FD-1): Questionnaire
ANNUAL FOLLOW-UP FORM-2 (FD-2): Cardiac/Diabetes Status
Complete at annual follow-up visits.

NUCLEAR CARDIOLOGY ACQUISITION FORM (NCA)
Complete for protocol annual stress SPECT imaging studies.

ANNUAL BRIEF FOLLOW-UP (AFD)
Complete ONLY for patients who have rescinded consent for the study, but have agreed to a brief annual contact.

FOLLOW-UP: UNSCHEDULED

CLINIC VISIT MONITORING FORM (CM)
Complete for unscheduled visits.

NON-PHARMACOLOGIC INTERVENTION FORM (NP)
Complete for any unscheduled visits

RESTING ECG LOG (RL)
Complete for suspected MI, pre-revascularization, and post-revascularization.

NUCLEAR CARDIOLOGY ACQUISITION FORM (NCA)
Complete for any unscheduled stress SPECT imaging studies done for clinical reasons.

PCI PROCEDURE (PP) OR SURGERY PROCEDURE (SP)
Complete for any unscheduled revascularization.

SUSPECTED MI (MI)
SUSPECTED MI CHECKLIST (MIL)
Complete for a suspected MI event as defined by the protocol.

MORTALITY FORM (MD)
MORTALITY CHECKLIST (DC)
Complete when a patient dies.

SERIOUS ADVERSE EVENT FORM (SAE)
Complete as soon as knowledge of a serious adverse event occurs.

SEVERE HYPOGLYCEMIA (SH)
Complete within one week of learning about the occurrence of the episode of a severe hypoglycemia episode.

CEREBROVASCULAR ACCIDENT (CVA)
CERBROVASCULAR CHECKLIST (CVAC)
Complete when coordinator learns of the occurrence of a stroke.

ID INACTIVATION (II)
Complete at the time a BARI 2D ID is inactivated for any reason.

ID REACTIVATION (IR)
Complete at the time of the reactivation of a BARI 2D ID.

OUTSIDE OF PROTOCOL STANDARDS (OP)
Complete for events that do not conform to the protocol.

NOTIFICATION OF PATIENT CONSENT (NPC) FOR IND
Complete after patient has signed an informed consent for use of combined therapy of insulin and rosiglitazone.

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CHAPTER THREE : SECTION TWO

CORE LAB MEASUREMENT/EVALUATION FOLLOW-UP SCHEDULE

CEL (Core ECG Laboratory)	Dr. Chaitman
BCC (Biochemistry Core Laboratory)	Dr. Steffes
FCC (Fibrinolysis and Coagulation Core Laboratory)	Dr. Sobel
NCL (Nuclear Cardiology Laboratory)	Dr. Iskandrian
ACL (Angiography Core Laboratory)	Dr. Alderman

Baseline	1 month	3 month	6 months
CEL: Resting ECG BCC: H_bA_{1c} & Lipids Albumin & Creatinine Genetic sample FCC: PAI –1, t-PA & Insulin NMR Lipids ACL: Angiogram	BCC: H_bA_{1c} FCC: PAI –1, t-PA & Insulin	CEL: Resting ECG BCC: HbA1c FCC: PAI –1, t-PA & Insulin	BCC: H_bA_{1c} & Lipids FCC:PAI –1, t-PA & Insulin
1 Year	**18 months**	**2 Year**	**30 months**
CEL: Resting ECG NCL: Nuclear Card. Study BCC: H_bA_{1c} & Lipids Albumin & Creatinine FCC: PAI –1, t-PA & Insulin NMR Lipids	BCC: H_bA_{1c} FCC: PAI –1, t-PA & Insulin	CEL: Resting ECG BCC: $H_{gb}A_{1c}$ & Lipids Albumin & Creatinine FCC: PAI –1, t-PA & Insulin	BCC: H_bA_{1c} FCC:PAI –1, t-PA & Insulin

3 Year	42 months	4 Year	54 months	5 Year
CEL: Resting ECG NCL: Nuclear Card. Study BCC: H_bA_{1c} & Lipids Albumin & Creatinine FCC: PAI –1, t-PA & Insulin	BCC: H_bA_{1c} FCC: PAI –1, t-PA & Insulin	CEL: Resting ECG BCC: H_bA_{1c} & Lipids Albumin & Creatinine FCC: PAI –1, t-PA & Insulin	BCC: H_bA_{1c} FCC:PAI –1, t-PA & Insulin	CEL: Resting ECG NCL: Nuclear Card. Study BCC: H_bA_{1c} & Lipids Albumin & Creatinine FCC: PAI –1, t-PA & Insulin

66 months	6 Year
BCC: H_bA_{1c} FCC: PAI –1, t-PA & Insulin	CEL: Resting ECG BCC: H_bA_{1c} & Lipids Albumin & Creatinine FCC: PAI –1, t-PA & Insulin

Note : Ad Hoc CEL Resting ECG evaluation to be done for pre and post any revascularization and any suspected MI even

CHAPTER THREE : SECTION THREE

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	X	X		X			X		X		X	
NMR Lipids	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**

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CHAPTER THREE : SECTION FOUR

DATA COLLECTION AND PATIENT MANAGEMENT BY CLINIC VISIT

Clinic Visit [1]	Data Form(s) [2]	Local Lab [3]	Core Lab[4]	Additional Component of Clinic Visit/Comments
Baseline – randomization	SL, ATS, PB, AA, RW, BF-1, BF-2, BF-3, BF-4, NP, CM, BLV, BLM, RL	Pre-randomization (within 90 days) serum creatinine, HbA1c, ALT, fasting triglycerides Other baseline labs (within 90 days prior to randomization): potassium, fasting lipids,[5] CK, random urine albumin and creatinine (albumin/creatinine ratio)	CEL: Resting ECG (completed within 7 days prior to randomization) BCC: HbA1c, fasting lipid profile, random urine albumin and creatinine, FCC: PAI-1, t-PA, fasting insulin level; NMR Lipids[6] ACL: Angiogram (document location on ATS form – film will be sent to the Angiographic Core Lab at a later time) ECON: Patient Information Sheet, Release of Information	Forward a written description of the study protocol and treatment aims along with a request for a referral letter from the primary care physician. Obtain informed consent from the patient for screening and study entry. Evaluate patient PRIOR to randomization for suitability for PCI or CABG (complete ATS Form). If randomized to revascularization – the procedure of choice needs to be done within 4 weeks of the randomization date (see Revascularization protocol). Evaluate cardiac medications[7] and management of hypertension if necessary (see Cardiovascular Pharmacologic & Hypertension Management protocol). Target BP $\leq$ 130/80. Evaluate lipid management drug therapy if necessary (see Lipid Management protocol). Target LDL < 100 mg/dl, triglycerides < 200 mg/dl. A cardiac rehab consult should be obtained as soon as clinically feasible for the patient. When a cardiac rehab program is unavailable, an exercise program should be prescribed by the cardiologist (see Exercise protocol). If patient smokes and is willing to stop, refer to local smoking cessation program and follow Smoking protocol for further intervention.[7] Schedule dietary counseling. A Registered Dietitian consult is recommended.[9] Referral to an opthalmologist is recommended for a dilated fundus exam.

Clinic Visit [1]	Data Form(s) [2]	Local Lab [3]	Core Lab[4]	Additional Component of Clinic Visit/Comments
Baseline – one week diabetology visit	CM	Point of service HbA1c		Begin patient on IS or IP treatment medications. Target HbA1c < 7.0 %. Patient education session is required which should include as appropriate: signs and symptoms of hypoglycemia, hyperglycemia, injection instructions, monitoring of home glucose levels,[10] target glucose levels, Glucagon injections if taking insulin, diabetic foot care, monitoring of home weight, signs of impending MI with emphasis on early hospitalization, life style modifications, to include the importance of physical activity, smoking cessation, sodium reduction, weight reduction, modification of alcohol intake, and prophylactic use of sublingual nitroglycerin prior to anticipated triggers of angina or anginal equivalents. Reinforcement teaching will be performed at each clinic visit as needed.
1 month	CM, NP, BLV, BLM	Point of service HbA1c	BCC: HbA1c FCC: PAI-1, t-PA, fasting insulin level	Evaluate glycemic management and adjust medications as appropriate. Evaluate cardiac medications and management of hypertension if necessary. Evaluate lipid management drug therapy if necessary. Assess adherence to therapy and reinforce patient education as appropriate. If patient smokes and is willing to stop, refer to local smoking cessation program and follow smoking protocol for further intervention.[7]
2 month	CM	Point of service HbA1c		Evaluate glycemic management and adjust medications as appropriate. Evaluate cardiac medications and management of hypertension if necessary. Evaluate lipid management drug therapy if necessary. Assess adherence to therapy and reinforce patient education as appropriate.

Clinic Visit [1]	Data Form(s) [2]	Local Lab [3]	Core Lab[4]	Additional Component of Clinic Visit/Comments
3 month	CM, BLV, BLM, NP, RL	Point of service HbA1c, potassium, fasting lipid profile if patient had an MI within 3 months prior to randomization or if patient not at goals levels	CEL: Resting ECG BCC: HbA1c FCC: PAI-1, t-PA, fasting insulin level	Evaluate glycemic management and adjust medications as appropriate. Evaluate cardiac medications and management of hypertension if necessary. Evaluate lipid management drug therapy if necessary. Assess adherence to therapy and reinforce patient education as appropriate. Follow-up dietary counseling is required. A Registered Dietitian consult is recommended.
4 month	CM	Point of service HbA1c		Evaluate glycemic management and adjust medications as appropriate. Evaluate cardiac medications and management of hypertension if necessary. Evaluate lipid management drug therapy if necessary. Assess adherence to therapy and reinforce patient education as appropriate.
5 month	CM	Point of service HbA1c		Evaluate glycemic management and adjust medications as appropriate. Evaluate cardiac medications and management of hypertension if necessary. Evaluate lipid management drug therapy if necessary. Assess adherence to therapy and reinforce patient education as appropriate.

Clinic Visit [1]	Data Form(s) [2]	Local Lab [3]	Core Lab[4]	Additional Component of Clinic Visit/Comments
6 month	CM, NP, BLV, BLM	Point of service HbA1c, random plasma glucose to check calibration of patient's home glucose machine, potassium, fasting lipid profile if patient not at goals levels	BCC: HbA1c, fasting lipid profile FCC: PAI-1, t-PA, fasting insulin level	Evaluate patient's technique of using home glucose machine when checking machine calibration (see local lab). Evaluate glycemic management and adjust medications as appropriate. Evaluate cardiac medications and management of hypertension if necessary. Evaluate lipid management drug therapy if necessary. Assess adherence to therapy and reinforce patient education as appropriate. If patient smokes and is willing to stop, refer to local smoking cessation program and follow smoking protocol for further intervention.[7]
9 month	CM	Point of service HbA1c, potassium, fasting lipid profile if patient not at goals levels		Evaluate glycemic management and adjust medications as appropriate. Evaluate cardiac medications and management of hypertension if necessary. Evaluate lipid management drug therapy if necessary. Assess adherence to therapy and reinforce patient education as appropriate.
1 year 2 year 3 year 4 year 5 year 6 year Quarter 1	CM, FD-1, FD-2, NCA, NP, BLV, BLM, RL	Point of service HbA1c,random plasma glucose to check calibration of patient's home glucose machine, potassium, fasting lipid profile, random albumin and creatinine (albumin/creatinine ratio)	CEL: Resting ECG NCL: Nuclear cardiology study (required at years 1, 3 and 5) BCC: HbA1c, fasting lipid profile, random urine albumin and creatinine FCC: PAI-1, t-PA, fasting insulin level ; NMR Lipids at one year only	Evaluate patient's technique of using home glucose machine when checking machine calibration (see local lab). Evaluate glycemic management and adjust medications as appropriate. Evaluate cardiac medications and management of hypertension if necessary. Evaluate lipid management drug therapy if necessary. Assess adherence to therapy and reinforce patient education as appropriate. If patient smokes and is willing to stop, refer to local smoking cessation program and follow smoking protocol for further intervention.[7] Follow-up dietary counseling is required. A Registered Dietitian consult is recommended. Referral to an opthalmologist is recommended for a dilated fundus exam.

Clinic Visit [1]	Data Form(s) [2]	Local Lab [3]	Core Lab[4]	Additional Component of Clinic Visit/Comments
Quarter 2	CM	Point of service HbA1c, potassium, fasting lipid profile if patient not at goal levels		Evaluate glycemia management and adjust medications as appropriate. Evaluate cardiac medications and management of hypertension if necessary. Evaluate lipid management drug therapy if necessary. Assess adherence to therapy and reinforce patient education as appropriate.
Quarter 3	CM, BLV, BLM, NP	Point of service HbA1c, random plasma glucose to check calibration of patient's home glucose machine, potassium, fasting lipid profile if patient not at goal levels	BCC: HbA1c FCC: PAI-1, t-PA, fasting insulin level	Evaluate patient's technique of using home glucose machine when checking machine calibration (see local lab). Evaluate glycemic management and adjust medications as appropriate. Evaluate cardiac medications and management of hypertension if necessary. Evaluate lipid management drug therapy if necessary. Assess adherence to therapy and reinforce patient education as appropriate.
Quarter 4	CM	Point of service HbA1c, potassium, fasting lipid profile if patient not at goal levels		Evaluate glycemic management and adjust medications as appropriate. Evaluate cardiac medications and management of hypertension if necessary. Evaluate lipid management drug therapy if necessary. Assess adherence to therapy and reinforce patient education as appropriate.

[1] Each clinic visit is a diabetology visit. A cardiologist visit is required at baseline and at least every 6 months. The cardiologist must be on call and available for each diabetology visit. In addition, the BARI 2D team at each clinic site including the diabetologist, cardiologist and nurse coordinators should meet weekly to discuss BARI 2D patients.

[2] In addition to the information outlined in this table, the following forms must be completed as specified:
AFD must be completed only for patients who have rescinded consent for the study, but have agreed to a brief annual contact.
CM must be completed for unscheduled clinic visits
CVA must be completed if patient has a stroke
II must be completed when it is necessary to inactivate a BARI 2D ID.
IR must be completed when it is necessary to reactivate a BARI 2D ID.
MD & DC must be completed when a study participant dies.
MI & MIL must be completed for a suspected MI event as defined by the protocol.
NCA must be completed for each unscheduled stress SPECT imaging study done for clinical reasons
OP must be completed when there is an out of protocol event as defined by the Coordinating Center.
PB must be completed if patient had a bypass prior to study entry
PP must be completed for each PCI procedure.
RL must be completed for each pre-revascularization, post-revascularization, and for a suspected MI.
SAE must be completed when a patient experiences a serious adverse event
SH must becompleted if patient has a severe hypoglycemic episode
SP must be completed for each CABG surgery.

[3] ALT will be monitored every 2 months during the first year of TZD use and quarterly thereafter. TZD will not be given to patients with ALT > 2.5 times the upper limit of normal.

ALT will be monitored every 3 months for patients taking a fibrate OR HMG-CoA reductase inhibitor.

ALT and CK will be monitored every 3 months for patients taking a fibrate AND HMG-CoA reductase inhibitor.

Creatinine will be monitored every 6 months for patients taking metformin and prior to and following administration of radiographic dye. Metformin will not be given to men with a creatinine > 1.5 mg/dl, and women with a creatinine > 1.4mg/dl.

[4] For all fasting core labs, patient is required to be fasting for at least 8 hours.

[5] If patient has hyperlipidemia, review secondary cause and order TSH plus chemistries as appropriate.

[6] Patients who have no NMR measure at Baseline should not be measured at one year.

[7] Ensure patient is taking aspirin, clopidogrel, or coumadin (All patients will be on aspirin 325 mg per day unless contraindicated or not tolerated. Lower doses may be applied if not tolerated).

Ensure patient is taking an ACE inhibitor, unless a contraindication exist. In which case a calcium channel blocker should be used to offer renoprotection or an angiotensin II inhibitor can be used.

Ensure patient is taking a beta-blocker, unless a contraindication exist. Cardioselective beta-blockers are recommended. Target HR <60.

[8] Once patient begins a smoking cessation plan, he/she must have a telephone call within 1 week to evaluate progress and monthly assessment thereafter.

[9] The following will prompt reinforcement of nutrition guidelines and may indicate further need for dietary consult: gain of 5% of original body weight, HbA1c is not <7.0% after maximum pharmacologic treatment - for 2 months in the IS arm and 1 month in the IP arm, worsened glycemic, lipid or blood pressure control since the previous measurement (see Nutrition protocol for specific guidelines).

[10] IS patients will be asked to do self-blood glucose monitoring before breakfast at least 3 days per week. IP patients will be asked to test blood glucose more frequently as needed in order to guide insulin therapy. Patients on multiple injections of insulin will be asked to monitor blood glucose 4 times daily. All values will be recorded. The initial target fasting glucose will be 80-120 mg/dl.

CHAPTER THREE : SECTION FIVE CONVERSION CHARTS

Years to Months Conversion Chart

YEAR	MONTHS	YEAR	MONTHS
1	12	26	312
2	24	27	324
3	36	28	336
4	48	29	348
5	60	30	360
6	72	31	372
7	84	32	384
8	96	33	396
9	108	34	408
10	120	35	420
11	132	36	432
12	144	37	444
13	156	38	456
14	168	39	468
15	180	40	480
16	192	41	492
17	204	42	504
18	216	43	516
19	228	44	528
20	240	45	540
21	252	46	552
22	264	47	564
23	276	48	576
24	288	49	588
25	300	50	600

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CHAPTER THREE : SECTION SIX INSTRUCTIONS FOR ENTERING DATES

I. INSTRUCTIONS FOR ENTERING DATES

A. DATES THAT ARE KEY FIELDS

These dates should be entered as one field with a format of mm/dd/yyyy.
Example: Patient received initial BARI 2D PCI procedure on May 10, 2000. The date would be entered as 5/10/2000.

Record date	mm/ dd/yyy
	5/10/2000

B. DATES THAT ARE NOT KEY FIELDS

1. Partially Known Date

If one or more of the date fields (i.e. month, day, or year) is unknown, enter the value -3 to indicate the specific date field that is unknown. Enter all available information.
Example: If a participant had a severe hypoglycemia episode in May, 2000, but does not remember the exact day, the date would be entered as:

month (mm) = 5
day (dd) = -3
year (yyyy) = 2000

Record date	5	-3	2000
	mm	dd	yyyy

2. Unknown Date

If the entire date field is unknown (month, day and year), enter the value -3 for each date field.
Example: If a participant had a severe hypoglycemia episode but does not remember when, the date would be entered as:

month (mm) = -3
date (dd) = -3
year (yyyy) = -3

Record date	-3	-3	-3
	mm	dd	yyyy

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CHAPTER FOUR

PHARMACOLOGIC THERAPY MANUAL

PREPARED BY:

Martin Rutter, MB
Gail Woodhead, RN
Richard Nesto, MD
Craig Donahue, RPh

Lahey Clinic Medical Center

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BARI-2D medication

GENERIC	TRADE	INDICATIONS	CAUTIONS / SIDE EFFECTS	COMMENTS
ACE Inhibitors **Quinapril** **Ramipril** Captopril Enalapril Fosinopril Lisinopril	 Accupril Altace Capoten Vasotec Monopril Zestril	Hypertension (first line especially if renal disease) Heart failure Diabetic renal disease (microalbuminuria, proteinuria and renal impairment), (captopril)	Absolute contraindications: serum creatinine > 2.0 mg/dl in BARI-2D, pregnancy, bilateral renal artery stenosis (RAS), well documented previous intolerance (e.g. cough or angioedema) Caution initiating if renal impairment or severe left ventricular dysfunction associated with systolic BP < 100 mm Hg. Incidence of RAS increases with age, presence of vascular disease (especially peripheral vascular disease) and renal impairment Side effects: dry cough (15 %), hyperkalemia (especially in the presence of diabetes and renal failure, renal tubular acidosis, bilateral RAS or beta blocker therapy), postural hypotension (especially if diuretic therapy or autonomic neuropathy), headache, nausea, rash, and rarely renal failure and angioedema	All patients in BARI-2D will be started on an ACE inhibitor unless contraindicated. AT- II blockers are not to be used as a replacement for ACE inhibitors in this situation. Initiate at low dose and increase monitoring for side effects and evidence of postural hypotension (e.g. Quinapril 10 mg qd increasing to a dose of 20-40 mg daily). Check blood for increasing potassium, BUN and creatinine 4 weeks after initiation or alteration of therapy (rising parameters may indicate renal artery stenosis) Caution in women of child bearing potential Drug interactions: hyperkalemia with potassium sparing diuretics. Avoid use with NSAID. Lithium levels increase 3-4 x with ACE inhibitors ACE inhibitors have been shown to reduce insulin resistance and may reduce the risk of new onset diabetes by as much as one third

BARI-2D medication

GENERIC	TRADE	INDICATIONS	CAUTIONS / SIDE EFFECTS	COMMENTS
Angiotensin II blockers **Losartan** **Candesartan** Irbesartan	 Cozaar Hyzaar Atacand Avapro	As above for ACE inhibitors	Similar to ACE inhibitors except for absence of cough Do not use in combination with ACE inhibitors	Comments for ACE inhibitors apply Use for patients who are intolerant to ACE inhibitors due to cough. Little evidence of other benefits over ACE inhibitors
Beta blockers Cardioselective **1. Metoprolol** **2. Atenolol** **3. Bisoprolol** **4. Betaxolol** Non-cardioselective **5. Carvedilol** (also α1blocker)	 Lopressor Tenormin Ziac Kerlone Coreg	 Angina (1, 2) Hypertension (2, 3, 4, 5) Class II and III heart failure (5)	Contra-indications: asthma, severe symptomatic peripheral vascular disease, AV block, bradycardia (< 50 bpm) Caution: elderly, renal and hepatic dysfunction (exclusion criteria in BARI-2D is creatinine > 2.0 mg/dl). Avoid initiation within one month of an episode of congestive heart failure. Never suddenly stop treatment; always taper to zero over weeks in order to minimize rebound angina Side effects: postural hypotension, worsening heart failure, tiredness, erectile dysfunction, cold extremities, bradycardia and AV conduction delays. In high doses, may mask symptoms of hypoglycemia in patients with Type 2 diabetes Cardioselective beta-blockers are preferred as these tend not to elevate glucose or retard the recovery from hypoglycemia (except carvedilol)	Usually initiate in stable patients and at low dose e.g. atenolol 50 mg once daily (see dosage guidelines algorithm). Consider giving first dose on a full stomach and separating other hypotensive agents. Increase dose slowly monitoring for side effects and hemodynamic instability. See BARI-2D dosage guideline algorithm In heart failure 40% patients feel worse before feeling better; support may be required Some studies in patients with diabetes have shown that beta-blockers have a small detrimental effect on blood glucose control. They have been shown to increase insulin resistance, lipid levels and increase the risk of new onset diabetes by approximately 25 %. However potential negative metabolic effects should not deter initiation of therapy Carvedilol may emerge as the preferred beta

			Beta blockers with intrinsic sympathomimetic activity (acebutolol, carteolol, penbutolol and pindolol) should be avoided in patients with diabetes	blocker as it has been shown to reduce insulin resistance and has no significant effect on lipids

BARI-2D medication

GENERIC	TRADE	INDICATIONS	CAUTIONS / SIDE EFFECTS	COMMENTS
Calcium channel blockers **Dihydropyridine (DHP)** **Amlodipine** **Felodipine** Nisoldipine Nicardipine Nifedipine GITS **Non-dihydropyridine** Diltiazem Verapamil	 Norvasc Plendil Sular Cardene Adalat CC Procardia XL Cardizem (SR,CD) Calan (SR)		Caution: impaired hepatic function. Patients starting short acting DHP should be started on a beta blocker prior to initiation Side effects: ankle edema (common, 10 %), bradycardia with non-dihydropyridine drugs especially if concomitant beta-blocker, postural hypotension especially with short acting DHP drugs if autonomic dysfunction or other antihypertensive medication. Flushing, headache, constipation, AV conduction disturbances occur with some agents, tachycardia with some agents	Amlodipine and felodipine are the preferred CCB's. Amlodipine is preferred in patients with heart failure and ejection fraction < 30 %. In this situation it may take several weeks for maximal clinical effect Monitor for worsening ankle edema (can easily be misinterpreted for worsening heart failure). Avoid abrupt stopping of treatment; better to taper to zero over 1-2 weeks Most studies have shown that calcium channel blockers have no adverse effects on lipids, glucose levels or insulin sensitivity and do not increase the incidence of diabetes in patients with hypertension

BARI-2D medication

GENERIC	TRADE	INDICATIONS	CAUTIONS / SIDE EFFECTS	COMMENTS
Loop diuretics **Furosemide**	Lasix	Heart failure Resistant hypertension especially if renal impairment Often used in conjunction with ACE inhibitor	Side effects: dehydration, hypotension, renal impairment, hypo and hyperkalemia, hypo and hypernatremia, low magnesium, tiredness, muscle cramps, erectile dysfunction, hyperuricemia and gout, rash, incontinence, impaired hearing in high doses and social inconvenience Usually have no significant effect on blood glucose control	Advise patients about potential side effects and the timing of medication Consider potassium supplement if not on potassium sparing diuretic or ACE inhibitor
Thiazide and related diuretics 1 **Hydrochlorothiazide** **Chlorthalidone** **Indapamide**	Hydrodiuril or Esidrex Thalitone Lozol	Hypertension (generally more effective than loop diuretics) Heart failure	Avoid in pregnancy, anuria, hypersensitivity to sulfonamides Side effects as above except diuretic effect is usually much less. Low dose thiazides (e.g. hydrochlorothiazide 6.25 mg or 12.5 mg) do not cause significant metabolic side effects or increase the risk of developing diabetes	Usually used in low doses e.g. 12.5 or 25 mg hydrochlorothiazide As for loop diuretics Potential negative metabolic effects should not deter initiation of therapy at low dose
Thiazide diuretic 2 Metolazone	Zaroxolyn	Hypertension Severe heart failure	Can cause extreme diuresis leading to renal failure and electrolyte disturbance when used with a loop diuretic	Usually only used under close medical supervision (as in-patient) with frequent monitoring of electrolytes and renal function

BARI-2D medication

GENERIC	TRADE	INDICATIONS	CAUTIONS / SIDE EFFECTS	COMMENTS
K- sparing diuretics Spironolactone Triamterene Amiloride	Aldactone Dyrenium Midamor	Edema associated with heart failure, liver disease, nephrotic syndrome Hypertension Primary hyperaldosteron-ism	Contraindications: anuria, acute renal failure, hyperkalemia, severe hepatic failure and lithium therapy Caution: care to be taken if used in patients with renal impairment or on ACE inhibitor (potential hyperkalemia) Side effects: hyperkalemia especially when used with ACE inhibitors or Angiotensin II blockers, dehydration and renal impairment, headache, drowsiness, erectile dysfunction, hyponatremia, rash, gynecomastia and agranulocytosis	Advise patients about the timing of medication Monitor renal function, electrolytes and for side effects Some patients with reduced ejection fraction may be taking spironolactone 25 mg QD. This does not usually cause problems with hyperkalemia Potassium sparing effect useful when used with loop diuretics
Alpha blockers Doxazosin Prazosin Terazosin	Cardura Minipress Hytrin	Hypertension Benign prostatic hypertrophy (doxazosin)	Caution in patients with heart failure (ALLHAT), renal or liver dysfunction Side effects: postural hypotension (especially on initiation), syncope, headache, tiredness, ankle swelling nausea and shortness of breath, priapism (rare)	Initiate at low dose (e.g. doxazosin 1 mg once daily) and increase slowly monitoring for symptoms and evidence of postural hypotension. Advise patients to observe for other potential side effects Many patients take doxazosin in low doses for BPH Some studies have shown that Doxazosin reduces insulin resistance

BARI-2D medication

GENERIC	TRADE	INDICATIONS	CAUTIONS / SIDE EFFECTS	COMMENTS
Alpha blockers Doxazosin Prazosin Terazosin	Cardura Minipress Hytrin	Hypertension Benign prostatic hypertrophy (doxazosin)	Caution in patients with heart failure (ALLHAT), renal or liver dysfunction Side effects: postural hypotension (especially on initiation), syncope, headache, tiredness, ankle swelling nausea and shortness of breath, priapism (rare)	Initiate at low dose (e.g. doxazosin 1 mg once daily) and increase slowly monitoring for symptoms and evidence of postural hypotension. Advise patients to observe for other potential side effects Many patients take doxazosin in low doses for BPH Some studies have shown that Doxazosin reduces insulin resistance
Centrally acting Clonidine	Catapres	Hypertension	Caution in recent myocardial infarction, severe coronary insufficiency, cerebrovascular disease, renal and heart failure Side effects: tiredness, symptoms of postural hypotension, dry mouth, constipation, erectile dysfunction, loss of libido	Initiate at low dose (e.g. clonidine 0.1 mg bid) and increase slowly monitoring for symptoms and evidence of postural hypotension. Advise patients to observe for other potential side effects. Medication should not be stopped abruptly. Discontinue concomitant beta blocker therapy
Vasodilators **Minoxidil**	Loniten	Hypertension	Contraindications: pheochromocytoma and lactation Caution in use after acute myocardial infarction and in renal failure Side effects: elongation, thickening and pigmentation of hair, salt and water	Concomitant use of diuretic and treatment to prevent tachycardia are required. Administer only under close supervision Fluid and electrolytes should be monitored on therapy. Observe patient

			retention, pericarditis, pericardial effusion, rash, abnormal liver, renal and hematological tests	for features of pericardial effusion.

BARI-2D medication

GENERIC	TRADE	INDICATIONS	CAUTIONS / SIDE EFFECTS	COMMENTS
Cardiac glycosides Digoxin	Lanoxin	Atrial fibrillation Heart failure especially if complicated by atrial fibrillation	Cautions: renal failure, hypokalemia Drug interactions are very important and include amiodarone (increases digoxin levels by 40-50 %), diuretics, verapamil, beta blockers, calcium channel blockers and some antibiotics Side effects (digoxin toxicity): nausea, anorexia, tiredness, conduction abnormalities, ventricular and atrial arrhythmias, yellow color vision	Small therapeutic window especially if renal impairment. If toxicity suspected check levels 6-8 hours post dose Digoxin immune Fab has been shown to reduce the length of hospital stay and is cost effective in the treatment of severe, symptomatic digoxin toxicity
Nitrates Isosorbide mononitrate Isosorbide dinitrate	Imdur Isordil or Dilatrate-SR	Angina Heart failure	Caution if volume depleted from diuretics or if systolic BP < 90 mm Hg. Side effects: headache and postural hypotension, (especially if autonomic dysfunction and/or dihydropyridine calcium channel blockers) Note: nitrate tolerance (reduced clinical effect) Drug interactions: severe hypotension may occur if used with sildenafil (Viagra)	Monitor for nitrate tolerance and try to ensure nitrate free period in the least symptomatic period of the day. Be aware of half life of different formulations and consider changing to alternative drug If headache occurs then this usually subsides after the first 1-2 weeks of therapy

BARI-2D MEDICATION

GENERIC	TRADE	INDICATIONS	CAUTIONS / SIDE EFFECTS	COMMENTS
Anticoagulation Warfarin	Coumadin	Atrial fibrillation Venous and arterial thrombosis or embolic disease Severe heart failure	Contra-indications: bleeding tendency, severe liver disease, active peptic ulcer disease, pregnancy, severe hypertension, lack of co-operation, lack of monitoring facilities, and alcohol abuse Side effects: bleeding, alopecia, urticaria, dermatitis, diarrhea, rash (rare) Extreme caution: use with aspirin only in situations where the risk of thrombosis clearly outweighs the risk of bleeding Multiple drug interactions exist. The following drugs increase warfarin effect: some statins, NSAID, amiodarone, cimetidine, and some antibiotics including metronidazole. The following decrease warfarin effect: steroids, carbamazepine. Alcohol may increase or decrease INR	Ensure patient is well educated regarding the detailed use of medication Monitor INR more frequently if patient is unwell or changes medication with potential drug interactions Advise patient to avoid alcohol and carry ID with the name of the drug
Amiodarone	Cordarone	Life threatening ventricular arrhythmias (class III antiarrhythmic drug)	Contra-indications: pregnancy, severe liver disease, severe sinus node dysfunction This is an effective but often toxic drug Side effects: photosensitive and other skin rashes and disorders, hyper and hypothyroidism, liver dysfunction, pulmonary fibrosis, reversible corneal opacities, peripheral neuropathy, cough, GI side effects Drug interactions: numerous including digoxin (reduce the dose by 50 % or stop), warfarin (reduce the dose by 30-50 % and monitor INR), beta blockers and phenytoin	Ensure patient is well educated regarding potential side effects Check thyroid and liver function before and 3-6 monthly while on therapy Corneal microdeposits occur in most patients and patients should have regular eye appointments.

BARI-2D medication

GENERIC	TRADE	INDICATIONS	CAUTIONS / SIDE EFFECTS	COMMENTS
Fibric acid derivatives Fenofibrate Gemfibrozil Clofibrate Bezafibrate (Canada only)	Tricor Lopid Atromid-S	Hypertriglyceridemia Mixed hyperlipidemia	Contraindicated in severe renal and liver disease, pregnancy, gall bladder disease Side effects: generally well tolerated but occasionally fatigue, headache, flu syndrome, rash, body pain, nausea, constipation, and rash. Rarely myositis (may present with aching muscles). Clofibrate can cause gall stones	Emphasize the importance of compliance In BARI-2D, ALT should be checked 6 monthly (3 monthly with CPK if also on statin) Fibrates reduce triglycerides, and may have a modest effect on LDL cholesterol and increase HDL cholesterol
HMG-CoA reductase inhibitors (statins) Simvastatin Pravastatin Atorvastatin Lovastatin Fluvastatin	Zocor Pravachol Lipitor Mevacor Lescol	Hypercholesterolemia Mixed hyperlipidemia	Contraindicated in severe liver disease, pregnancy and breast feeding mothers Caution in patients with elevated transaminases Side effects: generally well tolerated but occasionally nausea, headache, constipation, rash and erectile dysfunction. Rarely myositis (may present with muscle aches) and liver dysfunction Potential drug interactions between warfarin and most statins	Emphasis the importance of compliance ALT should be checked 6 monthly (3 monthly with CPK if also on fibrate) Medication is usually taken at bed time (except atorvastatin)

BARI-2D medication

GENERIC	TRADE	INDICATIONS	CAUTIONS / SIDE EFFECTS	COMMENTS
Omega 3 fatty acids Fish Oil		Hypertriglyceridemia	Side effects: generally well tolerated	Advise patients to take medication with meals
Bile acid resins	Colestid Questran WelChol LoCholest	Hypercholesterolemia	Contraindicated in biliary obstruction Caution in women of child bearing potential Drug interactions: may reduce or delay the absorption of some oral medications such as warfarin, propranolol, chlorothiazide, tetracycline, furosemide, penicillin, digoxin, fat soluble vitamins and gemfibrozil. Side effects: constipation, fecal impaction, abdominal discomfort, heartburn, flatulence, nausea, vomiting, diarrhea, osteoporosis, increased bleeding	Always mix with water or other foods Advise patients to take other medication > 1 hour before or 4 hours after medication May be used alone or in combination with a statin
Ezetimibe	Zetia	Hypercholesterolemia Homozygous familial hypercholesterolemia Homozygous sitosterolemia	Precautions: Use with caution in patients with moderate to severe hepatic dysfunction. Side effects: Generally well tolerated. May cause or exacerbate diarrhea. Drug interactions: Bile acid resins	Ezetimibe reduces total cholesterol, LDL-C. Apo-B, and triglycerides by inhibiting the intestinal absorption of cholesterol. Ezetimibe may also slightly raise HDL-C. Maximal effects on blood lipids are seen after 2 weeks of therapy.

			decrease absorption of ezetimibe. Administer ezetimibe ≥ 2 hours before or ≥ 4 hours after bile acid sequestrants.	Ezetimibe may be given concurrently with HMG-CoA reductase inhibitors (statins) with at least additive effects on blood lipids expected.

BARI-2D medication

GENERIC	TRADE	INDICATIONS	CAUTIONS / SIDE EFFECTS	COMMENTS
Niacin	Niaspan Slo-Niacin Generic versions	All types of dyslipidemia including elevated Lp(a)	Contraindicated in significant liver disease, active peptic ulceration and arterial bleeding May worsen blood glucose control in diabetes, IGT and IFG and therefore frequent blood monitoring is indicated at initiation or when dose increased Caution in unstable angina, acute myocardial infarction and renal dysfunction. Caution with concomitant anticoagulation Drug interactions: Statins and vasoactive drugs. Bile acid sequestrants have niacin binding capacity Side effects: flushing, dizziness, tachycardia, palpitations, shortness of breath, sweating, chills, edema, pain, GI upset and rash	Patients should take at bedtime after a low fat snack (Niaspan) or with meals with other preparations. Niaspan dose initially 500 mg per day increasing each week if necessary. Plain Niacin starting dose is 100 mg per day May give false elevation in some fluorometric determinations of plasma or urinary catecholamines and give false positive reactions with cupric sulphate in urine glucose tests Aspirin or NSAID taken 30 minutes before may prevent flushing Monitor serum transaminases before initiation and monitor 6 monthly for 1 year. Monitor for muscle pain, tenderness or weakness in patients taking statin

BARI-2D medication

GENERIC	TRADE	INDICATIONS	CAUTIONS / SIDE EFFECTS	COMMENTS
Platelet inhibitors **Aspirin**	Aspirin Regimen Bayer	Secondary and primary prevention of cardiovascular events	Contraindicated in active bleeding, intracranial hemorrhage, active peptic ulcer disease, genuine allergy and moderate-severe asthma Caution: history of peptic ulceration, uncontrolled hypertension, mild asthma, anemia, liver disease, pregnancy Side effects: peptic ulceration and bleeding Extreme caution: use with warfarin only in situations where the risk of thrombosis clearly outweighs the risk of bleeding	Advise patients to inform medical staff if symptoms of abdominal pain, indigestion, heartburn or bleeding Aspirin should be taken with food Usual dose in coronary artery disease is 325 mg daily
Platelet inhibitors Dipyridamole	Persantine	Reduction in the risk of stroke after TIA or thrombotic stroke	Contraindicated in pregnancy Caution in hypotension Side effects: dizziness, abdominal symptoms, headache, rash and rarely liver dysfunction	Dipyridamole may also be used as an adjunct to coumarin anticoagulants after cardiac valve replacement

BARI-2D medication

GENERIC	TRADE	INDICATIONS	CAUTIONS / SIDE EFFECTS	COMMENTS
Platelet inhibitors **Clopidogrel**	Plavix	Secondary prevention of cardiovascular events Prevention of stent related thrombosis	Contraindicated in active bleeding, intracranial hemorrhage, active peptic ulcer disease, genuine allergy and moderate-severe asthma Caution: history of peptic ulceration, hepatic impairment and in patients at increased risk of bleeding Side effects: chest pain, flu symptoms, dyspepsia, gastrointestinal bleeding and depression Extreme caution: use with warfarin only in situations where the risk of thrombosis clearly outweighs the risk of bleeding	Advise patients to inform medical staff if symptoms of abdominal pain, indigestion, heartburn or bleeding Clopidogrel is usually given for 30 days following stent placement

BARI-2D MEDICATION				
GENERIC	**TRADE**	**INDICATIONS**	**CAUTIONS / SIDE EFFECTS**	**COMMENTS**
INSULIN SENSITIZING MEDICATION (1 OF 2)				
Biguanides **Metformin**	Glucophage Avandamet	Diabetes especially if overweight	Contraindicated in pregnancy, acute or chronic metabolic acidosis, liver and renal and disease. Not to be started in BARI-2D if creatinine > 1.5 mg/dl Caution in moderate/severe heart failure, chronic lung disease and alcohol abuse. Reduce the dose in the elderly and avoid in those > 80 years of age Must be stopped at least 2 days prior to and after the administration of radiographic dye. Note patients coming for angiography, angioplasty and cardiac surgery Side effects: common if drug initiated too quickly. Diarrhea, nausea, vomiting, flatulence, reduced B12 levels and metallic taste. Risk of symptoms of hypoglycemia is very low. The risk of lactic acidosis is very low if the drug is avoided in high risk groups and if the drug is stopped in the situations described Drug interactions include nifedipine and furosemide	Avoid in women of childbearing potential Initiate the drug at low dose once daily and increase slowly to maximum tolerated or maximum dose. Advise patients of potential side effects and to reduce the dose temporarily until symptoms settle Advise the patient to stop the drug if any severe illness, fever, trauma, infection, surgery and prior to administration of radiographic dye Medical staff should stop the drug if cardiovascular collapse, acute heart failure, myocardial infarction, ketoacidosis or lactic acidosis Should be taken with food. Avoid XS alcohol Monitor creatinine at least 6 monthly in BARI-2D Avandamet is a fixed combination of rosiglitazone & metformin

BARI-2D medication

INSULIN SENSITIZING MEDICATION (2 OF 2)

GENERIC	TRADE	INDICATIONS	CAUTIONS / SIDE EFFECTS	COMMENTS
Thiazolidinedione **Rosiglitazone** Pioglitazone	Avandia Actos Avandamet	Type 2 diabetes and insulin resistance	Contra-indicated in liver disease (in BARI-2D these drugs should not be initiated if ALT > 2.5x ULN), pregnancy Maximum effect may take 4-8 weeks. About 25 % of patients will respond to the drug (C-peptide may be useful) Side effects: liver toxicity has occurred with other drugs in this class. Mild elevation of LDL-cholesterol (although LDL size is increased) and fluid retention (edema), upper respiratory infection, anemia and weight gain. Hypoglycemia is only a risk when combined with insulin or a sulfonylurea Caution: edema, macular edema, heart failure (NYHA class 3 and 4), may induce ovulation in previously infertile women with polycystic ovary syndrome Drug interactions: oral contraceptive pill	Avoid increasing dose for 4-6 weeks after starting the drug or altering the dose BID dosing seems to be better than QD dosing In BARI-2D liver function tests to be performed 2 monthly during the first year and then 3 monthly thereafter. Stop if ALT > x3 ULN Observe for features of heart failure Contraception may be required in anovulatory premenopausal women Avandamet is a fixed combination of rosiglitazone & metformin

BARI-2D MEDICATION

GENERIC	TRADE	INDICATIONS	CAUTIONS / SIDE EFFECTS	COMMENTS
Sulfonylureas Glipizide Glimepiride Glyburide	Glucotrol Amaryl Diabeta	Type 2 Diabetes	Contra-indicated in diabetic ketoacidosis and pregnancy Caution: renal failure Side effects: generally well tolerated but weight gain is common. Hypoglycemia is a potential risk especially if the patient misses meals and is active. Risk of hypoglycemia is also increased if renal or hepatic insufficiency, elderly, debilitated, malnourished, adrenal or pituitary insufficiency. Rarely GI upset, allergy and blood disorders occur Drug interactions: Increase hypoglycemic action: NSAID, aspirin, alcohol, beta-blockers. Decrease hypoglycemic action: steroids, diuretics, thyroxine, estrogens	Should be taken 20-30 minutes before a meal Generally little benefit observed beyond doses half of "maximal" Regular self monitoring of blood glucose will help to educate the patients about hypoglycemia. Patients and ideally relatives should be educated about the symptoms and treatment of hypoglycemia
Meglitinides Repaglinide	Prandin	Type 2 Diabetes	Contra-indicated in diabetic ketoacidosis and pregnancy The drug is more rapidly absorbed and has a shorter half life than the sulfonylureas Side effects: can cause weight gain and hypoglycemia like the sulfonylurea drugs (see above) Drug interactions: Erythromycin and other inducers of cytochrome P 450 3A4. NSAIDs, aspirin, coumarin and beta-blockers increase hypoglycemic action. Decreased hypoglycemic action may be seen with steroids, diuretics, calcium channel blockers, thyroxine and estrogens	Should be taken 0-30 minutes before meals In previously untreated patients with HbA1c < 8.0 % start with 0.5 mg before each meal. In previously treated patients with HbA1c > 8.0 % start with 1 or 2 mg before each meal Dose changes should be made cautiously in those with renal and hepatic disease Self monitoring and education as with sulfonylureas.

BARI-2D MEDICATION

INSULIN PROVIDING MEDICATION

GENERIC	TRADE	INDICATIONS	CAUTIONS / SIDE EFFECTS	COMMENTS
Phenylalanine derivatives Nateglinide	Starlix	Type 2 Diabetes	Contra-indicated in diabetic ketoacidosis, lactation and pregnancy Side effects: In clinical studies hypoglycemia (2.4 % of patients) was the only recorded side effect. Starlix has a "fast on, fast off" mode of action on the beta-cell In relation to meals Starlix has been shown to avoid the problem of late hyperinsulinemia thus reducing the risk of hypoglycemia	Starlix has recently been approved for use as monotherapy or use with Metformin For most patients the starting dose is 120 mg before meals
INSULINS Short acting Human and animal α Short acting Human high strength (500 units/ml)	 Humulin R Novolin R Velosulin BR Iletin II Regular Humulin R-U500	Diabetes Onset: 30-60 mins Peak: 2-5 hours Duration: 4-8 hours Onset: 30-60 mins Peak: 3-4 hours Duration: up to 24 hours	Side effects: hypoglycemia is by far the main side effect of insulin. Recognizing this can be a problem for patients and medical staff. Weakness, confusion, dizziness, sweating, hunger, headache, drowsiness, visual disturbance, irritability, anxiety, shaking, cold clammy skin, and altered behavior may indicate hypoglycemia. Unconsciousness and coma can occur in severe cases Loss (lip atrophy) and overgrowth (lip hypertrophy) of fat tissue and allergic	Educate patients about preventing, recognizing and treating hypoglycemia. Blood monitoring 2-4 times per day helps many patients to reduce the risk of hypoglycemia Insulin is usually given 2-3 times per day before meals and also before bed. The timing of injections depends of the type of insulin used Insulin may be drawn from a vial

Intermediate NPH Lente Isophane Long acting Ultralente	Humulin N Humulin L Novolin N Novolin L Iletin II NPH Iletin II Lente Humulin U	Onset: 1-4 Peak: 4-15 hours Duration: up to 24 hours Onset: 4-6 hours Peaks: 8-16 hours Duration: up to 36 hours	reactions at the site of injection can occur Diet, exercise, illness and emotional upset influence blood glucose in addition to insulin dose Insulin requirements may increase with oral contraceptives, steroids and thyroxine. Insulin requirements may decrease with oral hypoglycemics, salicylates, some antibiotics and antidepressants Also see notes on page 4 of 4	using a syringe and needle and then injected. More often it is given using a pen injector which is more convenient and eliminates the need to carry vials and syringes Insulin is normally made up to a concentration of 100 units per ml volume. It is important to note that Humulin R-U500 is 5 times this concentration Also see notes on page 4 of 4
Short acting analogues Mixed standard and analogue β insulins	Humalog Novolin 70/30 Humulin 70/30 Humulin 50/50 Humalog 75/50 β Humalog 50/50 β	Onset: 15-30 mins Peak: 1-2 hours Duration: 4 hours Onset: 30-60 mins Peaks: 2 hours and 6 hours Duration: up to 16 hours	Analogues have a more rapid onset of action and are usually taken immediately before meals Also see notes on page 3 of 4 Mixed insulins are combinations of short and intermediate acting insulins which are usually given twice daily before meals Injection sites may be more painful	For all insulins injection sites should be rotated Dose of insulin depends on stage of disease (most patients with Type 2 diabetes have some degree of insulin deficiency after 10 years of diabetes), weight, diet, physical activity and acute illness Changes in insulin doe should be made slowly and cautiously and based on the results of home blood glucose readings

			with insulin glargine than with other insulins Also see notes on page 3 of 4	Liaison with diabetes nurses, dieticians and medical staff usually helps the patient to maintain satisfactory blood glucose control Also see notes on page 3 of 4
Long acting analogues Insulin Glargine	Lantus	Onset: 2 hours Peaks: none Duration: 30 hours		
GENERIC	**TRADE**	**INDICATIONS**	**CAUTIONS / SIDE EFFECTS**	**COMMENTS**
Alpha-glycosides inhibitors Acarbose Miglitol	Precose Glyset	Diabetes, when control is unsatisfactory using other agents	Contraindications: diabetic ketoacidosis, severe renal dysfunction, cirrhosis, inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or predisposition to intestinal obstruction Side effects: flatulence, abdominal discomfort, diarrhea, abdominal pain, reversible elevated serum transaminases, reduced iron absorption. They do not cause hypoglycemia when used on their own	Initiate at low dose (e.g. Precose 25 mg once daily) and increase the dose slowly warning the patient of potential side effects. Advise the patient to reduce or stop the drug temporarily in the event of severe side effects If hypoglycemia occurs in a patient taking these drugs then the patient must be treated with pure glucose, fruit juice or milk (not table sugar) which contain sugars whose digestion is not blocked by the drugs Serum transaminases should be checked every 3 months for the first year

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CHAPTER FIVE

SCREENING AND RECRUITMENT

SECTION ONE: SCREENING AND RECRUITMENT PROTOCOL

SECTION TWO: CONSENT FORMS

- **PRIMARY/ECONOMICS**
- **GENETIC**

SECTION THREE: RECRUITMENT MATERIALS

- **RECRUITMENT BROCHURE**
- **RECRUITMENT DIALOG**
- **LETTER TO CONTACT PATIENT**
- **LETTER TO SEARCH RECORDS**
- **RECRUITMENT EDUCATION SLIDES**

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CHAPTER FIVE : SECTION ONE SCREENING AND RECRUITMENT PROTOCOL

I. SCREENING

A. Categories of Patients Screened for BARI 2D Eligibility

1. Diabetics having coronary arteriography as part of routine clinical care.

    a. At the BARI 2D site
    b. At another hospital, but referred to BARI 2D for potential eligibility

2. Diabetics undergoing testing for myocardial ischemia as part of routine care.

    a. At the BARI 2D site
    b. At another hospital, but referred to BARI 2D for potential eligibility

3. Asymptomatic or mildly symptomatic diabetics who agree to undergo screening for myocardial ischemia, and, if present, coronary arteriography, to qualify for BARI 2D. Such patients may be identified by multiple means, including the following:

    a. Database searches
    b. Outpatient clinic screens
    c. Inpatient ward screens
    d. Public appeals where allowed:

        1. newspaper, radio or TV ads
        2. posters, brochures
        3. churches, health fairs, clubs

NOTE: Some or all of the above screening methods may be limited by HIPAA regulations. Check with your local IRB to ensure that your screening practices are in full compliance with HIPAA and in no way jeopardize patient confidentiality and privacy.

B. Cardiac Testing Indications

It should be noted that the American Diabetic Association Consensus Development Conference on Diagnosis of Coronary Artery Disease in Diabetics (Diabetes Care 1998;21:1551-1559) listed the following indications for cardiac testing in diabetic patients:

1. Typical or atypical cardiac symptoms
2. Resting ECG suggestive of ischemia or infarction
3. Peripheral or carotid occlusive disease
4. Sedentary, age $\geq$ 35, planning vigorous exercise program
5. Two or more risk factors besides diabetes:

    a. total cholesterol $\geq$ 240, LDL-C $\geq$ 160 or HDL-C $\leq$ 35 mg/dl

b. blood pressure > 140/90 mm Hg
c. smoking
d. family history of premature coronary artery disease
e. positive test for micro or macroalbuminuria

II. ENTRY CRITERIA

A. Eligibility Criteria

To be eligible for BARI 2D randomization patients must satisfy all of the following criteria:

1. Type 2 diabetes[1], as defined by any one of the following:

   a. Confirmed (i.e. two or more readings) fasting glucose >125 mg/dl; **or**
   b. Random glucose ≥ 200 mg/dl; **or**
   c. 2 hour glucose ≥ 200 mg/dl following 75 grams of glucose; **or**
   d. Current treatment with diet or oral agents directed at the control of hyperglycemia either alone or in combination with insulin; **or**
   e. Current treatment with insulin with no prior history of diabetic ketoacidosis.

2. Coronary arteriogram showing one or more vessels amenable to revascularization (≥50% stenosis). Revascularization may include either percutaneous coronary intervention (PCI) or bypass surgery (CABG).

3. Evidence of myocardial ischemia, as defined either :

   a. Objectively, by any one of the following:

      1. Exercise or pharmacologically-induced ≥ 1 mm of horizontal or downsloping ST depression or elevation for ≥60-80 milliseconds after the end of the QRS complex.
      2. Exercise or pharmacologically-induced myocardial perfusion defect
      3. Exercise or pharmacologically-induced myocardial wall motion abnormality
      4. 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
      5. Doppler or pressure wire showing coronary flow reserve (CFR) < 2.0 or fractional flow reserve (FFR) < 0.75)

   b. **Or** Subjectively, by typical angina in a patient with ≥ 70% stenosis in at least one coronary 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.

1 Since Type 1 diabetes mellitus is excluded, if there is clinical uncertainty the principal investigator may wish to obtain C-peptide testing on a selected case basis.

8. **None of the following exclusion criteria**:

    a. Definite need for coronary revascularization (cardiologist's opinion).
    b. Prior bypass surgery (CABG) or prior catheter-based intervention within the past 12 months.
    c. Planned intervention for disease in bypass graft(s) if the patient is randomized to a strategy of initial revascularization.*
    d. Class III or IV CHF.
    e. Creatinine > 2.0 mg/dl.
    f. HbA1c > 13%.
    g. Need for major vascular surgery concomitant with revascularization (e.g., carotid endarterectomy).
    h. Left main stenosis $\geq$ 50%.***
    i. Non-cardiac illness expected to limit survival.
    j. Hepatic disease (ALT >2 times the ULN).
    k. Fasting triglycerides > 1000 mg/dl in the presence of moderate glycemic control (HbA1c < 9.0%).
    l. Current alcohol abuse.
    m. Chronic steroid use judged to interfere with the control of diabetes, exceeding 10 mg. of Prednisone per day or the equivalent.**
    n. Pregnancy, known, suspected, or planned in next 5 years.
    o. Geographically inaccessible or unable to return for follow-up.
    p. Enrolled in a competing randomized trial.
    q. Unable to understand or cooperate with protocol requirements.

* The intended revascularization must be on native vessel(s)

** For example, patients who systematically take moderate to large doses of steroids for chronic conditions such as asthma or SLE should be excluded

***Except patients with prior CABG who have protected LM disease (i.e. patient graft(s) sufficient to protect the left coronary circulation)

III. MECHANISM OF ENTRY

A. For patients undergoing coronary arteriography as part of routine care, either at BARI 2D site or elsewhere

1. The coronary arteriogram will be reviewed for criteria for revascularization.
2. If coronary anatomy is suitable for revascularization, patient's chart will be screened for eligibility criteria with permission of attending physician.
3. BARI 2D will be discussed with patient (in some cases this may occur prior to angiography)
4. If patient signs consent form for BARI 2D, a test for qualifying ischemia will be performed, if needed.
5. If ischemia documented, patient will be randomized.

B. For patients undergoing diagnostic testing for ischemia to qualify for BARI 2D rather than as part of standard care

1. Patient must have no known exclusions for BARI 2D entry.

2. Consent form for BARI 2D must be signed prior to diagnostic testing.
3. If ischemia is present and all clinical criteria are favorable for randomization, coronary arteriography will be performed.
4. If coronary anatomy is suitable for randomization to either medical therapy or revascularization, and patient and physicians are in agreement, patient will be randomized.

C. For any other patient undergoing coronary arteriography to qualify for BARI 2D, rather than as part of standard clinical care (such as a patient identified as having "mild ischemia" on stress test ordered by his private physician)

1. Patient must have no known exclusions for BARI 2D entry.
2. There must be evidence for ischemia, as defined above.
3. Consent form for BARI 2D must be signed prior to coronary arteriography.
4. If coronary anatomy is suitable for randomization to either medical therapy or revascularization, and patient and physicians are in agreement, patient will be randomized

D. All patients signing the BARI 2D consent form will be entered into a screening log

IV. TIME WINDOWS FOR DATA COLLECTION

A. Interval from obtaining serum assays (glucose, HbA1c, creatinine, ALT, triglycerides) to randomization should not exceed 90 days.
B. Interval from obtaining objective evidence of ischemia (if present) to randomization should not exceed 12 months.
C. Interval from obtaining coronary arteriograms to randomization should not exceed 6 months.

CHAPTER FIVE : SECTION TWO SAMPLE CONSENT FORMS : PRIMARY/ECONOMICS

(Division, Department or School Letterhead)Institutional Review Board
University of Pittsburgh
IRB Number:
Consent Form Approved: _____
Protocol Renewal Date: _____

Consent for Participation in the Research Study Entitled Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D)

Sponsor: National Institutes of Health
National Heart Lung and
Blood Institute (NHLBI)

Principal Investigator: _____

As a diabetic patient with heart disease, you are being asked to take part in a research study known as BARI 2D. This 2400 patient, 7-year study in the U.S., Canada, and other countries is designed to compare whether initial treatment of coronary artery disease with angioplasty (PTCA) or surgery (CABG) is better than starting with a medical program. At the same time, this study will compare two approaches for treatment of diabetes.

BACKGROUND:

CORONARY ARTERY DISEASE: Coronary artery disease is a condition where the arteries which deliver blood with oxygen and energy sources to the heart muscle itself become narrowed by a process called atherosclerosis. Patients with type 2 diabetes develop coronary artery disease and other cardiovascular complications 2-3 times as often as similarly aged persons without diabetes. In some cases, coronary artery disease can best be treated by optimal medical therapy with diet, exercise programs and drugs. In other cases, invasive procedures, like percutaneous coronary intervention (PCI) or bypass surgery (CABG), which increase blood flow to the heart (revascularization), offer the best chance of improving outcome. There are patients for whom we do not know whether optimal medical treatment alone or coronary revascularization combined with optimal medical treatment is better. You are being asked to volunteer for this research study because you are such a patient.

TYPE 2 DIABETES: Diabetes is a disease in which blood sugar (glucose) levels are abnormally high, causing damage to many organs, such as the eyes, the kidneys, and the nerves. Lowering blood glucose levels to normal helps to prevent such damage. We suspect that high blood glucose is also bad for the heart, because diabetic individuals with especially high blood glucose levels are more likely to suffer heart attacks and death.

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In type 2 diabetes, high blood glucose results from two things: (1) the pancreas does not supply enough insulin; and (2) the body does not react well enough to whatever insulin it receives. We now have drugs to improve both of these problems and bring blood glucose levels down close to normal. "Insulin providers" are drugs that increase the supply of insulin, and "insulin sensitizers" are drugs that increase the reaction of the body to insulin. However, we do not know whether insulin providers or insulin sensitizers are better, particularly for type 2 diabetic patients, like yourself, who have coronary artery disease.

THE RESEARCH QUESTIONS

This research study seeks to learn the answer to two main questions.

QUESTION 1: When pictures (coronary angiograms) show definitely narrowed coronary arteries, but not to the point that demands immediate intervention (revascularization), is it better to go ahead and do elective coronary bypass surgery, open arteries with a balloon catheter (angioplasty) or put in a tube for blood to get past a blockage (stent), or is it better to treat in a medically optimal way with diet, exercise and drugs and hold revascularization procedures for use later, should they become more urgently needed?

QUESTION 2: Is it better to lower blood glucose levels close to normal by giving insulin provider drugs or by giving insulin sensitizer drugs?

For each question, "Is it better?" means "will there be a better chance to live longer and avoid future heart attacks".

An additional goal in the BARI 2D study is to evaluate the effect of the treatments on your use of medical services and the cost of those services.

EXPLANATION OF TREATMENT

If you agree to join this study, several tests will be performed (if not already recently done) to verify that you are eligible for the study:

(1) Blood will be drawn (about 2 tablespoonfuls) to check levels of glucose, kidney function and other standard blood components
(2) A test for ischemia (abnormal blood flow to the heart) will be done. This may be one of many standard clinical tests, for example, an exercise or chemical heart stress test.
(3) Coronary arteriography (pictures of blood flow through your heart arteries) will be performed.

If the above tests show that you are eligible for BARI 2D, you will be randomly allocated (like flipping a coin) by a computer to one of 4 treatment groups:

(1) Optimal medical therapy and insulin providing drugs
(2) Optimal medical therapy and insulin sensitizing drugs

Participant's Initials_____

(3) Surgical or catheter-based revascularization plus optimal medical therapy and insulin providing drugs
(4) Surgical or catheter-based revascularization plus optimal medical therapy and insulin sensitizing drugs

OPTIMAL MEDICAL THERAPY will consist of medically approved medications to help improve supply of blood to your heart and reduce the heart's demand for oxygen. Additionally, you may receive medications to lessen the likelihood of blood clot formation in your heart's arteries as well as cholesterol-lowering and blood pressure-lowering medication, if needed.

You will receive detailed advice on steps to reduce your risk of progression of coronary heart disease including information on (1) stopping smoking, if you smoke; (2) a heart-healthy diet; and (3) exercise. Patients assigned to optimal medical therapy may still undergo revascularization in the future, should their symptoms worsen or do not improve.

If you are assigned to optimal medical therapy and revascularization, you and your doctor will decide whether percutaneous coronary intervention (PCI) or bypass surgery (CABG) is better for you. During PCI, which is performed under local anesthesia, a small plastic tube is inserted in your narrowed heart artery to open the narrowing. In many cases, a small tubular structure called a stent is placed in the artery at the site of the narrowing to help keep the artery open. Two major types of stent are used: bare metal stents and drug-eluting stents. Drug-eluting stents contain medications that are released over time to help reduce the chance that re-narrowing of the artery will occur. CABG is open heart surgery where a vein from your leg or an artery from your chest is used to bypass the narrowed heart artery.

If you are assigned to optimal medical therapy and insulin providing drugs and your blood glucose is only moderately elevated, you will receive a pill to cause your body to produce and release more insulin. If your blood sugar is very high, or later becomes very high, you will be given insulin injections, either alone or in combination with the pill.

If you are assigned to optimal medical therapy and insulin sensitizing drugs, you will receive a pill to reduce the body's need for insulin by making the available insulin act more strongly on the body's tissues.

Whichever blood glucose-lowering treatment you receive, you may receive medication from the other treatment arm if your blood glucose fails to come under control. Also, you may receive an additional pill to help lower your blood glucose by slowing the digestion of starches and sugars in meals.

The usual method for measuring how well diabetes is controlled is the hemoglobin A1c (HbA1c) level. HbA1c indicates the average level of blood glucose (sugar) that was present during the previous 4-12 weeks. Non-diabetic persons have a HbA1c of 4.0 to 6.0%. The usual target level of diabetes glucose control in BARI 2D will be a HbA1c less than 7.0%, and action must be taken if HbA1c is greater than 8.0%. We will strive to lower HbA1c to less than 7.0% in each research subject, so long as that can be accomplished using drugs from the assigned treatment arm. If necessary, we will use drugs from the opposite treatment arm if we cannot otherwise

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bring HbA1c to below 8.0%. We may also need to prescribe several injections of insulin per day to some research subjects to achieve these objectives, just as we would in excellent clinical practice. Research subjects with low risks of eye, kidney, or nerve complications, compared to the danger of cardiovascular complications, may be targeted to HbA1c levels of 7.0 to 8.0%. Your BARI 2D diabetes investigator will use his/her best judgment in selecting and seeking to achieve an optimum HbA1c for you within the framework of the BARI 2D research plan and your personal diabetes situation. You are encouraged to discuss these goals and the appropriate means to achieve them, with your BARI 2D diabetes caregivers.

Once you have been randomly assigned to either the insulin sensitizing or insulin providing treatment arm, to start with you will be prescribed only diabetes drugs from that treatment arm. If you were already taking only such drugs, there would be no change in diabetes medications for you. On the other hand, if you were previously taking diabetes drugs from the opposite treatment arm, they will be discontinued and you will be prescribed different drugs appropriate to your assigned treatment arm. This will be done even if your diabetes control had been satisfactory on your former pre-BARI 2D drug regimen. Therefore, at first your blood glucose level might actually go up temporarily, before the new drugs fully take hold. However, we will raise the doses of the new drugs as quickly as we can, with due regard for safety, in order to return your blood glucose to satisfactory levels. If this cannot be achieved with the new drugs, we will add back as necessary any of your old drug(s), including insulin, until your diabetes control becomes satisfactory again. This process might take several months, and in some instances a temporary increase in urinary and intake of fluids might occur. We will ask you to test your blood glucose at home more frequently during such a transition period. We will frequently review those numbers with you by phone, fax, or e-mail on a regular basis, so that we can make prompt changes in drug doses and prevent symptoms.

You will be asked to prick your finger and test your own blood glucose levels at home on a schedule that may vary from 3 times a day to only several times a week, depending upon what drugs you are receiving. In addition, you will return to our clinic to meet with a diabetologist (doctor who is an expert in diabetes management) and/or cardiologist (doctor who is an expert in cardiac management) once a month for the first six months, then every three months afterward. During these visits, up to 2 tablespoonfuls of blood will be drawn from an arm vein to check how well your diabetes, cholesterol and other blood components are being controlled with treatment. It may be necessary to redraw some of these samples if for some reason the first sample is unusable. You will also be offered counseling for smoking cessation, nutrition and physical activity, and will be given a pedometer and other materials as appropriate to help you monitor and manage your risk factors (such as smoking, obesity, and sedentary lifestyle). You will be asked questions about your symptoms.

You will have an electrocardiogram (ECG) at study entry and every year afterward until the end of the study. You should expect to be followed for at least 5 years in this study.

You will have a nuclear imaging test one year after study entry and every other year afterward until the end of the study. Nuclear imaging of the heart is a standard of care technique used to detect blockages in the arteries feeding the heart muscle and to examine the degree of damage and also the heart function. The study is a stress study done with a radioisotope and a special camera.

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ECONOMIC METHODS: An interviewer at Stanford University in California will contact you by phone every three months to ask you about recent doctor visits, outpatient procedures or hospital stays you may have had. If you have been in the hospital, a copy of the hospital bill will be requested. The interview will take only a few minutes to complete.

BENEFITS

Your benefits from participating in this study may include better control of your diabetes and heart disease related to the intensive follow-up you will receive. Your participation in this study will also provide future benefits to society as we find out which approach to treating diabetes and heart disease is better for patients like you.

Some of the medications and supplies to manage your diabetes and heart disease may be made available to you at no cost. These are standard of care medications that would normally be prescribed independent of the fact that they are being provided free of charge. Your BARI 2D physician will choose the best medications for your care independent of whether the medication may be available to you at no cost.

If you are assigned to revascularization, your BARI 2D physician may determine that a drug-eluting stent is most appropriate. This device is available at many institutions as part of standard medical care, and either you or your insurance provider will be responsible for this payment. If a drug-eluting stent is not available as standard medical care at your institution, the study will provide it at no cost to you.

RISKS OR DISCOMFORTS

You will receive medically approved treatments, and there are no risks beyond those of standard clinical care. Blood drawing can cause temporary discomfort or bruising at the skin puncture site, and, in rare instances, fainting can occur. Stress testing may cause abnormal blood pressure, fainting, disorders of the heart beat, and, in rare instances, heart attack and a 1 in 10,000 chance of death. Coronary arteriography can cause temporary discomfort at the skin puncture or incision site in the arm or groin, bleeding, bruising, clot formation, infection, irregularities in the heart beat, and in very rare instances (less than 0.5 %) stroke or death.

Nuclear cardiology imaging uses a pharmacologic agent that simulates cardiac stress. Intravenous injections could produce bruises or infection. Adenosine could produce chest pains, shortness of breath, flushing, dizziness, headaches, and stomach pains. On rare occasions, it produces changes in EKG or heart rhythm. These tend to be short lived because the drug is short lived. More serious side effects such as heart attack or death are extremely unusual for nuclear imaging tests. The amount of radiation is well below the limits set for research uses. Emergency equipment and trained personnel are available at all times.

A common risk (occurring in 10-20 out of 100 patients) associated with stenting -- one form of Percutaneous Coronary Intervention (PCI) -- that occurs within the first 6 months is re-narrowing of the artery. This complication occurs less frequently in most patient subgroups by use of drug-eluting stents as compared to procedures performed with conventional bare metal stents. The

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risk of thrombosis (clotting) in the stent is infrequent irrespective of whether a bare-metal or drug-eluting stent is implanted (approximately 1 in 100 patients). On average, patients who undergo a stenting procedure can be expected to remain in the hospital for about 1 to 2 days.

Re-narrowing of the artery within the first six months is also a common risk (occurring in 10-25 out of 100 patients) associated with balloon angioplasty without stenting – another form of PCI (performed infrequently today due to the overall benefits of stenting). Usually, this re-narrowing can be successfully treated with a second angioplasty procedure. On average, patients who undergo balloon angioplasty can be expected to remain in the hospital for about 1 to 3 days.

Other infrequent (occurring in 1 to 5 out of 100 people) procedural-related complications in all types of PCI (bare-metal stent, drug-eluting stent, or balloon angioplasty) include emergency bypass surgery, failure to completely open the heart artery, damage to the heart including myocardial infarction, spasm (twinge) of the artery, permanent scarring and damage to the artery, stroke and/or paralysis (loss of speech, inability to understand, weakness or inability to move your arms or legs), transient ischemic episodes (small temporary strokes, where symptoms go away), increase or decrease in blood pressure, chest pain, change in heart rhythm (including a slow heart rate or fast heart rate), internal hemorrhage (bleeding inside the body), fever, infection, and death. On rare occasions (occurring in less than 1 out of 100 people), the dye used during the PCI procedure may cause renal (kidney) insufficiency, and bleeding may occur with anti-clotting drugs that are used at the time of the procedure.

With the Cypher drug-eluting stent, there have been reports, including some deaths, that are considered possible hypersensitivity reactions. The symptoms reported include pain, rash, respiratory alterations, hives, itching, fever, and blood pressure changes. The FDA does not have sufficient data to establish rates for these events, nor can it determine whether these rates are different from those experienced with bare metal stents.

For patients who undergo CABG, an infrequent risk (occurring in 1-10 out of 100 patients) is a temporary change in cognitive status (such as memory difficulty). Other infrequent complications (occurring in 1 to 5 out of 100 people) include bleeding that requires re-operation, infection, heart damage during the procedure including myocardial infarction, stroke, renal (kidney) failure, respiratory failure, prolonged need for insertion of a tube in the chest after surgery, and death. In addition, in rare instances (occurring in less than 1 out of 100 people), patients may experience reactions to anesthesia. On average, patients who undergo CABG can be expected to remain in the hospital for approximately 5-7 days. Many patients may require a blood transfusion during surgery.

All insulin providing drugs can cause an abnormally low blood glucose (hypoglycemia). None of the insulin sensitizing drugs cause hypoglycemia when used by themselves, but they can provoke hypoglycemia when added to one of the insulin providing drugs. Each of the FDA-approved drugs for diabetes treatment used in this study is currently in widespread use, but complications can occur such as diarrhea, abdominal cramping, nausea, vomiting, gas, liver test abnormalities, weight gain, leg swelling or other rare side effects.

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ALTERNATIVE TREATMENTS

The alternative to joining this study is to receive your doctor's standard treatment for coronary heart disease and diabetes which can include some or all of the medications being used in this study as well as PCI and CABG.

MEDICAL RECORDS

Your medical records will be reviewed and information collected for the purpose of this research study. Information resulting from your participation in this research which may be important for your current or future medical care will be placed in your medical record and may be shared with others to address standard payment, treatment, and health care operations.

COSTS AND PAYMENTS

You will be billed in the standard fashion for routine medical care for which you are scheduled and either you or your insurance provider will be responsible for this payment. Neither you, nor your third-party insurance provider will be billed for any research procedures that are not part of your routine medical care. **Optional: There will be no payment to you for participating in this study but you will be reimbursed for parking expense during clinic visits.**

PAYMENT FOR RESEARCH-RELATED INJURIES ****Statement will vary by institution****

(Your Hospital) and the study sponsor, the National Heart, Lung, and Blood Institute (NHLBI), have made no provision for monetary compensation to you in the event of physical injury resulting from this study. Should physical injury occur, treatment is available, but treatment is not provided free of charge.

CONFIDENTIALITY

In this study, the doctors will make note of your initials, sex, age, weight, height, and other facts. These details will be stored in a private Coordinating Center on a computer. The facts stored in the computer may be seen by staff at the National Heart, Lung, and Blood Institute, the drug companies which provide the study drugs and the Food and Drug Administration. Some patient data and samples (e.g. blood, urine) collected during the course of the study will be sent to research laboratories. Whenever possible, the data, samples and medical information are coded such that the individual patient cannot be identified. However, some information may still contain patient identifiers when it reaches the core laboratories, and complete confidentiality cannot be guaranteed. All computer data used for analysis of the study results includes only a research ID code for each patient without name or personal information. You will not be identified personally in any reports from this study. Every effort will be made to keep your personal medical data confidential.

WITHDRAWAL FROM STUDY AND NEW INFORMATION

You are free to withdraw your consent and to stop participation in any part of this project at any time without affecting future medical care you may receive at this institution. Your refusal to

Participant's Initials_____

answer any of the questions will not result in any loss of benefit to which you are otherwise entitled. Any significant new findings that develop during the course of the study which may affect your willingness to continue in the research will be provided to you by the study physician.

Your study doctor may end your participation in this research study without your consent for any reason which they feel is appropriate, including an adverse event, failure to take the medication as instructed, failure to keep your scheduled appointments, cancellation of the study by the Sponsor, injury or medical condition which may place you at risk of further complications if you continue to participate, or other administrative reasons. If this occurs, you will be informed by your doctor of the reason for your withdrawal from the study and you will be advised of available treatment that may be of benefit at that time. Being removed from study participation will not result in any loss of benefit to which you are otherwise entitled.

QUESTIONS

If you have any questions about the research, Dr. _____ will be glad to answer them. Dr _____'s number is _____. If you have any questions about your rights as a research subject, _____ (title _____) will answer them. Mr. (Ms) _____ number is _____.

LEGAL RIGHTS AND SIGNATURES

You will receive a copy of this informed consent. You are not waiving any of your legal rights by signing this consent form.

(1) Your signature below indicates that you agree to participate in the **primary BARI 2D** study as described above.

_____ _____
DATE PARTICIPANT'S SIGNATURE

_____ _____
DATE WITNESS'S SIGNATURE

(2) Your signature below indicates that you agree to participate in the **economic research** of cost data related to medical care costs of the BARI 2D study as described above.

_____ _____
DATE PARTICIPANT'S SIGNATURE

_____ _____
DATE WITNESS'S SIGNATURE

I confirm that I have explained to this patient the nature and purpose, and the possible benefits and risks of the study procedures and drugs.

_____ _____
DATE INVESTIGATOR'S SIGNATURE

Participant's Initials_____

CHAPTER FIVE : SECTION TWO SAMPLE CONSENT FORMS : GENETIC

(Division, Department or School Letterhead)Institutional Review Board
Institution Name:
IRB Number:
Consent Form Approved:_____
Protocol Renewal Date: _____

CONSENT TO ACT AS A SUBJECT IN A RESEARCH STUDY

Title: Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Study
(Genetic Banking Research Study Addendum)

Principal Investigator: (name, address, phone number)

Co-Investigators: (name, address, phone number)

Sponsor: National Institutes of Health National Heart, Lung and Blood Institute

Why is this research being done?

The purpose of this research study is to collect and store blood samples for future genetic research studies (genetic bank) related to diabetes and/or heart disease. The specific testing to be performed on the blood samples has not been established at this time. The purpose of this consent form is to give you information so that you can decide whether you want to provide an additional blood sample.

Techniques have been developed which allow evaluation of the inherited factors called genes, as well as of the genetic make-up of your cells, called DNA. By studying material obtained from your blood sample, researchers might identify the gene(s) that carry the trait(s) for diabetes and/or heart diseases and risk factors.

Who is being asked to take part in this research study?

You are being asked to participate in the genetic research bank because you are currently participating in the BARI 2D study. This consent form is in addition to, and is not intended to replace or modify, the consent form for the research study (BARI 2D). Participation in this genetic research study is entirely voluntary. If you decide that you do not want to participate in this genetic research study, you may still continue participation the BARI 2D study. Approximately 2400 subjects will be asked to participate in this genetic bank research study.

What procedures will be performed for research purposes?

If you agree to participate, study personnel will draw one blood sample of approximately two tablespoons from your arm during the BARI 2D study. The blood will be collected and stored for future genetic analysis involving heart disease and/or diabetes. These samples will be stored indefinitely or until the

Participant's Initials_____

genetic material (DNA) used for testing is no longer useful. It may be necessary to redraw this sample if for some reason the first sample is unusable.

Personal genetic information obtained through the study will not be provided to you. This research will not have an effect on your care, therefore, you, your family, or your doctor will not receive results of these studies, and the results will not become a part of your medical record. The laboratory performing the analysis of the genetic material has not yet been determined and therefore it is not known whether the laboratory performing the testing will be certified by the Clinical Laboratory Improvement Act (CLIA), and further research would be necessary before any study results could be used in decisions about your clinical care.

What are the possible risks, side effects, and discomforts of this research study?

Risks associated with drawing blood from your arm include pain, bruising, lightheadedness and, on rare occasion, infection. Precautions will be taken to avoid these difficulties. Whenever possible, blood for the genetic research discussed above will be drawn at the same time as samples for other required laboratory tests. If not, an additional needle stick might be required.

There is the possibility that if the results of the research studies involving your biologic samples or genetic material were to become generally known this information could affect your ability to be insured, your ability to be employed, your future plans for children, or your family relationships.

What are possible benefits from taking part in this study?

There will be no direct benefit to you as a result of the genetic research performed with the material obtained from your blood sample. A possible indirect benefit is that your participation might contribute to the knowledge of the causes of the medical condition you have, or might help in developing early diagnosis methods or new treatments.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?

You have been informed previously that the personal results of the genetic research as described above will not be provided to you. You or your representative will be promptly notified if any other information about this research study develops during the course of the study which might cause you to change your mind about continuing to participate.

Will I or my insurance provider be charged for the costs of any procedures performed as part of this research study?

There will be no cost to you for participation in this genetic research study. You or your insurance carrier will not be billed for either the preparation of your biologic samples, or genetic material or the shipping and handling of these samples.

Will I be paid if I take part in this research study?

You will not be paid for participation in this genetic research study. Your biologic samples and genetic material might lead, in the future, to new inventions or products. If the research investigators are able to develop new products from the use of your biologic sample or genetic material, there are currently no plans to share with you any money or other rewards that may result from the development of the new product.

Participant's Initials_____

Who will pay if I am injured as a result of taking part in this study?

[Institution Name] and their associates who provide services at the [institution name] recognize the importance of your voluntary participation in their research studies. These individuals and their staffs will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research. If you believe that you are injured as a result of the research procedures being performed, please contact immediately the Principal Investigator listed on the first page of this form.

Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the [institution name]. It is possible that the [institution name] may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care unless otherwise specifically stated below. You will not receive any monetary payment for, or associated with, any injury that you suffer in relation to this research.

Who will know about my participation in this research study?

The use of your biological sample will be under the control of the Principal Investigator of this research project, Dr. Katherine Detre, and the Study Chair, Dr. Robert Frye. The biological samples will be stored at the BARI 2D Biochemistry Core Laboratory at the University of Minnesota. To protect your confidentiality, your biologic samples and genetic material, will be assigned a code number. The samples stored at the Core Laboratory will not contain personal identifiers but the records linking your personal identity with the blood samples to this code number will be stored in locked research files at the [institution name] (local site).

Any information about you obtained from this research will be kept as confidential (private) as possible. You will not be identified by name in any publication of research results unless you sign a separate form giving your permission (release). In unusual cases, your research records may be released in response to an order from a court of law. It is also possible that authorized representatives of the Food and Drug Administration, the National Institutes of Health, and/or the [institution name] may inspect your research records. The fact that you are participating in a research study and that you are undergoing certain research procedures (but not the results of the procedures) may also be made known to individuals involved in insurance billing and/or other administrative activities associated with the conduct of the study. Information resulting from the research will not be entered into your medical records.

Is my participation in this research study voluntary?

Your participation in this research study is completely voluntary. You do not have to take part in this research study and, should you change your mind, you can withdraw from the study at any time.

May I withdraw, at a future date, my consent for participation in this research study?

If you should decide to withdraw your consent for the use of your biologic samples or genetic material, please indicate this request in writing to the study doctor listed on the front page of this consent form. Upon receipt of this request, your biologic samples, genetic material, and related personal information will be destroyed. However, any sample or portion of a sample that has been already used in research or distributed to another investigator anonymously cannot be retrieved and destroyed. Withdrawal from the genetic study will not affect your participation in the BARI 2D study. The Principal Investigator of this research project, Dr. Katherine Detre, shall be entitled to retain and use any research results obtained prior to your withdrawal of consent.

Participant's Initials_____

VOLUNTARY CONSENT:

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form.

Any questions I have about my rights as a research participant will be answered by [contact name and phone number].

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

_____ _____
Participant's Signature Date

_____ _____
Witness Signature Date

INVESTIGATOR'S CERTIFICATION:

I certify that the nature and purpose, the potential benefits and possible risks associated with participation in this research study have been explained to the above individual and that any questions about this information have been answered.

_____ _____
Investigator's Signature Date

Participant's Initials_____

CHAPTER FIVE : SECTION TWO SAMPLE CONSENT FORMS : IND

(Division, Department or School Letterhead)Institutional Review Board
Institution Name:
IRB Number:
Consent Form Approved:_____
Protocol Renewal Date: _____

CONSENT TO ACT AS A SUBJECT IN A RESEARCH STUDY

(Addendum for the use of Rosiglitazone combined with Insulin)

Title: Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Study
(Rosiglitazone with Insulin Addendum)

Principal Investigator: (name, address, phone number)

Co-Investigators: (name, address, phone number)

Sponsor: National Institutes of Health National Heart, Lung and Blood Institute

NEW INFORMATION:

You are currently a participant in a research study designed to compare whether initial treatment of coronary artery disease with angioplasty (PTCA) or surgery (CABG) is better than starting with a medical program. At the same time, this study will compare two approaches for treatment of diabetes.

One way to measure how well your diabetes is controlled is to measure and control the hemoglobin A1c (HbA1c) level in your blood. The BARI 2D study investigators strive to keep your HbA1c level at approximately 7.0%, as recommended by the American Diabetes Association. To do this your BARI 2D diabetes investigator will use his/her best judgment in choosing the study drugs to control your blood sugar levels. At this point, your BARI 2D diabetes investigator has determined that maintaining your HbA1c at the recommended level will require the use of a thiazolidinedione (TZD) in combination with insulin.

In BARI 2D, the preferred TZD is rosiglitazone, which will be provided without cost to participants. The FDA has approved the use of rosiglitazone up to a dose of 4 mg. for use in combination with insulin. The BARI 2D trial has applied for, and received, an Investigational New Drug (IND) waiver from the United States' Food and Drug Administration (IND #62577), and a Control Number from the Canadian Health Products and Food Branch (#073613), for this

Participant's Initials_____

specific combination use at any approved dose. This means the use of rosiglitazone in doses exceeding 4 mg. and up to 8mg. combined with insulin is considered experimental.

The FDA has also approved a new drug named Avandamet. This drug is a combination of rosiglitazone and metformin, an insulin sensitizin drug. You may be placed on a combination of Avandamet and insulin, which is included in the IND received by the BARI 2D trial. The Canadian Health Products and Food Branch has issued a separate Control Number (#085734) for this specific combination. This means that the use of Avandamet in combination with insulin is considered experimental.

ALTERNATIVE TREATMENTS

You and your BARI 2D diabetes investigator have the option of using pioglitazone instead of rosiglitazone. Pioglitazone is another TZD, and it does have FDA approval for combination use with insulin. However, only rosiglitazone is provided free of charge, so you would be responsible for the costs of using pioglitazone. NOTE: Pioglitazone is *not* approved for combination use with Insulin in Canada.

BENEFITS

The potential benefit from the use of the combination of insulin and rosiglitazone is better control of your blood sugar levels.

RISKS OR DISCOMFORTS

The adverse events for the combined use of insulin and rosiglitazone are low blood sugar (hypoglycemia), weight gain, edema (swelling), and congestive heart failure. There are no clear indications that these risks would differ from combined use of any other TZD with insulin. In clinical trials, edema was reported in approximately 15% (15 out of 100) of the patients who took rosiglitazone with insulin, as compared to approximately 5% (5 out of 100) on insulin alone or on rosiglitazone alone. During these trials, there was an increased incidence of new onset or worsening of congestive heart failure (CHF). 1% (1 out of 100) of the patients on insulin alone developed new onset or worsening of CHF, while 2% (2 out of 100) of patients on insulin and rosiglitazone at 4 mg, and 3% (3 out of 100) of patients on insulin and rosiglitazone at 8 mg developed this complication. Development of hypoglycemia classified as mild or moderate was reported in 38% (38 out of 100) of patients on insulin alone compared to 53% (53 out of 100) of patients on insulin and rosiglitazone at 4 mg and 67% (67 out of 100) on insulin and rosiglitazone at 8 mg. For patients on insulin alone, an average weight gain of 0.9 kg was observed. This compares to an average weight gain of 4.0 kg in patients on insulin and rosiglitazone at 4 mg and 5.3 kg in patients on insulin and rosiglitazone at 8 mg.

The adverse events for the combined use of insulin and pioglitazone are edema (swelling), low blood sugar (hypoglycemia) and anemia. In clinical trials, among patients who took pioglitazone with insulin, 15% (15 out of 100) experienced edema, 2% (2 out of 100) experienced hypoglycemia and 2% (2 out of 100) developed anemia.

In clinical trials of Avandamet, the following adverse events were reported most frequently: upper respiratory tract infection, diarrhea, injury, anemia, headache, sinusitis, fatigue, back pain, viral infection, arthralgia, and hyperglycemia. A small number of people who have been treated with metformin (with and without rosiglitazone) have developed the serious yet rare condition called lactic acidosis (a build-up of lactic acid in the blood). Lactic acidosis has been reported in about 1 in 33,000 patient taking

Participant's Initials_____

metformin over the course of a year. Although rare, if lactic acidosis does occur, it can be fatal in up to half the people who develop it.

RIGHT TO WITHDRAW

You understand that you can choose to discontinue this combination therapy at any time. Your other care and benefits related to the BARI 2D study will be the same whether you participate in this combination therapy or not. You also understand that you may be removed from this combination therapy by the study investigators in the event of a significant risk to your health.

VOLUNTARY CONSENT:

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during its course, and that such future questions will be answered by the researchers listed on the first page of this form.

Any questions I have about my rights as a research participant will be answered by [contact name and phone number].

By signing this form, I agree to allow my BARI 2D diabetes investigator to place me on rosiglitazone in combination with insulin. A copy of this consent form will be given to me.

_____ _____
Participant's Signature Date

_____ _____
Witness Signature Date

INVESTIGATOR'S CERTIFICATION:

I certify that the nature and purpose, the potential benefits and possible risks associated with participation in this aspect of the research study have been explained to the above individual and that any questions about this information have been answered.

_____ _____
Investigator's Signature Date

Participant's Initials_____

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CHAPTER FIVE : SECTION TWO SAMPLE CONSENT FORMS : HIPAA AUTHORIZATION

(Division, Department or School Letterhead) Institutional Review Board
Institution Name:
IRB Number:
Consent Form Approved:_____
Protocol Renewal Date: _____

CONSENT TO ACT AS A SUBJECT IN A RESEARCH STUDY

(Addendum for authorization to use and disclose Protected Health Information)

Title: Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Study
(HIPAA Authorization Addendum)

Principal Investigator: (name, address, phone number)

Co-Investigators: (name, address, phone number)

Sponsor: National Institutes of Health National Heart, Lung and Blood Institute

Why is my additional consent being requested?

You have previously given your consent to participate in the above-named research study. The purpose of this additional consent form is to provide you with specific knowledge regarding the use and disclosure of your identifiable medical record information for the purpose of this research study. While much of this knowledge was provided to you previously, recently enacted laws focused on the privacy of medical record information require that this knowledge be addressed in certain manner. Through the use of this additional consent form, we are seeking your authorization (consent) for the use and disclosure of your identifiable medical record information for the purpose of this research study as per the requirements addressed in these recently enacted laws.

What uses of my identifiable medical record information will this research study involve?

This research study will involve the recording of current and/or future identifiable medical information from your hospital and/or other health care provider (e.g., physician office) records. The information that will be recorded will be limited to information concerning diabetes and heart disease, potential eligibility for this research study, and health information relevant to your treatment. This information will be used for the purpose of determining whether or not you are eligible, and making clinical decisions as part of your ongoing care.

Participant's Initials_____

This research study will result in identifiable information that will be placed into your medical records held at **[institution name].** The nature of the identifiable information resulting from your participation in this research study that will be recorded in your medical record includes information relating to the treatment of your diabetes and heart disease during the period you were a participant in BARI 2D.

Who will have access to my identifiable medical record information related to my participation in this research study?

In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to your identifiable medical record information related to your participation in this research study:

> Authorized representatives of the ***[institution name]*** Research Conduct and Compliance Office may review your identifiable medical record information for the purpose of monitoring the appropriate conduct of this research study.
>
> Authorized representatives of the ***[institution name]*** or other affiliated health care providers may have access to your identifiable medical record information for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and (3) for internal hospital operations (i.e. quality assurance).
>
> The primary sponsor of BARI 2D is the National Heart, Lung and Blood Institute (NHLBI). A Coordinating Center at the University of Pittsburgh oversees the study under a Cooperative Agreement with the NHLBI. In addition, several drug companies have provided financial support and/or study medications. Authorized representatives of these sponsors may review and/or obtain your identifiable medical record information for the purpose of monitoring the accuracy and completeness of the research data. All scientific analyses of the research data will be performed on computer data that includes only a research ID code for each patient without name or personal information.

In unusual cases, the investigators may be required to release your identifiable research information (which may include your identifiable medical record information) in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by ***[state or province name]*** law, the appropriate agencies.

In this study, the doctors will make note of your initials, sex, age, weight, height, and other facts. These details will be stored in a private Coordinating Center on a computer. All computer data used for analysis of the study results includes only a research ID code for each patient without name or personal information. The facts stored in the computer may be seen by the staff at the National Heart, Lung and Blood Institute, the drug companies which provide the study drugs, and the Food and Drug Administration. You will not be identified personally in any reports from this study. Every effort will be made to keep your personal medical data confidential. There are a few cases in which it is possible that complete confidentiality cannot be maintained:

1) Some patient data and samples (e.g. blood, urine) collected during the course of the study will be sent to research laboratories. Whoever possible, the data, samples and medical information are coded such that the individual patient cannot be identified. However some information may still contain patient identifiers when it reaches the core laboratories.
2) An Economics Core Laboratory at Stanford University will evaluate the long-term costs of the treatments being studied in BARI 2D. You will be asked to sign a separate Release Authorization

Participant's Initials_____

to allow this Core Laboratory to receive personal contact information and copies of hospital bills. If you choose not to sign the Release Authorization, the Economics Core Laboratory will receive none of your identifiable medical information.

3) DuPont Pharmaceuticals is donating two drugs used for Nuclear Perfusion Imaging Tests. DuPont can only send these supplies as a prescription, so your institution will provide your name and the fact that you are enrolled in BARI 2D to DuPont. DuPont will not receive any other identifiable health information.
4) NetGroup Diabetic Services provides some diabetic testing supplies to BARI 2D participants. You will be asked to fill out a form to provide personal contact information and insurance information to NetGroup. NetGroup will not use this information for any other purpose than to mail supplies to you.

May I have access to my medical record information resulting from participation in this research study?

In accordance with the ***[institution name]*** Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in this research study) contained within your medical records filed with your health care provider unless otherwise specifically stated below.

May I refuse to provide my authorization (consent) for the use of my identifiable medical record information for the purpose of this research study?

Your authorization (consent) to use and disclose your identifiable medical record information for the purpose of this research study is completely voluntary. However, if you do not provide your written authorization (consent) for the use and disclosure of your identifiable medical record information, you will not be allowed to participate or continue to participate in the research study.

Whether or not you provide your authorization (consent) for the research use and disclosure of your medical record information will have no affect on your current or future medical care at a ***[institution name]*** hospital or affiliated health care provider or your current or future relationship with a health care insurance provider. Whether or not you provide this written authorization (consent) will have no affect on your current or future relationship with the ***[institution name]***.

May I withdraw, at a future date, my authorization (consent) for the use of my identifiable medical record information for the purpose of this research study?

You may withdraw, at any time, your authorization (consent) for the use and disclosure of your identifiable medical record information for the purpose of this research study. However, if you withdraw your authorization (consent) for the use and disclosure of your identifiable medical record information, you will also be withdrawn from further participation in this research study. Any identifiable medical record information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your authorization may continue to be used and disclosed by the investigators for the purposes described above

To formally withdraw your authorization (consent) you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your authorization (consent) for the research use and disclosure of your medical record information will have no affect on your current or future medical care at a ***[institution name]*** hospital or affiliated health care provider or your current or future relationship with a health care insurance provider. Your decision to withdraw this authorization will have no affect on your current or future relationship with the ***[institution name]***.

Participant's Initials_____

For how long will the investigators be permitted to use my identifiable medical record information?

The investigators may continue to use and disclose your identifiable medical record information for the purposes described above for an indefinite period of time.

****

VOLUNTARY CONSENT

All of the above has been explained to me and all of my current questions have been answered. I understand that, throughout my participation in this research study, I am encouraged to ask any additional questions I may have about the research use and disclosure of my identifiable medical record information. Such future questions will be answered by the investigators listed on the first page of this form.

Any questions I have about my rights associated with the research use of my medical record information will be answered by the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh (412-578-8570).

By signing this form, I agree to allow the use and disclosure of my medical record information for the purposes described above. A copy of this authorization (consent) form will be given to me.

_____ _____

Participant's Signature Date

CHAPTER FIVE : SECTION THREE

RECRUITMENT MATERIALS

RECRUITMENT DIALOG

LETTER TO CONTACT PATIENT

LETTER TO SEARCH RECORDS

RECRUITMENT EDUCATION SLIDES

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CHAPTER FIVE : SECTION THREE RECRUITMENT MATERIALS : RECRUITMENT DIALOG

You have been diagnosed as having diabetes mellitus.

We also know that you have coronary artery disease on the basis of your angina and/or of your abnormal stress electrocardiogram or abnormal radionuclide scan. We have documented on your coronary angiogram that you have one, two or three narrowed coronary vessels.

Patients who suffer from diabetes mellitus have an at least two to three times increased chance of developing coronary artery disease as compared with patients who do not suffer from diabetes mellitus.

Once they have been diagnosed as having coronary artery disease, as you have, patients with diabetes mellitus have a greater risk of complications from coronary artery disease, such as suffering from a heart attack, over a 5-year period.

Diabetes mellitus is very often accompanied by high cholesterol and excessive levels of other blood lipids, by hypertension and by being overweight. Smoking for a diabetic individual is like holding a bomb waiting to explode.

Recently, there have been some very interesting developments which have shown that if the elevated blood glucose level is treated intensively so that the glucose level in the blood is decreased and maintained to a near normal level, it is possible in the long term to counteract the adverse effects of diabetes on the blood vessels. This is particularly true for what we call the microcirculation, the small vessels in the kidneys, the eyes and the peripheral nerves, reducing the risk of kidney failure, blindness and neuropathy. This is also true for the larger circulation, in the heart and in the brain, improving the symptoms of angina and reducing the risk of heart attack and stroke.

In addition to giving insulin and some oral agents to reduce and control blood glucose levels, we now have a new class of drug, which stimulates the effect of the insulin produced internally on the tissues of your body.

We also now have definite proof that lowering blood lipids aggressively and lowering blood pressure also aggressively, to normal or near normal levels strongly reduces the risk of cardiovascular complications in diabetic patients.

Finally, you have been told about the interventions such as coronary angioplasty and coronary bypass surgery which act by directly increasing the circulation of blood in your coronary arteries. These interventions are extremely effective in relieving angina. However, they do not retard the progression of the atherosclerosis process which underlines coronary disease and, as you know, they have some inherent limitations. Coronary angioplasty, not infrequently, requires reinterventions soon after the procedure and cardiac surgery is invasive. Each has its indications and, in your case, if you were to undergo one of them, we concur with your private physician that A would be more indicated than B.

In this study, we want to implement strict diabetic control and strict control of cholesterol and blood pressure levels in all patients and this includes you. We also want to take appropriate measures to relieve

angina whenever it is present, and this may include medical therapy, that is the administration of drugs against angina, or an intervention, that is either angioplasty or bypass surgery. In addition, we want to pursue two major objectives which are the main reasons for doing the study. First, we have reasons to think, although we have no proof of that, that intensive medical treatment of angina and ischemia, strict diabetic control and strict control of other risk factors (obesity, cholesterol, hypertension) alone may perhaps be as good as strict control of these factors plus an intervention on the risk of complications of coronary disease over a 5-year period. Therefore, we want to compare, in patients like you, a trial of intensive medical therapy alone initially with the option of recommending an intervention later if, for example, angina is not relieved by medical therapy with intensive therapy plus an immediate intervention which would be the one that is considered the best for you, i. e. intervention A (or B). In other words, we want to see if, in the presence of intensive medical therapy, no intervention or a delayed intervention is as good as an immediate intervention in patients like you who have both diabetes and coronary artery disease. Unlike you, many patients would not be candidates for this study because they need an immediate intervention to treat severe angina or a recent heart attack. Because you have relatively mild angina, you do not need an immediate intervention and we do not know at this time whether an early intervention decreases the long-term complications of coronary artery disease in patients like yourself, especially in the presence of intensive medical therapy. Second, as part of the intensive medical therapy that we will implement in this study, we want to evaluate whether the administration of oral drugs that enhance the effect of insulin in your body such as metphormin which is an old drug plus new agents of its class, is as efficacious for glucose control and prevention of events related to coronary disease as the subcutaneous administration of insulin.

To enable us to reach valid conclusions at the end of 5 years, conclusions that may affect the future treatment of a countless number of patients, we must allow a completely unbiased allocation to two treatment choices for all the patients participating in this study, the choice between immediate and delayed intervention and the choice between the administration of insulin versus the administration of drugs that will sensitize your body to the available insulin. Both choices must be made at random and you will have a 50-50 chance of having one or the other. If we had serious reasons to think that, for either of these two treatment choices, one was superior to the other, it would be against our duty as physicians (first do no harm) to even suggest to you to participate in this study. If we were to pool the opinion of experts on these two choices, half would probably favor one option and half would favor the other. Therefore, your decision to participate in this study should not penalize you in any way.

On the other hand, if you agree to participate in this study, you will benefit from the constant expert care of highly experienced teams of cardiologists and diabetologists including nurses, pharmacists and physicians. You will have access to these specialists and to the hospital facilities whenever you need them during the course of the study. We can assure you that these people will always act in your best interest.

CHAPTER FIVE : SECTION THREE RECRUITMENT MATERIALS : SAMPLE LETTER – REQUEST TO CONTACT PATIENT

[UNIVERSITY / BARI 2D LETTERHEAD]

Dear Dr.

I (We) are writing for your permission to approach the above patient for enrollment in BARI 2D (Bypass Angioplasty Revascularization Investigation 2 in Type 2 Diabetes Mellitus), a multicenter clinical trial supported by the National Institute of Health and conducted in the United States and Canada. The purpose of BARI 2D is to determine the optimal interventions for management of patients with coexistent type 2 diabetes mellitus and coronary artery disease (CAD). BARI 2D will investigate the optimal approach to hyperglycemia by randomization of participants to a regimen of primary insulin augmentation or sensitization, as well as the optimal approach to CAD by randomization to revascularization with PTCA or CABG or aggressive medical therapy.

It is estimated that there are 14 million people with type 2 diabetes in the United States. In Canada, there are 2 million people with diabetes. Heart disease is the number one cause of mortality and morbidity in both men and women with diabetes. To date, most studies that have investigated methods of both primary and secondary prevention of recurrent cardiac events have included only small numbers of diabetic subjects. There is also a concern that some of the therapies directed at treating hyperglycemia, such as sulfonylureas and insulin, may further increase the risk for cardiac events.

In BARI 2D, patients with a diagnosis of type 2 diabetes and documentation of myocardial ischemia by stress testing and/or angiographic confirmation of CAD will have the following:

1. At study entry, randomization to an immediate revascularization procedure or aggressive medical therapy. If selected for revascularization, the procedure of choice (angioplasty or bypass) will be that recommended by the interventional cardiologist.
2. Follow-up within one week by an endocrinologist/diabetologist with randomization to a program of insulin augmentation or sensitization to control hyperglycemia (target HbA1c < 7.0%).
3. Periodic follow-up by the BARI 2 study team for ongoing management of hyperglycemia, hypertension, and dyslipidemia, with additional interventions directed at secondary prevention of CAD (e.g. aspirin therapy, beta blockers) for up to four years.
4. Travel reimbursement to/from BARI 2D site (optional)
5. Continued follow-up as usual in your office or clinic

Before we contact the above patient, we must have your approval. Either my study nurse or I will telephone you in several days. If you wish, you may respond below, then fax this letter to me at XXXXXX. Should your patient consent to participation in this trial, regular progress reports will be sent to your office by the BARI 2D study investigators. Thank you for your consideration regarding this request.

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CHAPTER FIVE : SECTION THREE RECRUITMENT MATERIALS : SAMPLE LETTER – REQUEST TO SEARCH RECORDS

[UNIVERSITY / BARI 2D LETTERHEAD]

Dear Dr.

I (We) are currently recruiting patients with coexistent type 2 diabetes mellitus and coronary artery disease for BARI 2D (Bypass Angioplasty Revascularization Investigation 2 in type 2 Diabetes Mellitus), a multicenter clinical trial supported by the National Institute of Health and conducted in the United States and Canada. The purpose of BARI 2D is to determine the optimal interventions for management of patients with coexistent type 2 diabetes mellitus and coronary artery disease (CAD). BARI 2D will investigate the optimal approach to hyperglycemia by randomization of participants to a regimen of primary insulin augmentation or sensitization, as well as the optimal approach to CAD by randomization to revascularization (with PTCA or CABG) or aggressive medical therapy.

In order to effectively identify potential participants for this study, we are requesting your permission to perform a search of the XXXXXXX electronic medical records for all patients you have seen in the past two years. The search structure will be tailored to the inclusion and exclusion criteria of the study (see attached protocol summary).

The study investigators of BARI 2D will generate a tabulation of those patients who meet the entry criteria for this study, which will be provided for you to review and ascertain whether or not it would be suitable to contact these patients regarding participation. This review is intended to identify any factors other than what is available in the medical record that might preclude a patient from participating in this study. Only those patients authorized by you will be contacted after this review. These patients would be contacted by phone by one of the study investigators to determine their potential willingness to participate.

We sincerely appreciate your time in evaluating this request and hope that you will be willing to assist us in the process of building a framework for the efficient conduction of this very important clinical trial. Please indicate your response by checking the box below and faxing your response to XXXXXXX. Should you have a patient who consents to participate in this trial, regular progress reports will be sent to your office by the BARI 2D study investigators.

Should you have additional questions, please feel free to contact me at XXXXXXXXX. .

Sincerely,

XXXXXXXX

_____ Yes, you may search my patient records

_____ No, I do not wish to have my patient records searched

Comments: _____

_____

Please FAX to xxxxxxxxxxxxxxxxxxx

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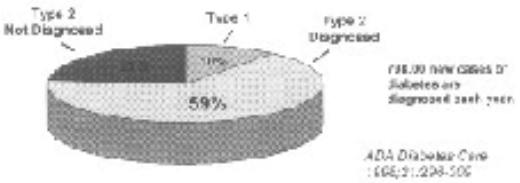
BARI 2D MANUAL OF OPERATIONS RECRUITMENT EDUCATION SLIDES

BARI 2D

Bypass
Angioplasty
Revascularization
Investigation 2D

Prevalence of Diabetes in the U.S.

More than 16 million Americans have diabetes



ADA Diabetes Care

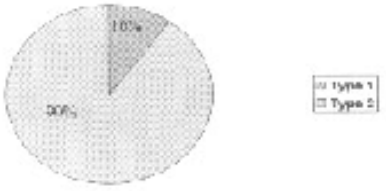
Diabetes in the U.S.

- Affects 16 million people
- Many are undiagnosed because onset of disease precedes diagnosis by 4-7 yrs
- Costs economy about $100 billion per year
- Accounts for about 1 of every 10 dollars allocated to health care and about 1 of every 4 Medicare dollars.

Increasing Deaths from Diabetes in U.S., 1980-96

Prevalence of diabetes in Canada

More than 2 million Canadians have diabetes



Canadian Diabetes Association 2002

Diabetes in Canada

Risk for developing type 2 diabetes is 3-5x higher in those of Aboriginal descent than in general population

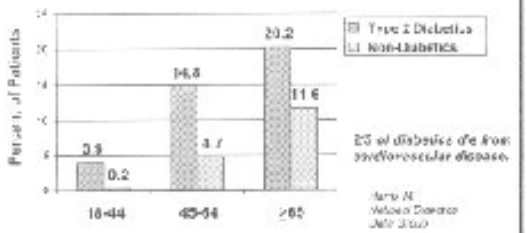
Health care costs are 2-5x higher than for those without diabetes

Accounts for $9 billion of health care costs annually

6/25/02

BARI 2D MANUAL OF OPERATIONS RECRUITMENT EDUCATION SLIDES

Prevalence of Ischemic Heart Disease

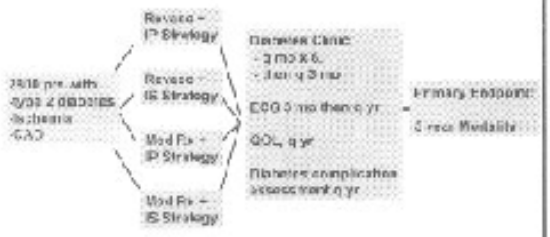


BARI 2D: *Goals*

In patients with Type 2 diabetes and stable documented CAD, to simultaneously test whether 5-year mortality is lower if:

- **myocardial ischemia** is managed by immediate revascularization plus aggressive medical therapy vs aggressive medical therapy alone, and if
- **diabetes** is managed by an insulin providing strategy vs an insulin sensitizing strategy.

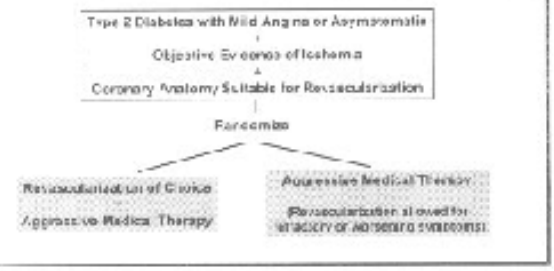
BARI 2D: *Overview*



BARI 2D: *Ischemia Management*

Why compare **revascularization** with **medical therapy** in **diabetics?**

BARI 2D: *Randomization to Therapy for Ischemia*



Why Compare Revascularization with Medical Therapy in Diabetics?

- Medical therapy has improved since prior randomized trials of medical therapy vs revascularization.
- Outcome is poorer with revascularization in diabetics than non-diabetics.
- Preliminary data suggest that medical therapy may be equivalent to revascularization in diabetics.

8/23/02

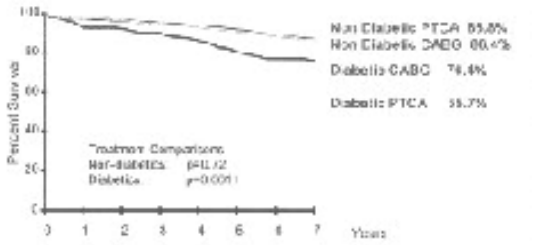
BARI 2D MANUAL OF OPERATIONS RECRUITMENT EDUCATION SLIDES

Medical Therapy for Myocardial Ischemia Since CASS*

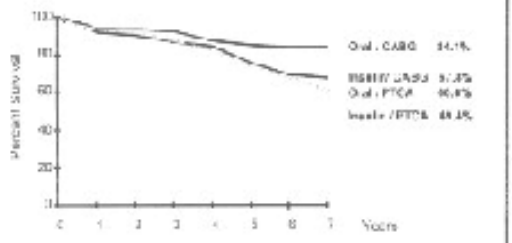
- Antiplatelet therapy
  - Aspirin
  - Thienopyridines
  - IIb/IIIa (GP IIb/IIIa receptor blockers)
- Antithrombin therapy for acute ischemic syndromes:
  - unfractionated heparin
  - low molecular weight heparin
- Fibrinolytic therapy for AMI
- Isosorbide mononitrate
- Beta blockers post-MI
- Calcium channel blockers
- ACE inhibitors
- HMG Co-A Reductase Inhibitors and other lipid-lowering therapy
- Smoking cessation aids

* CASS = Coronary Artery Surgery Study which compared CABG with medical therapy in stable CAD. Circulation 1983;68:I-1-81.

BARI I: *Poorer Outcome with Revascularization in Diabetics*



BARI I: *Poorer Outcome in Insulin-treated than Oral-Treated, Revascularized Diabetics*



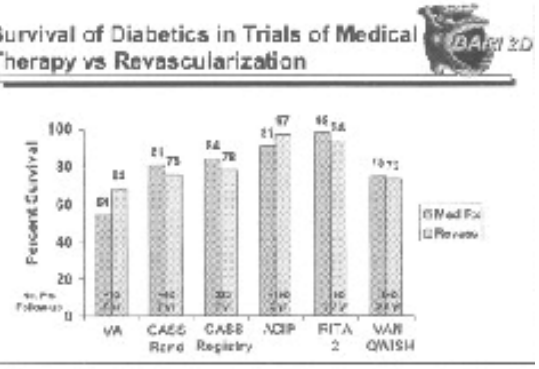
Revascularization in Diabetes: *The Problems*

- Co morbidity (PVD ↑, CRF ↑)
- Peri-procedural complications ↑
- Worse long-term clinical outcomes
  - death ↑, MI ↑, stroke ↑
- Excessive restenosis
  - *intimal hyperplasia* ↑
  - *negative remodeling* ↑
- Accelerated all encompassing
  - *progression of disease* ↑
  - *small vessel/diffuse disease* ↑

Revascularization in Diabetes: *Mechanistic Insight*

- Endothelial function ↓
- Endothelial regeneration ↓
- Pro-thrombotic state
  - *thrombosis* ↑, *fibrinolysis* ↓
- Intimal hyperplasia ↑
  - *mitogenicity* ↑ (TGF, IGF)
- Negative remodeling ↑
- Protein glycosylation ↑
- Vascular matrix deposition ↑
- Collateral formation ↓

Survival of Diabetics in Trials of Medical Therapy vs Revascularization



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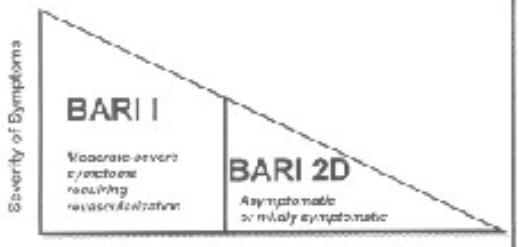
BARI 2D MANUAL OF OPERATIONS RECRUITMENT EDUCATION SLIDES

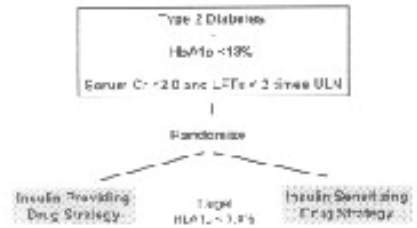
BARI 2D: *Target Population*



BARI 2D: *Diabetes Management*

Why **compare** an **insulin** providing **with** an **insulin sensitizing strategy?**

BARI 2D: *Randomization to Therapy for Glycemic Control*



BARI 2D: *Glycemic Control Question*

Will treatment of hyperglycemia with agents directed at reducing insulin resistance (i.e. improving insulin sensitivity) result in lower CVD event rates than treatment directed at increasing insulin availability to tissues (i.e. providing more insulin) if an HbA1c of ≤7.0 % is achieved and is maintained in each of the two treatment arms?

Rationale for comparing insulin providing vs insulin sensitizing regimens

- Insulin resistance is an independent risk factor for CVD.
- Hyperinsulinemia is implicated in the pathogenesis of atherosclerosis.
- It is so important know whether decreasing insulin resistance is beneficial to CVD risk.
- It is important to know whether enhancing circulating insulin is detrimental to CVD risk.

BARI 2D: *Diabetes Drug Classification*

- Insulin providing (IP) drugs:
  - Sulfonylureas
  - Repaglinide
  - Nateglinide
  - Insulin
- Insulin sensitizing (IS) drugs
  - Thiazolidinediones (glitazones)
  - Metformin
- IP/IS neutral drugs
  - α-glucosidase inhibitors

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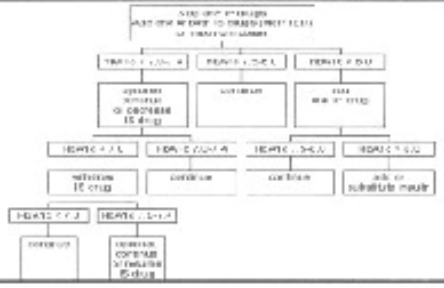
BARI 2D MANUAL OF OPERATIONS RECRUITMENT EDUCATION SLIDES

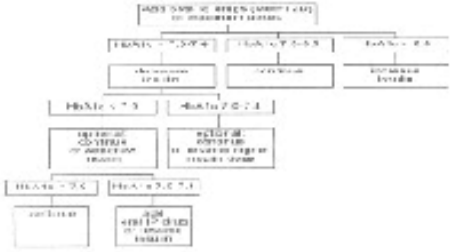
Rationale for Target HbA_{1c} < 7.0%

- This provides good, though not absolute, protection from retinopathy, nephropathy, and neuropathy
- This is the median/mean reached or approached by the UKPDS
- The actual median/mean is likely to exceed the target
- It is consistent with the goal in the ADA standards of care

Insulin Sensitizing (IS) Algorithm:
Patients not on insulin at entry



Insulin Sensitizing (IS) Algorithm:
Patients using insulin at entry



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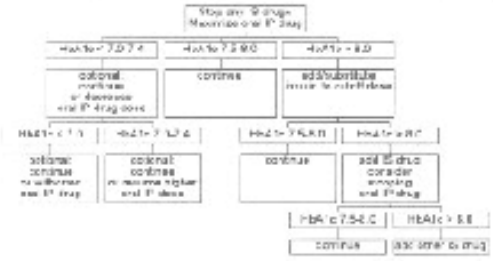
Patients not on insulin at entry



Insulin Providing (IP) Algorithm:
Patients on insulin at entry

Operational Challenges of BARI 2D Glycemic Control Experiment

- Achieve the HbA_{1c} target in as many subjects as possible
- Maintain similar and acceptable median/mean HbA_{1c} levels in the IP and IS treatment groups
- Minimize drug crossovers, i.e. use of IP drugs in IS subjects and IS drugs in IP subjects.

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BARI 2D MANUAL OF OPERATIONS RECRUITMENT EDUCATION SLIDES

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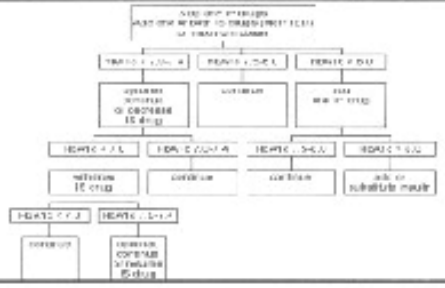

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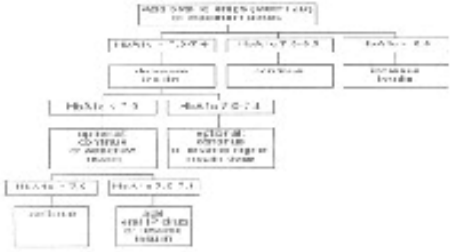
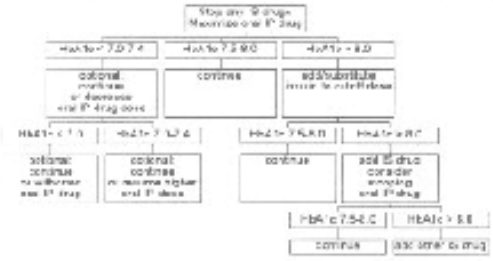


Insulin Providing (IP) Algorithm:
Patients not on insulin at entry



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BARI 2D MANUAL OF OPERATIONS RECRUITMENT EDUCATION SLIDES

BARI 2D: *Randomization Scheme*

- Patient randomized to one of four cells
- Randomization will be stratified by:
  - clinical site
  - intended type of revascularization

PCI Intended — Randomize — PCI / Medical

CABG Intended — Randomize — CABG / Medical

BARI 2D: *Endpoints*

- All-cause mortality
- Death or Q-wave myocardial infarction or stroke
- Cardiac mortality, myocardial infarction
- Angina, quality of life, employment
- Retinopathy, neuropathy, nephropathy, peripheral vascular disease
- HbA1c, blood pressure, cholesterol
- Cost and cost effectiveness

BARI 2D: *Statistical Design*

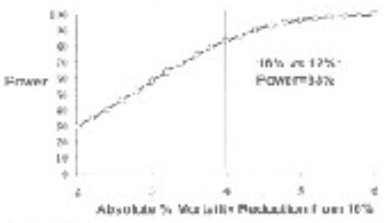
- Intention-to-treat principle
- Two-sided confidence intervals and *p*-values
- Each hypothesis will be considered statistically significant if $\alpha \leq 0.05$ for the log rank statistic
- Primary outcome is 5-year all-cause mortality

BARI 2D: *Sample Size Assumptions*

- Detect 25% reduction in mortality with at least 80% power
- Base rate 16% mortality
- Average patient follow-up is 5 years (range: 4 and 6 years)
- 3% of patients lost to follow-up

Power for BARI 2D

Sample Size=2800



BARI 2D: *Pre-specified Subgroup Analyses*

- Variables will be selected prior to the beginning of trial
- Use $\alpha \leq 0.01$ boundary for significance
- Examples include LV function, creatinine level, history of prior revascularization, receiving insulin at baseline

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BARI 2D MANUAL OF OPERATIONS RECRUITMENT EDUCATION SLIDES

BARI 2D: *Initial Treatment Timetable*

Following patient randomization:

- initial meeting with diabetdogy investigator within 1 week
- if assigned to immediate revascularization, initial intervention to be performed by certified operator/surgeon within 4 weeks

BARI 2D Follow-up: *Diabetologist Visits*

After initial meeting with diabetologist:

- Monthly visits to diabetologist during first 6 months, with additional nurse coordinator contact as needed
- Quarterly visits thereafter
- Extensive data collection (e.g., H_bA_{1c}, microalbuminuria, risk factor goals,...)

Additional Follow-up Data Collection

BARI 2D: *Interim Monitoring*

- Data Safety Monitoring Board will meet every 6 months to review the trial data
- Two primary treatment comparisons will be monitored annually
- Early termination of a treatment comparison will be considered if mortality is significantly worse in one treatment group based on sequential monitoring boundaries

BARI 2D: *Advantages for Patients*

- Intensive management of diabetes, lipids, BP, other risk factors by BARI 2D team
- Periodic follow-up by BARI 2D cardiologists and diabetologists
  - exams, ECGs, stress tests, HbA1c
- Access to diabetic and cardiac medications
- Satisfaction of participating in trial to advance knowledge of treatment of diabetes and CAD.

This Powerpoint presentation is available on the BARI 2D website: www.bari2d.org

8/23/02

CHAPTER SIX

DIABETES PHARMACOLOGICAL MANAGEMENT PROTOCOL

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CHAPTER SIX : SECTION ONE GLYCEMIC CONTROL GUIDELINES

I. GLYCEMIC CONTROL HYPOTHESIS

Hyperglycemia, insulin resistance and hyperinsulinemia are all risk factors for cardiovascular disease (CVD) in Type 2 diabetes. Because hyperinsulinemia is associated with and likely secondary to insulin resistance, these two risk factors may be combined into one in the present context. Although a risk factor is not synonymous with a causative factor, both hyperglycemia and insulin resistance/hyperinsulinemia are the two most prominent metabolic candidates in the causation of CVD. To prove in the human setting that hyperglycemia is likely causative and, more important, that reduction of hyperglycemia decreases CVD outcomes, requires a randomized clinical trial in which two levels of chronic hyperglycemia are compared with intensive treatment versus less intensive treatment, while holding other risk factors particularly insulin resistance/hyperinsulinemia, equal in the two treatment groups. Likewise, to prove that insulin resistance/hyperinsulinemia is causative and that improving this abnormal state decreases CVD outcomes, requires a randomized clinical trial in which insulin resistance/hyperinsulinemia is kept at a lower level in one treatment group than the other by comparing two different pharmacologic treatment strategies, while holding other risk factors, particularly hyperglycemia, equal in the two groups.

Complicating the experimental designs that would address either of these two unanswered fundamental questions is the fact that reduction in hyperglycemia is already known to be of benefit in Type 2 diabetes by decreasing retinopathy and nephropathy, both of which can produce serious morbidity. Choosing two levels of hyperglycemia to compare in addressing the hyperglycemia question or choosing the single level of hyperglycemia to maintain in addressing the insulin resistance/hyperinsulinemia question constitutes a major challenge.

BARI 2 Diabetes (BARI 2D) will test the hypothesis that a treatment strategy which lowers insulin resistance/hyperinsulinemia will lead to a reduction in CVD outcomes, when glycemia is held at standard of care levels known to be beneficial for retinopathy and nephropathy. This question was chosen in preference to the hyperglycemia question for several reasons. First, no randomized trial to date has demonstrated with statistical significance that lowering blood glucose can decrease CVD outcomes. The UKPDS came the closest, observing a 16% reduction ($p = .052$) in myocardial infarction at a mean HbAlc of 7.0% versus 7.9%. Second, the BARI 2D sample size was calculated to provide sufficient power to detect a 25% reduction in CVD events, in the cardiac procedure intervention part of this factorial trial. From UKPDS epidemiological analyses, it can be estimated that a 25% reduction in myocardial infarctions would require a HbAlc difference of l.4% between treatment groups. From Wisconsin Epidemiology of Diabetic Retinopathy (WESDR) data, the required difference in HbAlc might be as great as 2.5%. Such differences would entail significantly different absolute risks of microvascular complications, unless the more intensively treated group could be held to a mean HbAlc less than 6.0%, a difficult feat that thus far has not been achieved in previous trials. Third, an important confounding differential in drug use would likely arise in a glycemic level trial, because insulin would very likely have to be given to the more intensively treated group more often and in larger doses than in the less intensively treated group. If insulin actually has an adverse effect on CVD, this disparity in insulin use could blunt a true beneficial effect caused by reducing hyperglycemia. Fourth, lowering blood glucose is already known to be beneficial in Type 2 diabetes and should be practiced routinely even in the absence of a CVD benefit. Fifth, aggressive, management of hypertension and dyslipidemia are both known to decrease substantially CVD risks in Type 2 diabetes. Whether a small additional benefit from lowering blood glucose can be shown in patients whose blood pressure and serum lipids are kept at optimal levels throughout the trial is problematic. Finally, a positive reason for choosing the insulin resistance/ hyperinsulinemia question is that the UKPDS did observe in an obese sub-cohort a reduction in CVD events with metformin, an insulin sensitizer in the liver, which only reduced mean HbAlc to 7.4%, compared to a control group HbAlc of 8.0%.

II. GLYCEMIC CONTROL TREATMENT STRATEGIES

There are at present 2 classes of pharmacologic agents for the treatment of Type 2 diabetes, which can be characterized as insulin sensitizers, biguanides and thiazolidinediones (TZD). Studies of mechanism of action have shown that the biguanide metformin lowers hyperglycemia by decreasing hepatic glucose production and ameliorating insulin resistance in the liver, as well as by diminishing insulin resistance in peripheral tissues. Troglitazone was the first of the TZD class to gain approval for clinical use and was shown to reduce insulin resistance in skeletal muscle and adipocytes, across the effective blood glucose lowering dose range. This effect may be more potent than that of metformin, whereas metformin appears to have a stronger effect upon hepatic insulin resistance. Combination therapy with both metformin and TZD drugs has been shown to have greater efficacy for lowering hyperglycemia than monotherapy with either agent. Both agents can lower fasting and postprandial triglycerides, and have positive effects on other manifestations of insulin resistance related to cardiovascular risk, such as decreasing plasma insulin levels and plasminogen activator inhibitor – 1 (PAI-1) levels. Troglitazone proved to have serious toxicity in clinical use and has been withdrawn from the market. Pioglitazone and rosiglitazone have since been approved by the FDA because neither appears to cause serious liver toxicity with the frequency of troglitazone. Given the potential link between insulin resistance and CVD, it is important to know whether there is a specific advantage, separate from the potentially beneficial effect of good glycemic control, for emphasizing the use of insulin sensitizing agents in proper management of patients with stable coronary artery disease and Type 2 diabetes.

All patients will be randomly assigned to two treatment arms dubbed IS (increasing insulin sensitivity) and IP (providing more insulin). The IS agents will be metformin and FDA approved TZD drugs. The IP agents will be sulfonylurea drugs, repaglinide and nateglinide, and insulin itself. The use of all these agents will be nominally restricted to patients randomized to the corresponding arm of therapy. Thus sulfonylurea drugs, repaglinide, nateglinide, and insulin will not ordinarily be administered to patients in the IS group; likewise, metformin and TZD drugs will not ordinarily be administered to patients in the IP group. These prohibitions may only be broken if the HbAlc level remains > 8.0% in particular patients, despite using maximum doses of the allowed drugs in those patients' treatment arms. Such drug crossovers will be closely monitored for their appropriateness by the Diabetes Management Center (DMC).

Because the alpha-glucosidase inhibitors (acarbose and miglitol) have an entirely different primary mechanism of action than either insulin sensitizing or insulin providing, they may be used as adjunctive drugs in either in the IP or IS treatment arm. Although drugs in this class do decrease plasma insulin levels slightly when used as monotherapy to lower post-prandial glucose levels, this small effect is deemed an acceptable tradeoff, in exchange for the enhanced ability to maintain excellent glycemic control in both treatment arms.

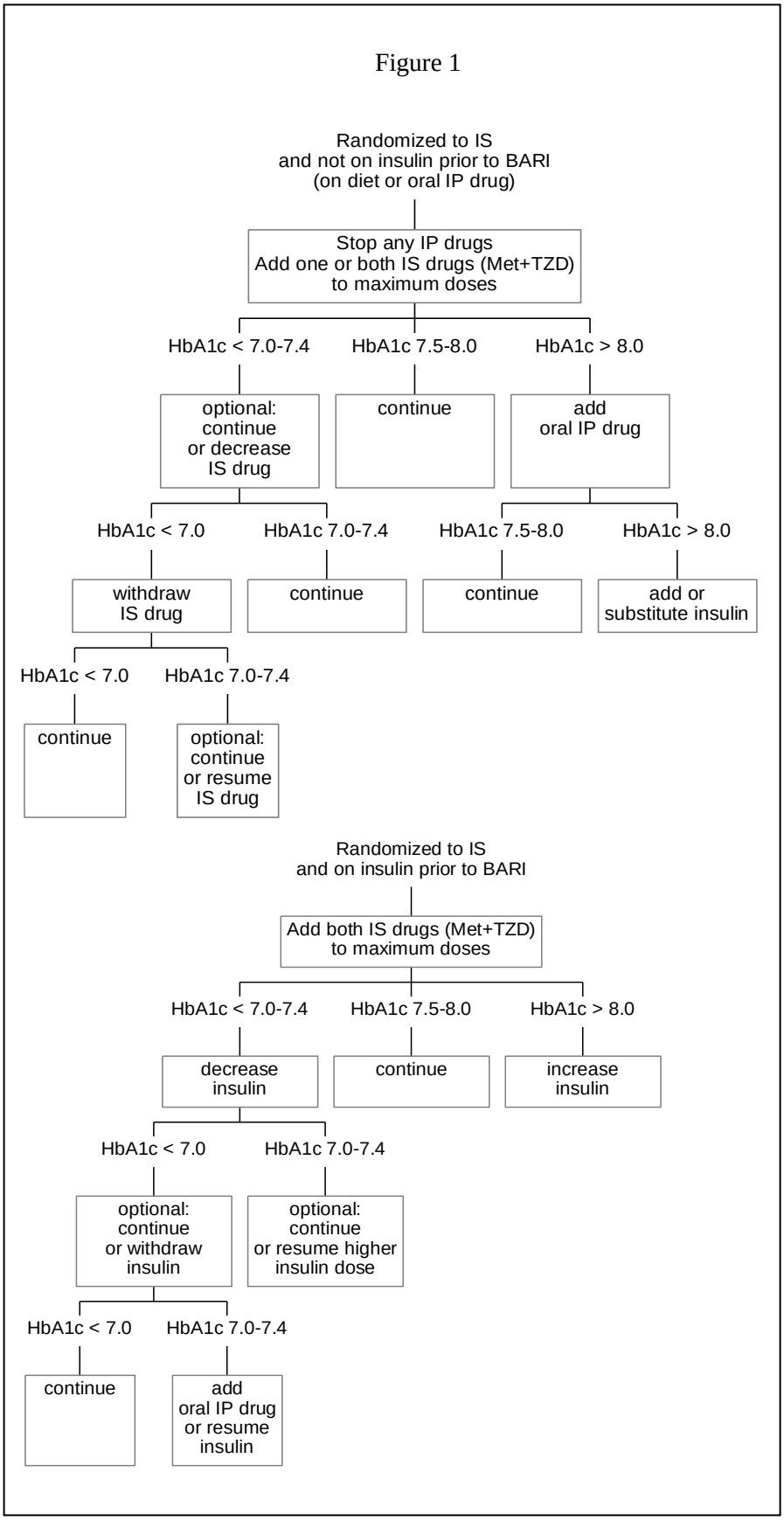
The initial target HbAlc value for all randomized patients will be < 7.0%. This HbAlc value is the current goal recommended by the American Diabetes Association, is similar to that achieved in the UKPDS and Veteran's Administration Study, and is deemed safely attainable in many or most patients with coronary artery disease. The expanded range of antihyperglycemic medications now available will facilitate this therapeutic objective. However, such a target will sometimes require forms of combination therapy that would constitute drug crossovers; IS drugs might be required by an IP patient and vice versa. These cases will reduce the ability to discriminate between the effects on CVD outcomes of increasing insulin sensitivity and the effects of providing more insulin. The BARI 2D goal will be to limit these cases while still striving to provide the benefits of near normal glycemia, with regard to preventing progression of retinopathy, nephropathy and neuropathy, in as many patients as possible.

Prior to entering the trial, the study participants will have been on previous treatment for their diabetes. This may range from diet/exercise alone, to oral IP or IS drugs, to insulin injections and to combination therapy. The goal will be to transfer patients from their pre-entry drugs to only those drugs allowed in the assigned treatment arm, if they are different. The mode of initiation of BARI 2D IS or IP therapy will, therefore, depend upon the patient's prior therapeutic regimen and the randomized treatment assignments they

receive. Whether the patient was previously on insulin therapy or not is the most critical factor influencing the BARI 2D treatment algorithms. Therefore, those particular algorithms are presented in Figures 1-2. Patients previously on IS drugs will have these stopped; either oral IP drugs or insulin will be substituted or added, based upon the entry HbAlc, overall diabetes treatment history, patients acceptance of the initial recommendation, and the investigator's judgment.

It is essential that the median HbAlc of the IP group and that of the IS group be kept closely similar throughout the trial to avoid any confounding that might result from the putative effects of the blood glucose level per se on CVD. Because massive unlimited doses of insulin could theoretically drive HbAlc to < 7.0% in all IP patients, whereas the same outcome is not likely to be accomplished using maximum doses of metformin or TZD drugs in IS patients, a strategy to balance the distribution of HbAlc in the two treatment arms is necessary. This strategy is also illustrated in Figures 1-2. It is expected that patients with relatively high HbAlc on entry will have much greater difficulty achieving a target of less than 7.0% and will more realistically be able to maintain HbAlc level between 7.0 and 8.0%. The latter is the current upper action limit of the American Diabetes Association Standards of Care. Patients with evidence of diabetic retinopathy, nephropathy and neuropathy and/or younger patients will warrant the most aggressive attempts to reach a HbAlc level < 7.0% in order to minimize the risk that those complications will progress during the trial. Barring circumstances such as in the above example, if IP drugs must be given to an IS patient, or IS drugs must given to an IP patient, the HbAlc target will be somewhat moderated in order to limit the doses of crossover drugs and in particular their effects on plasma insulin levels (Figures 1-2).

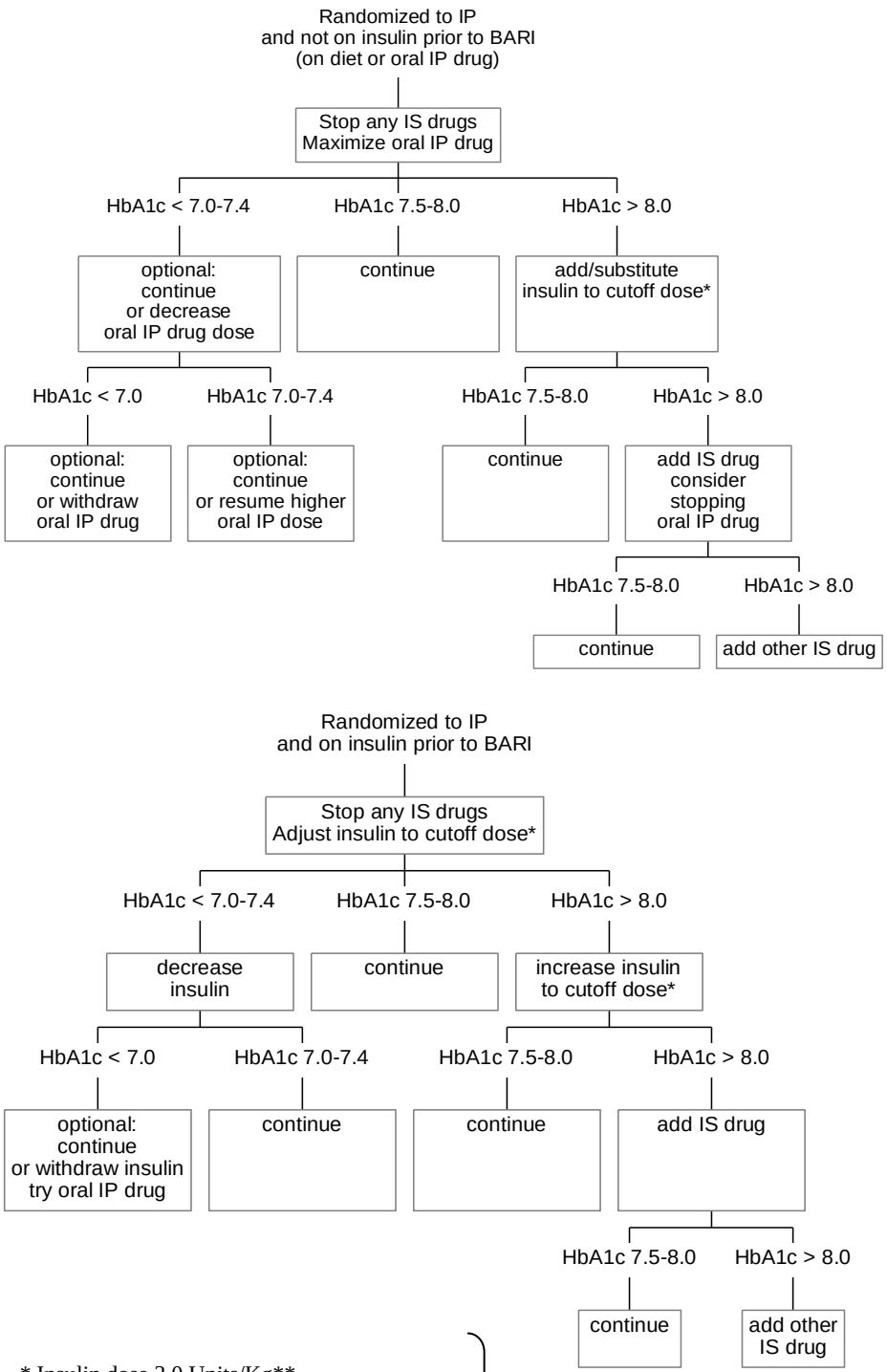
Figure 1



In all patients taking insulin, the frequency, type and doses of insulin injections will be individually determined at the clinical sites. In IP patients, the use of multiple daily injections with doses of pre-prandial short acting insulin based on the before meal blood glucose level and the anticipated number of carbohydrate portions will be emphasized as needed, and the use of IS drugs will be eliminated, avoided or minimized. On the other hand, in IS patients, if insulin or beta cell stimulants are needed, beta cell stimulant or insulin doses will be moderated and the complexity of insulin regimens will be minimized, always seeking to eliminate use of insulin or insulin secretogogues in the IS treatment arm.

In BARI 2D, the preferred TZD is rosiglitazone, which will be provided without cost to participants through arrangement with GlaxoSmithKline. However, rosiglitazone does not have FDA approval for combined use with insulin. The BARI 2D trial has applied for, and received, an Investigational New Drug (IND) waiver from the United States' Food and Drug Administration (IND #62577), and a Control Number from the Canadian Health Products and Food Branch (#073613) for this specific combination use. Investigators in BARI 2D also have the option of using the combination of insulin and pioglitazone, which does have FDA approval. However, at this point, participants in BARI 2D would be responsible for the costs of using pioglitazone. Since rosiglitazone is an insulin sensitizing drug and insulin is by definition an insulin providing drug, we would

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 it can be done safely and without antagonizing the patient.

ideally never use this combination in BARI 2D.

There are, however, two circumstances in which the use of these two agents together may be required, in the best interests of the patients. 1) At entry into the trial, some patients already on insulin therapy will be randomly assigned to the insulin sensitizing arm. Rather than abruptly stop the insulin, which might lead to inordinate hyperglycemia and symptoms (polyuria, polydipsia, blurred vision, vaganitis, etc.), such patients will have rosiglitazone or metformin or both added to their insulin therapy temporarily. Then insulin will be gradually withdrawn as the insulin sensitizing therapy becomes effective. 2) The BARI 2D protocol allows insulin to be given to a patient taking rosiglitazone in the insulin sensitizing arm or rosiglitazone to be given to a patient taking insulin in the insulin providing arm, if such patients' HbA1c levels cannot be brought below 8.0% by any other therapeutic maneuver. This is permitted in order to keep the risk of microvascular complications low and to meet current ADA standards of care. We hope to limit the use of combination therapy for the second purpose to less than 10% of the subjects. In any event, patients with a history or current evidence of congestive heart failure will not be candidates for combined rosiglitazone and insulin therapy.

At entry into BARI 2D and continuing throughout their participation, patients will undergo a comprehensive program of diabetes education, including self blood glucose monitoring, and individualized nutritional counseling. At each center, the diabetes treatment team will be comprised of a nurse coordinator, who has clinical experience with diabetes mellitus, and an experienced diabetologist. The availability of a nurse with certification in diabetes education and a nutritionist will be strongly encouraged. Nutritional interventions will include an attempt at gradual weight loss in patients with body mass index (BMI) > 25 kg/m2 and even more vigorous attempts in those with BMI > 30 kg/m2. For patients who have not been on antihyperglycemic medications, diet plus prescribed exercise may be used as initial treatment. However, these patients will have been randomized to either
IP or IS treatment arms and will receive the appropriate drug therapy, if their glucose control subsequently deteriorates.

During the first 6 months of participation, patients will be seen at monthly intervals by the diabetes team including the diabetologist. Additional contact by phone, fax, or e-mail will be made by the nurse coordinator, as needed to monitor home blood glucose levels and carry out dose adjustments. Patients in the IS treatment arm will be asked to do self-blood glucose testing before breakfast at least 3 days per week. All values will be recorded, using blood glucose meters equipped with memory. Patients in the IP group will be asked to test blood glucose more frequently as needed in order to guide insulin therapy in particular. Patients on multiple daily injections of insulin will be asked to monitor blood glucose 4 times daily. The initial target fasting blood glucose will be 80-140 mg/dl (90-130 mg/dl, if a meter and strips are used which read out in values corrected to plasma levels).

The primary outcome measure of glycemic control will be the HbAlc, which will be measured for data analysis purposes by the central biochemistry laboratory, at baseline, 1 month, 3 month, 6 month and 6 month intervals thereafter throughout the trial. A HbAlc measurement will also be performed with a point of service device at each clinic visit. This local value will be used to guide immediate therapy adjustments and to provide quick feedback to the patient. However, these data will not substitute for central biochemistry laboratory data in the final data analysis. Every six months, a random laboratory plasma glucose determination will be obtained to calibrate the patient's home blood glucose meter and to assess the accuracy of the patient's technique. Home blood glucose monitoring results will be reviewed.

Adjustment of therapy will take into account that steady state values of HbAlc will not be obtained within the frequency of the initial phase of monthly clinic visits. Accurate home blood glucose monitoring will also be used. Mean fasting and pre-prandial blood glucose values within the target range of 80-140 mg/dl (90-130 mg/dl, if a meter and strips are used which read out in values corrected to plasma levels) will be criteria that the present treatment is meeting target levels, provided that the corresponding point of service HbAlc value is either at or is approaching the target level. If HbAlc is well above target despite acceptable pre-prandial glucose values, then selective post-prandial blood glucose testing will be requested and the treatment staff will carefully review the accuracy of home monitoring. If neither home blood glucose values nor immediate HbAlc values

meet the stipulated targets, then doses of the appropriate drugs will be increased or the regimen changed. For oral drugs, if 2 months of maximal doses fail to achieve the target value for glycemic control, then the next step within the treatment algorithm will be employed. The one exception to this may be the use of TZD drugs which are recognized to have a slow onset of action, especially when used as a monotherapy. Drug doses may be kept the same, as long as HbAlc is decreasing.

III. SAFETY OF GLYCEMIC CONTOL

All oral agents will be used in accordance with dose recommendations as recommended by the FDA. Metformin will not be given to male patients with serum creatinine > 1.5 mg/dl or female patients with serum creatinine > 1.4 mg/dl, and TZD drugs will not be given to patients with ALT >2.5 times the upper limit of normal. Safety monitoring will also conform to FDA requirements. An ALT test will be performed bimonthly during the first year of using TZD drugs and quarterly thereafter. Serum creatinine will be measured every 6 months to monitor the safety of metformin therapy and will also be measured prior to and following any intravenous administration of radiographic dye. Metformin treatment will be interrupted as recommended for these procedures.

Particular attention will be paid to the frequency of hypoglycemia, especially of severe episodes. In BARI 2D, severe hypoglycemia is defined as an event characterized by the patient's inability to self-treat, and one of the following two conditions: (i) blood glucose <50 mg/dl determined in a health care facility or a finger stick reading determined by non-medical or EMS personnel, or (ii) confusion, irrational or uncontrollable behavior, convulsions, or coma reversed by treatment that raises blood glucose. Home glucose records will be inspected for episodes of asymptomatic or symptomatic hypoglycemia. Patients and close family members will be educated in the signs, symptoms, and treatment of hypoglycemia and will be encouraged to obtain confirming blood glucose readings whenever possible if hypoglycemia is suspected on clinical grounds. If the hypoglycemia episode experienced by the participant is severe, BARI 2D staff should document the episode and attempt to determine the cause (overdose of medication, delayed or missed meal, reduced meal size, increased physical activity, alcohol consumption, etc.). If a cause for the episode of severe hypoglycemia is identified, a plan should be developed to prevent similar episodes in the future. If a participant experiences more than two episodes of sever hypoglycemia, insulin providing therapy should be reduced as necessary to maintain HbA1c about 7%, as well as self-monitored preprandial glucose between 100 and 140 mg/dL and bedtime glucose between 120 and 160 mg/dL.

Severe hypoglycemia can be expected to occur with greater frequency in the IP treatment group than the IS treatment group. However, data from the UKPDS as well as the Veteran's Administration Feasibility Study indicates an expected prevalence of sever hypoglycemia of 2-3% patients per year, associated with intensive treatment that produces a mean HbA1c of 7.0-7.3%. Much lower incidences of sever hypoglycemia were noted with sulfonylurea drugs and metformin in the UKPDS. For each patient who either is prescribed insulin treatment or has experienced an episode of severe hypoglycemia, whenever possible a family member will be taught to give a glucagons injection for treatment of sever hypoglycemia.

Weight gain is another adverse effect to expected more frequently in the IP than the IS treatment group. In the UKPDS, the average weight gain over 10 years of insulin treatment was approximately 5 kg. Both the prevalence of severe hypoglycemia and of excessive weight gain will be monitored by the DMC. As noted in Figures 1-2, severe hypoglycemia and excessive weight gain will both serve as outcomes that may limit the use of insulin.

The main adverse events for the combined use of insulin and rosiglitazone are hypoglycemia, weight gain, edema, and precipitation of congestive heart failure. Edema was reported in approximately 15% of the patients who took rosiglitazone with insulin, as compared to approximately 5% on insulin alone or on rosiglitazone alone (data on file from GlaxoSmithKline). In the study population, apparently no patient was withdrawn due to edema per se, but there was an increased incidence of new onset or exacerbation of congestive heart failure (CHF). During these trials, 1% of the patients on insulin alone developed new onset or exacerbation of CHF, while 2% of patients on insulin and rosiglitazone at 4 mg, and 3% of patients on insulin and rosiglitazone at 8 mg developed this complication. To forestall CHF, participants in BARI 2D will be monitored by a

diabetologist and a cardiologist on a regular basis (one to three month intervals) and this will include an examination for edema and signs or symptoms of congestive heart failure. Participants will be instructed to call if such symptoms develop between visits. For hypoglycemia, participants will be instructed to perform home glucose monitoring, and to notify the investigators promptly of more than rare low glucose values and of any severe hypoglycemic episode. For moderate weight gain, participants will have regular contact with a nutritionist to help with weight management.

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CHAPTER SIX : SECTION TWO ASSESSMENT OF DIABETES MICROVASCULAR COMPLICATIONS

I. INTRODUCTION

Given the lack of a pure glycemic intervention arm (e.g. tight vs conventional glycemic control) and a common HbA1c goal for all patients (i.e. to a HbA1c of 7.0-7.5%), the scientific rationale for a heavy investment in this area is limited. Nonetheless, it is proposed that simple history and clinical exam measures be collected for retinopathy, neuropathy, and lower extremity arterial disease. In the case of nephropathy, however, a more intensive assessment is proposed, including the collection of multiple urine specimens. The justification for this is the association between microalbuminuria and insulin resistance in both the general and diabetic populations, the BARI 2D hypotheses concerning insulin provision versus insulin sensitization, and the predictive value of microalbuminuria for cardiovascular disease.

II. RETINOPATHY

A. Definitions

Retinopathy is a microvascular complication affecting the retinal vasculature that is associated with loss of vision when proliferative changes occur in the advanced stages and the resulting new vessels rupture, causing bleeding into the vitreous. Patients with diabetes are also at increased risk of macular edema (swelling of the visual "center" of the retina). As both processes can be treated with laser therapy (photocoagulation) in the early stages, with a resulting preservation of vision, one useful clinical endpoint is the need for photocoagulation/blindness as used in the composite UKPDS endpoint. This will be collected annually. After careful consideration, it was decided not to incorporate stereo fundus photography with centralized reading on logistical and economic grounds. Such an approach might have to be limited to a subset of centers, and would require extensive training and certification of photography technicians (even though some centers may have EDIC/DCCT certified technicians available), increase patient burden (a second and/or prolonged visit would be needed) and add considerable expense. Though BARI 2D patients will be referred annually to an ophthalmologist for a dilated eye (fundus) examination, it is not thought logistically, or scientifically, feasible to use these examinations for precise retinal grading.

B. Measurements

1. History of laser therapy, legal blindness

III. NEUROPATHY

A. Definition

Diabetic neuropathy has many manifestations including the common Distal Symmetric Polyneuropathy with glove and stocking distribution of early sensory loss and dysathesiae, combined with decreased deep tendon reflexes. Consideration was given to the DCCT clinical definition based on two of three findings, namely:

1. Consistent Symptoms (numbness, parathesiae, dysathesiae, hypersensitivity, stabbing/aching/burning pain, ankle weakness, muscle cramps).
2. Consistent Signs (decreased vibratory sensation and/or pin prick/light touch).
3. Decreased or absent reflexes in the absence of any other more likely cause.

However this and similar clinical exam protocols are difficult to standardize and also are time consuming.

The Michigan Neuropathy Screening Instrument is a validated assessment of DSP, which is being utilized in EDIC and many other studies. It consists of a series of 11 questions and a brief examination (visual foot examination, tuning fork vibration, ankle reflex, and monofilament testing). The procedure takes approximately 10 minutes in all (including the questions). The clinical examination portion has, for a score of 2 or more (out of 8), a high specificity (95%) and sensitivity (80%) for detecting neuropathy (as defined by Mayo Clinic, stages 1-3), and is recommended for inclusion.

B. Measures

1. Annual MNSI questions and clinical exam

IV. NEPHROPATHY

A. Definition

Diabetic nephropathy is classically determined clinically by proteinuria (dipstick positive, i.e. 300 mg albumin/24 hrs or ≅ 500 mg protein per 24 hrs). A sometimes reversible, intermediate stage, microalbuminuria is also seen (30-300 mg/24 hr), which interestingly is also a feature of insulin resistance and a marker of enhanced cardiovascular risk in both diabetic and non-diabetic subjects. This diabetes complication (albuminuria) is, thus, of central interest to BARI 2D. Though proteinuria is the hallmark of diabetic neuropathy, it may not always closely correspond to renal function (measured ideally by GFR testing, e.g. Iothalamate clearance) or less accurately, creatinine clearance, based on a 24-hour urine collection. Thus, in the more advanced stages of diabetic nephropathy, progression of renal disease is best determined by measures of function, e.g. GFR, or its surrogate marker, serum creatinine. A doubling of serum creatinine is, also, commonly used as a progression and/or endpoint measure in trials in advanced renal disease. However, it is unlikely in BARI 2D that there will be a sufficient number of advanced cases to permit meaningful use of either GFR measures or creatinine. Nonetheless, annual creatinine measures should be made as they are inexpensive and are indicated in many cases as a safety measure for metformin users. It has become increasingly accepted to use an albumin/creatinine (A/C) ratio in a spot urine sample (e.g. during a clinic visit) as a screen for microalbuminuria. We will thus also obtain annual measures of albuminuria using the A/C ratio from spot clinic urine samples. This will be the primary renal outcome, with categorical outcomes defined as microalbuminuria A/C ratio of >0.03 and <0.31 (:g/mg) and overt nephropathy A/C ratio of >0.31 (:g/mg). This will be determined at the annual visit using the DCA 2000 A/C assay along with regular dip stick for proteinuria. An aliquot of urine will also be frozen and sent to the CBL.

B. Measures

1. History of ESRD
2. Annual Serum creatinine
3. Annual albumin/creatinine ratio, measured locally for clinical purposes and centrally for study outcomes.

V. PVD (I.E. LOWER EXTREMITY ARTERIAL DISASE)

A. Definition

As BARI 2D subjects all have CAD, it could be argued that a measure of LEA disease is of little benefit as an indicator of atherosclerosis. However the glycemic treatments may differ in their effect on LEAD incidence and progression and it is therefore recommended that the procedures below be adopted.

Obstructive LEAD can be clinically assessed by symptomatology (e.g. intermittent claudication – IC) and clinical signs (e.g. absent or diminished pulses). These measures are, however, weak in terms of validity, reproducibility and inter-observer variation. In addition to clinical examination, the need for revascularization procedures, which could be validated by hospital records, and amputation for vascular cause will be recorded. A further, more advanced and, therefore, less frequent outcome would be foot ulcers, often a mixed vascular/neuropathic occurrence. As the clinical assessment of ulcers is difficult to standardize, we propose limiting our assessment of this feature to hospital admission for diabetic ulcer therapy (again validated by hospital records). As this is a major cause of health care expense for those with diabetes, this endpoint would also have economic importance.

In addition to the above, measurement of the ankle brachial index (ABI) will be performed. This measure of subclinical LEAD is now commonly used in many diabetes trials including DPP and EDIC. While it requires central training and certification, it is a fairly time and cost effective procedure taking approximately 10 minutes to perform and only minor cost (approximately $500 for an ultrasound doppler stethoscope). It can be reliably performed by trained nurses or clinical research assistants. It also has the advantages of providing: a) a subclinical measure with its resulting higher frequency than the advanced clinical endpoints listed above, and b) a continuous measure allowing, again, post-pre mean group differences being compared across intervention groups. The categorical outcome would be defined as an ABI <0.9 in any of the four ratios measured (e.g. right brachial/right posterial tibial; right brachial/ right dorsalis pedis; right brachial/left posterior tibial; right brachial/left dorsalis pedis). Progression could be compared across groups by post-pre ABI taking the greatest post-pre difference for each subject from the four available.

B. Measures

1. Annual query for hospitalizations, with hospital record validation of:
    a. LEA revascularization
    b. Amputation for vascular cause
    c. Ulcer treatment
2. Annual ABI

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CHAPTER SIX : SECTION THREE MANAGEMENT OF GLUCOSE DURING ACUTE HOSPITALIZATIONS

I. INTRODUCTION

Rigid glucose control, using insulin-glucose infusion to stimulate cellular glucose uptake and lower plasma free fatty acid concentration, has been shown to reduce mortality in patients with acute myocardial infarction. Other investigators have observed that the degree of hyperglycemia on admission contributed significantly to the length of hospital stay among patients admitted with acute medical problems such as pneumonia and acute MI. While diabetic patients are at two to four times higher risk for macrovascular complications, even patients with impaired fasting glucose (fasting glucose between 110 and 126 mg/dl) are at a higher risk of macrovascular events, compared to those with fasting glucose less than 100 mg/dl. It is therefore important to maintain very targeted glycemic control in our high-risk study patients during episodes of acute hospitalizations.

II. GENERAL CONSIDERATIONS

When a study patient undergoes a planned intervention (e.g., CABG or a percutaneous coronary intervention) or is hospitalized for another reason, the study diabetologist should be contacted whenever possible. The study diabetologist needs to determine whether the acute condition requires discontinuation of the study drug regimen. If not contraindicated, the study medication should be continued. This decision will be made on a case by case basis by the study diabetologist in consultation with the health team responsible for the patient's care during the hospitalization. On the other hand, there are conditions requiring acute hospitalization (i.e. surgery, acute CVD event, etc) for which it is clear that oral antihyperglycemic therapy is inadequate or contraindicated. In this case, the study diabetologist should be consulted to help in the management of the glycemic control.

III. SUGGESTED PROTOCOLS

It is suggested that when a study patient is admitted for cardiovascular surgery (e.g., CABG), a cardiovascular event, severe medical illness, or other non-cardiovascular surgery, the study regimen should be stopped and insulin therapy implemented. When determining the goals for glycemic control, the considerations are to avoid hypoglycemia and/or severe hyperglycemia. It is desirable to maintain targeted glucose levels in the 100-175mg/dl range. This range will allow for avoidance of the acute metabolic complications of diabetes, maintenance of fluid and electrolyte balance, and optimization of wound healing and WBC function.

A. Intravenous Insulin Regimens

As studies demonstrate the importance of glycemic control and the feasibility of achieving control with intravenous insulin, it is suggested that if the clinical and the institutional situation permits, the study patient be placed on intravenous insulin therapy. This may be particularly important following CABG or a percutaneous coronary intervention. A standard solution of 250 units human regular insulin in 250 of .45% NaCl is suggested for initial therapy. The initial insulin infusion rate can be set by the study diabetologist or from the attached insulin infusion algorithm. The insulin infusion rate should be progressively increased by increments for each glucose level $\geq$ 200 mg/dl if glucose does not decrease into goal range. This decision should be based on the results of bedside capillary glucose monitoring and requires frequent, regular and rapid determination of blood glucose levels.

During insulin infusion, it is recommended that glucose levels be done hourly until the glucose levels have stabilized in the goal range of 100-175mg%. Frequency at that time can generally be decreased to every 2-4 hours depending on the clinical situation. A representative order sheet for intravenous insulin infusion is attached. After stabilization of the acute event, the intravenous insulin dosing should be converted to a subcutaneous regimen consisting of BID intermediate insulin mixed with short-acting insulin. In some cases, this may appropriately serve as the suggested discharge regimen until the patient is seen and placed back on the randomized study regimen. In other instances, the study regimen may be resumed prior to discharge.

B. Subcutaneous Regimens

Whereas intravenous insulin infusion would be considered the preferred regimen for study subjects admitted for hospitalization, unfortunately, this may be limited to the setting of intensive care units or step down units depending on the policy of the hospital. Further, it may be limited by the training of the nursing staff. In addition, a study subject may have been admitted to an outlying hospital where the physician is uncomfortable in using intravenous insulin therapy. In this case, the following guidelines for insulin use can be given. If the individual is on combination insulin and oral agents, the oral agents should be stopped and patient continued on his usual insulin regimen. If the patient is NPO, preprandial short acting insulin is discontinued and intermediate acting insulin may be either substantially reduced (i.e., generally by 50%), or discontinued. In many instances it is appropriate to continue long acting insulin use as part of a "basal bolus" program, and supplemental insulin coverage provided through administration of regular insulin SQ every 4 hours is commonly needed to achieve glycemic goals (100-175 mg/dl). A common error committed in the inpatient setting is discontinuing previously established dosages of intermediate-acting insulin in the patient whose caloric intake is unpredictable. Insulin requirements may rise in the setting of acute illness from several mechanisms. However, caloric restriction may result in significant lowering or elimination of the need for intermediate acting insulin. Thus, the decision to maintain depot insulin therapy (BID NPH, ultralente) must be based on close monitoring of glucose. An assessment for supplemental short-acting insulin dosing is required. Sliding scale regimens have been used for decades for inpatient glycemic control, but sliding scale regimens are non-physiologic and rely upon retrospective treatment of blood glucose. It is suggested and preferable that insulin be given in anticipation of upward glycemic excursions in order to prospectively keep glucose levels within an individual's target range.

IV. POST HOSPITALIZATION COURSE

Under the guidance of the study diabetologist, regardless of whether intravenous or subcutaneous insulin is chosen initially in the management, it is anticipated that all patients may need BID intermediate/regular insulin for glycemic control for several weeks post hospitalization. During this limited outpatient period, the coordinator/study nurse should make phone/clinic contact to adjust dosing to keep blood glucose in the target range, and plans be made to switch the subject back to the randomized study medicine as soon as the patient's condition allows.

V. MANAGEMENT ISSUES

It is imperative that once study subjects are admitted, that the clinical center's diabetologist and/or cardiologist be notified. Whereas this may not be a problem if the patient seeks care at the facility the study is based, it may be problematic if the subject is admitted to an outlying hospital. In that case, patients should be instructed to inform their attending physician of participation in BARI 2D, and provide contact information for the clinical center's diabetologist and/or cardiologist. In this way, guidance from the study site to the outlying facility can help facilitate a more consistent treatment regimen across all clinical centers.

CHAPTER SIX : SECTION FOUR DIABETES MANAGEMENT CENTER (DMC) OPERATIONS

The BARI 2D Coordinating Center (CC) will forward data to the DMC to track all patients regarding their HbA1c measurements from baseline on. The CC will calculate and track both an overall BARI 2D average (and median) and a one-year moving average (and median) for each patient. This will provide an overall and a contemporary updated glycemic control profile for each patient. The CC will forward the number and dates of all severe hypoglycemic events as well as the body weight and BMI recorded at each clinic visit. In addition, the CC will calculate the mean value of each of the above glycemic profile parameters for every BARI 2D clinical site every two months. All the above data will be provided to the DMC on a timely basis in the following fashion: As a single histogram of all BARI 2D subjects trial wide; as separate histograms of all the subjects within each clinical site; and as a single histogram of the mean/median HbA1c values of each clinical site. Accompanying these histograms will be tables of the distribution of each parameter that indicates the 10th, 25th, 50th, 75th, and 90th percentile values. All of the above analyses will be carried out separately for the two treatment strategies, IP and IS, and, within each treatment strategy, by whether patients were previously on insulin or not. In similar fashion, adverse event rates (hypoglycemia, excess weight gain, serious drug side effects) will be tabulated. The identity of each clinical site in these reports will remain anonymous unless the DMC considers it necessary to take some action regarding the performance of a particular clinical site.

A survey of the above HbA1c data will enable the DMC to judge the quality of glycemic control being provided to all the BARI 2D patients, to the BARI 2D patients at each clinical site, and the comparative performance of each clinical site. Clinical sites with mean/median HbA1c values greater than 7.5% or above the 90th percentile for all the clinical site mean/median HbA1c values will be prospects for investigation by the DMC with regard to the adequacy of treatment and treatment effects. Clinical sites with mean/median HbA1c below the 10th percentile for all clinical sites will be prospects for investigation with regard to the safety of treatment, i.e. the frequency of severe hypoglycemic events and the frequency of inordinate weight gain. When adverse events are deemed to be too frequent (greater than the 75th percentile of all the clinics), the adequacy of patient education and of nutritional counseling and the appropriateness of drug use will need to be investigated at any such clinical site.

To ascertain drug use, a standardized form will be used at each clinical site with a drug checkoff list; the form will be updated whenever a new drug for treating Type 2 diabetes is introduced into the protocol. The study coordinator at each clinical site will record the start and discontinuation dates of each drug used for glycemic control. These data will be sent to the CC, which will maintain in its database the drug use history of each BARI 2D subject from entry on and updated periodically.

In its report to the DMC, the CC will calculate the percentage of subjects using each drug for the entire BARI 2D subject population and the same percentages will be calculated for the subjects in each individual clinical site. In addition, the DMC will calculate the mean/median months of drug exposure for each drug over the entire BARI 2D subject population and for the subjects in each individual clinical site. Tables of the percentage of patients using each drug and of the months of drug exposure will be stratified by the two treatment groups, IP vs IS. These data will allow the DMC to monitor adherence to the BARI 2D protocol and specifically monitor the degree of crossover of IP drugs into the IS group and crossover of IS drugs into the IP group. While some crossover will likely be inevitable in order to reach the HbA1c target in all patients and to avoid adverse drug effects (such as severe diarrhea from metformin), the DMC will work to minimize such drug crossovers. Clinics in which more than 20% of the patients in the IS arm are using IP drugs or clinics in which more than 20% of total drug exposure in the IS arm is accounted for by IP drugs will be queried by the DMC. Crossover of IS drugs into patients

in the IP arm, which is expected to be less frequent, will be queried by the DMC if it exceeds the rate of 10% (instead of 20%). The purpose will be to determine whether unusually high rates of drug crossover are justified by the need to achieve the HbA1c target or if they reflect a lack of adherence to the BARI protocol because of misunderstanding or bias.

The accuracy of drug use data will be critical to the final analysis comparing cardiovascular events and mortality between the IS and IP groups. Since these data will be provided by the BARI 2D clinical sites, it would be prudent for the DMC to conduct site visits for auditing. Although ideally each clinical site should be audited once, the expense, effort and time required would be excessive. The DMC therefore proposes to undertake auditing one-fourth to one-third of the clinical sites chosen randomly throughout the trial and any additional sites where the clinical site performance raises serious concerns. These visits should be made on relatively short notice. The site team should be provided a random sample of subject ID numbers constituting a significant proportion of all of that clinic's subjects. The site visit team would then review the actual clinic charts of those randomly chosen subjects, comparing the drug use and other glycemic control information to print outs of the same data that had been previously provided to the CC. Discrepancies would be noted and discussed with the clinic staff, seeking explanations and resolution. A written report would be provided to the DMC by the site visit team and appropriate actions would be taken by the DMC to correct any errors in clinic procedures or operations. If inadequate clinic leadership is deemed to be a problem, the matter will be referred to the CC.

Diabetes Treatment Committee: The plan for monitoring glycemic control and the implementation of treatment strategies cannot be carried out by a single individual. A BARI 2D Diabetes Treatment Committee will be constituted to serve under the director of the DMC. This committee would initially be composed of 5 senior diabetologists participating as clinical site investigators in BARI 2D and 5 diabetes nurse coordinators working at BARI 2D clinical sites as well as a cardiologist liaison. The bi-monthly reports from the CC to the DMC would be first reviewed by the DMC director and then distributed to the Diabetes Treatment Committee. This would be followed by a routine regularly scheduled (at least bimonthly) telephone conference call during which the committee would discuss the overall progress of glycemic control in BARI 2D and any problems apparent at individual clinic sites. Ad hoc telephone conference calls would also be conducted if urgent problems arose. In these calls, decisions would be taken and action plans formed. The members of this committee would share in the work of remediating inadequate clinic performances in any of the above spheres and would also participate in auditing or problem solving site visits. For practical, tactical, and even professional political reasons, it is desirable that both clinical diabetologists and diabetes nurses share in this oversight function. It is important that in the beginning, the Diabetes Treatment Committee should consist of individuals who are well respected in the diabetes clinical research community. This will help ensure that their questions, investigations, suggestions, criticisms and decisions are accepted in a constructive positive spirit. Later, other BARI 2D diabetologist investigators and diabetes nurse coordinators may rotate onto the Diabetes Treatment Committee as the study progresses, although members of the committee should serve for at least two years. This will help ensure that there is a strong core and an increasing number of BARI 2D investigators and nurses who are concerned with and involved in the operation of BARI 2D outside of their own clinics, and who are committed to the overall success of BARI 2D.

The DMC will have two other important responsibilities to fulfill. The first will be to help the CC prepare its reports to the NHLBI-appointed DSMB for BARI 2D. The second will be to give the entire BARI 2D Steering Committee a periodic progress report on the glycemic control achieved and the implementation of the IP and IS treatment strategies at BARI 2D Steering Committee meetings. This feedback will afford all investigators an opportunity to discuss this critical aspect of BARI 2D and offer suggestions to the DMC director for improvement in its monitoring procedures or in the diabetes management techniques being employed. In addition, the DMC will arrange educational sessions at the annual BARI 2D meeting, as new drugs or techniques for Type 2 diabetes management appear that would contribute to the success of glycemic control in the IP and IS treatment groups.

CHAPTER SEVEN

CARDIOVASCULAR PHARMACOLOGICAL AND HYPERTENSION MANAGEMENT PROTOCOL

SECTION ONE: **MEDICAL THERAPY GUIDELINES**

SECTION TWO: **MANAGEMENT OF HYPERTENSION**

SECTION THREE: **CARDIOVASCULAR PHARMACOLOGICAL AND HYPERTENSION MANAGEMENT OVERVIEW**

- **HYPERTENSION ALGORITHM**
- **BACKGROUND MEDICAL THERAPY**

SECTION FOUR: **HYPERTENSION MANAGEMENT CENTER (HMC) OPERATIONS**

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CHAPTER SEVEN : SECTION ONE MEDICAL THERAPY GUIDELINES

I. 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 antianginal therapy unless symptoms occur. The basic strategy will be 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. The specific details for cardiovascular pharmacological and hypertension therapy dosage are outlined in the flow charts that follow. 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, and other therapy/interventions as described below. Beta-blockers, ACE inhibitors, and aspirin will be standard ("background") medical therapy for all BARI 2D patients, unless contraindicated.

II. ANTI-ANGINAL AND ANTI-ISCHEMIC THERAPY

A major objective of BARI 2D is to ascertain whether adding revascularization to a baseline therapy of aggressive medical treatment results in improved outcomes among diabetic patients with stable symptomatic coronary artery disease. All patients, therefore, will be treated with the same guidelines for drug selection and/or dose medication to reduce symptoms of angina and/or ischemia.

There are numerous considerations which will impact on such guidelines given the particular patient population in BARI 2D and the manner in which anti-anginal drugs are likely to be used in each treatment arm. First, patients with diabetes may have a defective anginal warning system making the goal of therapy ambiguous in individual patients. To accurately test the primary hypothesis of BARI 2D, medical therapy can be considered "aggressive" when it reduces or eliminates angina, symptoms construed to be angina (anginal equivalents) and/or episodes of ischemia. Secondly, anti-anginal drugs can affect diabetic patients in a number of important ways. Beta-blockers can mask warning signs of hypoglycemia and interfere with the management of diabetes. Nitrates and calcium channel blockers can produce hypotension if diabetes-related autonomic neuropathy is present. Furthermore, medical therapy will be used differently in each treatment arm. Patients randomized to revascularization are likely to have fewer anginal symptoms (at least initially) and need less medication(s) whereas patients randomized to medical therapy alone will likely require more medication(s) with dose adjustments at more frequent intervals.

A cornerstone of anti-anginal treatment for all patients in BARI 2D will be beta-blockers. Cardioselective beta-blockers are recommended as these agents tend not to elevate glucose or retard glucose recovery in the setting of hypoglycemia compared to non-selective beta-blockers. Furthermore, numerous clinical trials and observational studies of beta-blocker treatment in diabetic patients have established a major survival benefit when these agents are used as secondary prevention. To assure adequate beta-blocker effect, a target heart rate of <60 bpm with treatment will be required unless contraindications exist (e.g. asthma, bradycardia, atrio-ventricular block, systolic blood pressure < 100 mmHg) or previous

intolerance to beta-blockers has been established. Attainment of this benchmark heart rate (even though angina may have been eliminated) assures a dose that has been shown to offer secondary protection and provides further suppression of ischemia if asymptomatic episodes are still present. In UKPDS, the incidence of clinically significant hypoglycemia was <2% with a similar target HbA1c as in BARI 2D. Recent data has shown that the use of cardioselective beta-blockers in hypertensive type 2 diabetes was associated with a rate of serious hypoglycemia comparable to ACE-inhibitors.

If symptoms of angina or ischemia persist despite the use of beta-blockers, long-acting nitrates can be added. Oral formulations of long-acting nitrates are preferred compared to topical nitrates to facilitate standardization of doses among patients. Patients will receive instruction on the prophylactic use of sublingual nitroglycerin prior to anticipated triggers of angina or anginal equivalents. Calcium channel blockers can also be added to the combination of beta-blockers and long-acting nitrates as needed. Use of a non-dihydropyridine calcium channel blocker such as diltiazem or verapamil will require careful monitoring for symptomatic bradycardia as many patients will likely be on a dose of beta-blocker sufficient to reduce resting heart rate to <60 bpm. Amlodipine may be preferred under these circumstances. A maximally tolerated dose of a long-acting nitrate or calcium channel blocker will be defined as that dose that either reduces or eliminates angina or produces intolerable side effects. Anti-ischemic medications will be titrated over 4-8 weeks to maximally titrated doses.

It is likely that many patients in BARI 2D will have been on one or a combination of anti-anginal drugs at the time of enrollment. It is also likely that these drugs in many cases will not be at their maximally effective or tolerated doses. The initial modification of an existing drug regimen will be to maximize the dose of beta-blocker followed with adjustments of nitrates or calcium channel blockers as necessary.

III. ANTI-THROMBOTIC THERAPY

All patients will be on enteric coated aspirin 325 mgm per day unless contraindicated or not tolerated. The beneficial effect of aspirin in reducing cardiac events in diabetics is established. For those who do not tolerate aspirin at the dosage of 325 mg per day, a lower dosage of 81 mg per day will be instituted. Lower doses may be applied, but it appears that antiplatelet effects of aspirin are reduced in patients with hyperglycemia. All patients will be instructed in the importance of prompt attention to symptoms of impending myocardial infarction with emphasis on early institution of reperfusion therapy. Reperfusion may be achieved by either thrombolytic therapy or primary percutaneous coronary intervention based on the availability of resources.

IV. NEED FOR SUBSEQUENT REVASCULARIZATION

Crossover from the medical arm to a revascularization procedure is recognized as a serious concern of the investigators, and the medical management working group will monitor crossover rates throughout the follow-up of the trial. While the decision whether to revascularize an initially medically treated patient will always be based upon best medical judgment, the following represents a framework for judging the need for an invasive intervention in those patients randomized to initial medical therapy without an initial revascularization procedure. Such crossovers may be justified if:

1. Severity of angina progresses to unacceptable levels in spite of medical therapy adjustments to provide control of angina. All such patients should have been on triple therapy (i.e. beta blockers, nitrates and calcium channel blocker) with adjustments in dose to provide maximal therapy.

2. Acute coronary syndrome with hemodynamic instability. In such patients, if initial efforts to stabilize the patients are not successful, repeat angiography and revascularization may be the best medical management and should be accomplished without undue delay. In those

presenting with acute myocardial infarction and ST elevation, primary PTCA may be judged to be the preferred initial management rather than thrombolytic therapy; if so, proceeding without undue delay is appropriate.

3. Severity of anatomic disease to justify a revascularization procedure and noninvasive stress testing which demonstrates severe ischemia defined as the results of testing listed below:

    a. 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 as having severe ischemia if the ischemic changes occur within the first 6 minutes and the patient is judged to be a candidate for revascularization.

    b. Exercise myocardial perfusion imaging: 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.

    c. Non-exercise stress myocardial perfusion imaging: multiple reversible defects and one reversible and one fixed defect.

    d. Exercise radionuclide ventriculography: resting ejection fraction $\geq$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 $\geq$0.50, with a severe ST segment response and work load <450 kpm.

In all such decisions, patient safety and well being is the primary concern and any crossover should be consistent with current ACC/AHA guidelines for revascularization procedures.

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CHAPTER SEVEN : SECTION TWO MANAGEMENT OF HYPERTENSION

It is estimated that 50% of patients with newly diagnosed Type 2 diabetes mellitus will have hypertension. Hypertension in such patients will account for 35-75% of diabetic-related cardiovascular and renal complications. Aggressive blood pressure control with lower target blood pressures in diabetic patients has been recommended as an important strategy to prevent and/or retard the progression of cardiovascular morbidity and mortality. It is likely that up to 70% of patients enrolled in BARI 2D will have hypertension, and incorporation of these recently recommended treatment guidelines represents a cornerstone of medical care for these patients who are at very high risk for early cardiac mortality as significant coronary artery disease has already been established.

A blood pressure level >130 mmHg systolic or >80 mmHg diastolic is the definition of hypertension and will be considered the target level for non-pharmacologic and/or pharmacologic treatment. At study entry, patients will be specifically questioned regarding prior history, duration, and treatment of hypertension. Blood pressure will be measured using an appropriately sized cuff after 5 minutes of rest and recorded to the nearest 2 mmHg for systolic and diastolic levels. As outlined in Sixth Joint National Commission (JNC VI), blood pressure will be recorded in the supine, sitting and standing positions as patients with Type 2 diabetes may have decreased baroreceptor sensitivity and/or autonomic neuropathy resulting in postural hypotension. Sitting blood pressure will be regarded as the level of diagnosis and/or treatment. The level of blood pressure and the diagnosis of hypertension will be based on measurements obtained on 3 occasions at the same time of day over 8-12 weeks. All patients will receive counseling on lifestyle modifications including: a) physical activity, b) reduction of sodium intake, c) smoking cessation, d) weight reduction, and e) modification of alcohol intake. Failure to achieve target blood pressure level, 130/80 mmHg after 3 months in patients not already diagnosed with hypertension on pharmacologic treatment at the time of enrollment in BARI 2D will result in the initiation or modification of pharmacologic treatment. The response to treatment will be assessed at clinic visits every 3 months.

As stated in the JNC VI, ACE inhibitors, alpha-blockers, diuretics in low doses, and calcium channel blockers are preferred because of fewer adverse side effects on glucose metabolism, lipid levels, and renal function. Most patients in BARI 2D will be treated with beta-blockers either as treatment for angina pectoris or as secondary prevention for CAD events. If hypertensive, such patients may have the dose of beta-blocker increased to achieve target blood pressure level. Caution is warranted, however, as beta-blockers in diabetic patients may reduce peripheral blood flow (incur or exacerbate symptoms of claudication), mask warning signs of hypoglycemia, and/or impair recovery of glucose in the setting of hypoglycemia. Adding another drug is a more prudent approach in these patients, particularly if the dose of the prescribed beta blocker is sufficient to provide secondary prevention against CAD. ACE-inhibitors will be preferred in patients with diabetic nephropathy. In the event ACE-inhibitors cannot be used, calcium channel blockers may also offer renoprotection. In this regard, the recently published results of the UKPDS demonstrated that in Type 2 hypertensive diabetic patients, rates of development of albuminuria, 2-fold increase in creatinine, or end-stage renal failure were similar in the cohorts assigned to either capatopril or atenolol indicating that successful blood pressure lowering may be the key variable in renoprotection and not necessarily the particular drug chosen. Angiotensin II inhibitors can be used in the place of ACE-inhibitors in the event of side effects or contraindications.

It is probable that the majority of hypertensive patients in BARI 2D will require two or more drugs to attain the target blood pressure of 130/80 mmHg or less. In UKPDS at 9 years of follow up, over 60% of

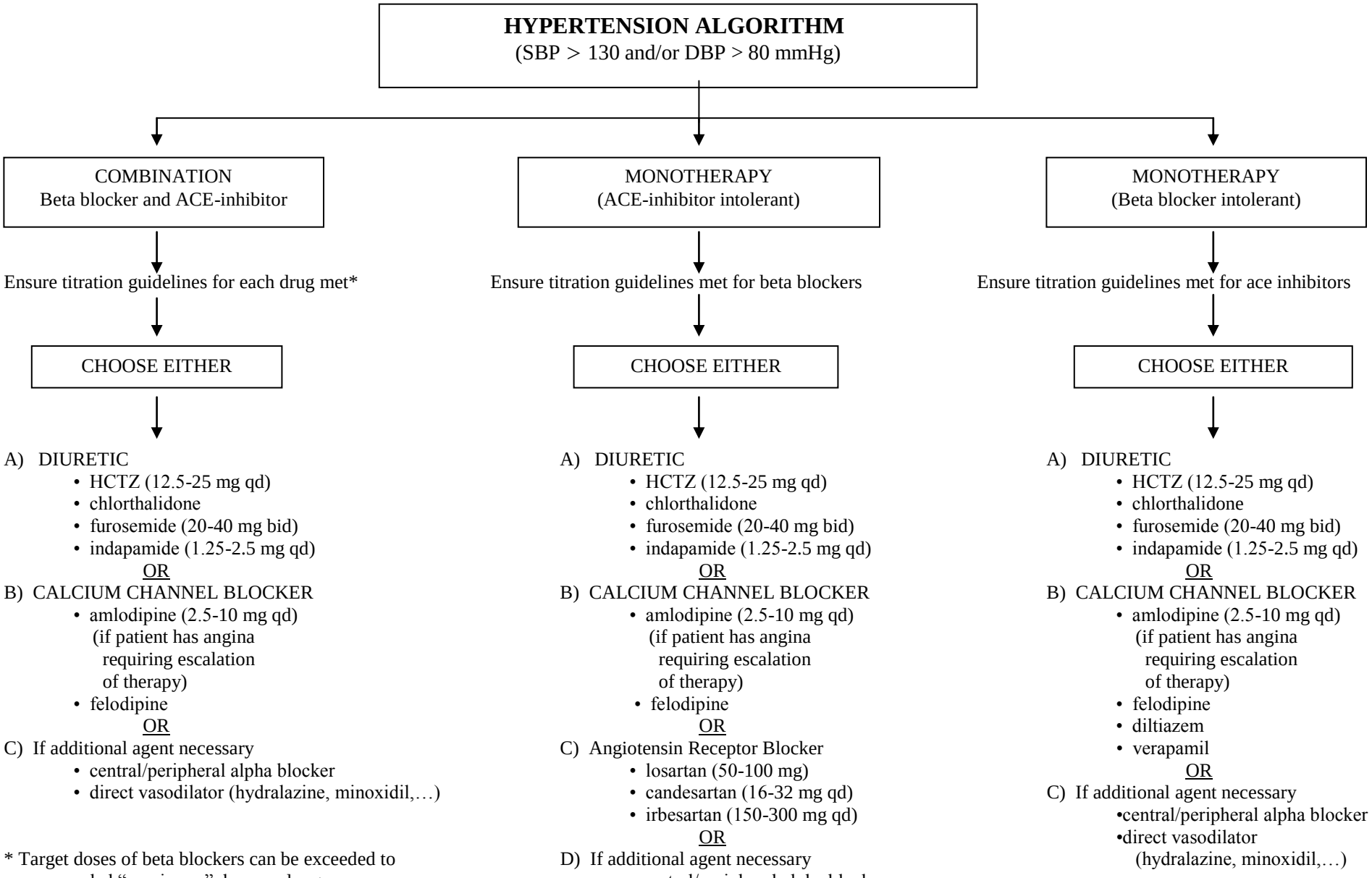
patients assigned to tight blood pressure control required 2 or more drugs to achieve a target blood pressure <150/80 mmHg - a level substantially higher than the currently recommended target level of ≤130/80 mmHg to be used in BARI 2D. Compared to the patients in UKPDS for whom diabetes was a new diagnosis, BARI 2D patients will be older, have established diabetes, and will have had hypertension a longer period of time increasing the likelihood that multiple antihypertensive drugs in combination will be required.

Numerous and recent clinical trials have established the classes of antihypertensive drugs effective in reducing total and particularly cardiac mortality in patients with Type 2 diabetes mellitus. UKPDS has shown that a tight blood pressure control policy with either an ACE-inhibitor (captopril) or a beta-blocker (atenolol) reduces microvascular disease, stroke, and heart failure with a non-significant reduction of risk (21%) in myocardial infarction. The SHEP trial indicated that in the subgroup of elderly hypertensive subjects with diabetes, diuretic (thiazide) treatment was associated with a significant reduction in cardiovascular events. In patients with proteinuria, ACE-inhibitors may be preferred based on their ability to retard the progression of diabetic nephropathy, particularly in Type 1 diabetics although a singular benefit of ACE-inhibitors in this setting has recently been questioned.

It is quite likely that a substantial number of patients in BARI 2D will be on calcium channel blockers. Part of the indication for coronary arteriography in these patients will be persistent angina despite calcium channel therapy. Furthermore, the need for several drugs to lower blood pressure will lead to the prescription of this class of drugs in many patients. Several trials such as ABCD and FACET have indicated a higher relative risk of myocardial infarction with calcium channel blockers (nisoldipine, amiodipine respectively) compared to ACE-inhibitors (enalapril and fosinopril respectively) despite equipotent ability to lower blood pressure in Type 2 diabetic patients. Analysis of the diabetic subgroups in other large clinical trials, however, have not suggested an adverse cardiovascular mortality in hypertensive diabetic patients. The HOT study and Syst-Eur trial demonstrated a reduction in cardiovascular mortality with calcium channel blocker treatment (felodipine and nitrendipine respectively) for hypertension in the subgroups of diabetic patients. Furthermore compared to placebo, amiodipine did not increase mortality in diabetic patients with class III or IV CHF in the PRAISE study.

Dr. Richard Nesto and Dr. Phyllis August will oversee hypertension management and monitoring across BARI 2D clinical sites. As well as reporting achievement of target blood pressure goals, investigators will report side effects or factors limting treatment with a specific agent. For example, heart rate less than 60 bpm, development of 1st degree (or higher) AV block, or side effects such as claudication, fatigue, or impotence may preclude initiation or dose escalation of beta blockers. Hyperkalemia ($K^+ > 5.6$-6.0 mg/dl), seen in some patients with renal impairment and type 4 renal tubular acdosis, may exclude ACE inhibitors or AII receptor blockers. Alpha blockers may cause lightheadedness or postural hypotension, especially if autonomic neuropathy is present. The effect of beta blockers and diuretics on metabolic parameters (glucose control, uric acid, lipids, K^+) will be monitored. Potassium levels will be obtained on all BARI 2D patients at baseline, 3 months, 6 months and quarterly thereafter.

CHAPTER SEVEN : SECTION THREE HYPERTENSION OVERVIEW



* Target doses of beta blockers can be exceeded to recommended "maximum" doses as long as HR ≥ 60 bpm

BACKGROUND MEDICAL THERAPY

BETA BLOCKER

Beta blockers will be used for BARI 2D (unless contraindications exist) as all patients will have CAD. Variations in the indications of beta blocker exist and the selection of particular agents can depend on the patient's clinical profile (presence or absence of HTN, angina, CHF)

Choose or maintain either a beta blocker:

- Cardioselective
  - metoprolol
  - atenolol

  indicated for both hypertension and angina

  or

  - bisoprolol
  - betaxolol

  indicated for hypertension

  or
- Non-cardioselective
  - carvedilol - indicated for hypertension and Class II & III CHF

TITRATE

- To target doses:
  - metoprolol 50-100 mg bid
  - atenolol 100 mg qd
  - metoprolol XL 100 mg qd
  - betaxolol 10 mg qd
  - bisoprolol 5 mg qd
  - carvedilol 12.5 mg bid

  unless

  - HR ≤ 60 bpm or systolic BP ≤ 100 mmHg

  or

  - to maximum tolerated dose

ACE-INHIBITOR

- if BP ≤ 130/80
  - ramipril
- if BP > 130/80
  - any ACE-inhibitor (unless ramipril provided by industry)

TITRATE

- ramipril 10 mg qd or to BP ≥ 100 mmHg
- other ACE-inhibitor to target dose (i.e., quinapril 20 mg qd)

ASPIRIN

- 325 mg qd

or

- clopidogrel 75 mg qd

or

- neither if on Coumadin

CHAPTER SEVEN : SECTION FOUR HYPERTENSION MANAGEMENT CENTER (HMC) OPERATIONS

The HMC will perform the following functions: (a) ensure that all patients enrolled in BARI 2D are on appropriate standard ("background") medications as outlined in the Manual of Operations (MOP); and (b) monitor systolic and diastolic blood pressures in all patients from each site to ensure that BARI 2D blood pressure treatment goals (≤ 130mmHg systolic and ≤ 80mmHg diastolic) are obtained. Hypertension is an important risk factor related to cardiovascular disease mortality and diabetes. The BARI 2D Coordinating Center (CC) will provide data to the HMC regarding the levels of systolic and diastolic blood pressure in all patients from all sites. The HMC will also intervene and assist sites when individual patients are identified whose blood pressure is persistently elevated and/or the average blood pressure of all patients from a particular site are persistently elevated. Consistent management of hypertension and adherence to recommendations for "background" medication is essential to ensure that the medical care of BARI 2D patients is optimal regardless of randomized treatment assignments.

The CC will forward data to the HMC to track all patients regarding their blood pressure measurements throughout the course of the trial. The CC will calculate and track both an overall BARI 2D average (and median) systolic and diastolic blood pressure and a center specific percent of subjects at goal (systolic ≤ 130mmHg and diastolic ≤ 80mmHg). The CC will forward to the HMC the systolic and diastolic blood pressure recorded at each clinic visit. The HMC will also track that each patient will be on the three components of "background" medical therapy (beta-blocker, ACE-inhibitor and ASA) by the first visit after randomization. The CC will calculate the mean value of the systolic and diastolic blood pressure for every BARI 2D clinical site every three months by visit number. These data will be provided to the HMC on a timely basis in the following fashion: As a single histogram of all BARI 2D subjects across all centers, as separate histograms of all the subjects within each center, and as a single histogram of the mean systolic and mean diastolic blood pressure levels of each center. Accompanying these histograms will be tables of the distribution of the systolic and diastolic blood pressure levels that indicate the 10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th} percentile values and the percent of patients above and below systolic and diastolic blood pressure goals (130mmHg and 80mmHg respectively). Individual patients whose blood pressure levels are such will have their medications reported to the HMC. The HMC will make recommendations regarding the management of these patients. The identity of each clinical site in these reports will remain anonymous, as will the names of individual patients, unless the HMC considers it necessary to take specific action regarding the performance of a particular clinical site.

Clinical sites with mean/median systolic and diastolic blood pressure levels > 150mmHg systolic or 95mmHg diastolic or with 50% of subjects above goal (130mmHg systolic and/or 80mmHg diastolic) will be investigated by the HMC with regard to the adequacy of treatment for those subjects.

To monitor medications used as background medical therapy and for the treatment of hypertension, a standardized form will be used at each clinical site with a drug check-off list; the form will be updated whenever a new drug for lowering blood pressure is introduced into the protocol. The study coordinator at each clinical site will record the start and discontinuation dates of each drug used for blood pressure management. These data will be sent to the HMC, which will maintain in its database the drug use history of each BARI 2D subject from entry into the protocol until study completion. Implementation of treatment will be carried out by Dr. Richard Nesto and Dr. Phyllis August who will consult the Cardiovascular Pharmacotherapy Management Group (CPMG) on an as needed basis. Twice a year reports from the CC will be made available to the HMC and circulated to the CPMG for review.

Hypertension Treatment Committee: The plan for monitoring management of blood pressure and HMC will have two other important responsibilities. The first will be to help the CC prepare reports for the NHLBI-appointed DSMB for BARI 2D. The second will be to give the BARI 2D Steering Committee a periodic progress report on the management of hypertension during the study and the implementation of the protocol at BARI 2D Steering Committee Meetings. Review of these data at BARI 2D Steering Committee Meetings will enable investigators to review this aspect of medical treatment and to offer suggestions to the HMC director for improvement related to monitoring procedures or to management. The HMC will inform the sites of changes in blood pressure treatment targets and/or changes in recommended medication during the course of the study.

CHAPTER EIGHT

LIPID MANAGEMENT PROTOCOL

SECTION ONE: LIPID MANAGEMENT GUIDELINES

SECTION TWO: LIPID PROCEDURES/DATA COLLECTION

SECTION THREE: LIPID MANAGEMENT OVERVIEW

SECTION FOUR: LIPID MANAGEMENT CENTER OPERATIONS

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CHAPTER EIGHT : SECTION ONE LIPID MANAGEMENT GUIDELINES

I. INTRODUCTION

The value of lipid lowering for secondary prevention of CVD in diabetes is now fairly well established, especially for LDL cholesterol (4S, CARE, LIPID). In the BARI 2D trial, the purpose of the lipid management protocol is to ensure that all participants, in each of the four experimental groups, receive optimal lipid management consistent with current clinical guidelines (NCEP/ADA).

II. GENERAL PRINCIPLES OF MANAGEMENT

A. Appropriate dietary counseling (AHA Step One Diet with appropriate modification in the presence of hypertriglyceridemia) should be given to all subjects and documented in study records.

B. Protocol guidelines are intended as suggestive rather than mandatory, and do not override individual physicians exercising discretion in their application. However, where goals are not achieved and suggested therapy is not being given, study-monitoring procedures require documentation of proposed treatment plan and why suggested therapy is not prescribed.

C. For patients with moderate (150-199 mg/dl) or severe (>200 mg/dl) hypertriglyceridemia, a period of improved glycemic control (for 3-6 months) should generally precede initiation of fibrate or fish oil therapy unless the patient is already at goal HbA1c. Earlier initiation of fibrate or fish oil therapy is up to the local investigator**.** It should be noted that in diabetes, a raised level of triglycerides is a major contributor to recurrent vessel disease.

D. Fish oil therapy (i.e. increased omega-3 fatty acid intake using fish oil concentrate) will be encouraged as a further adjunct to triglyceride control. A dose of 2-3 gms of omega-3 fatty acids daily is advocated, e.g. three standard capsules, each containing 300 mg of omega-3 (DHA/EPA), three times daily with meals. Omega-3 enriched fish oil is noted not to be reliably available in Canada.

E. There is no overwhelming scientific reason for advocating any one of the available statin drugs or of the available fibrate drugs.

F. Patients will not be switched from a lipid-lowering drug on entry to the study drug unless treatment goals are not being achieved or the participant desires to switch.

G. Serum for a fasting lipid profile (total and HDL cholesterol, triglycerides and calculated LDL cholesterol or direct LDLc if triglycerides >400 mg/dl) will be drawn and sent to the central laboratory at baseline and each annual visit. Local values obtained through the patient's usual health care provider/insurance, will determine therapy and be reported to the Coordinating Center. For patients without insurance coverage, the central laboratory may be used to provide lipid profiles for clinical management.

H. ALT will be obtained on all subjects receiving either statin or fibrates or niacin every 3 months and reported to the Coordinating Center.

I. ALT and CPK (CK) will be performed every 3 months on all subjects receiving combination statin and fibrate therapy.

J. Because of potential adverse effects on the study's aims, the use of Niacin is strongly discouraged.

K. It is anticipated that all drugs provided through BARI 2D will be used in a manner consistent with their product labeling.

III. GOAL/ACTION LEVELS

	LDL cholesterol	Triglycerides
Goal/ Action*	<100 mg/dl	<150 mg/dl

*Action implies a definitive plan to lower lipid level, usually the initiation or increase of specific drug therapy (statin or fibrate), but could include the initiation of diet when that has not been previously advised, fish oil therapy and intensification of glycemic control (e.g. initiation of insulin therapy or new oral agent), if goal HbA1c is not achieved. Although "action" is encouraged for subjects with triglycerides above 150 mg/dl, for study monitoring purposes, treatment plans need only be specified for those with values > 200 mg/dl.

IV. EXCLUSION CRITERIA

Subjects with triglycerides > 1000 mg/dl will be excluded in the presence of moderate glycemic control (i.e. HbA1c < 9.0 %). The recruitment of subjects who are thought by either the diabetologist or the cardiologist to need Niacin therapy is strongly discouraged.

CHAPTER EIGHT : SECTION TWO LIPID MANAGEMENT PROCEDURES/ DATA COLLECTION

I. BASELINE VISIT

The following items will be addressed:

A. History of lipid disorders/previous levels (especially prior to drug therapy)

B. Current diet

C. Current medication (lipid)

D. History of prior adverse reactions to lipid medications

E. Fasting blood draw

1. 5 ml serum to core blood laboratories

2. 5 ml serum to local laboratory (except in the absence of insurance coverage, in which case a profile within 3 months of baseline is acceptable).

F. Baseline ALT and CPK (CK)

G. Review for possible secondary causes of hyperlipidemia and order TSH plus blood chemistries as appropriate (note that in BARI 2D, renal function and liver injury tests will be checked at baseline). Check urine for proteinuria.

H. Appropriate diet counseling by dietician, Certified Diabetes Educator, Diabetes Nurse Educator, or physician. Wherever possible, this should be done by a dietician or Certified Diabetes Educator.

I. Possible initiation of drug therapy

1. LDL cholesterol > 100 mg/dl - Statin
   If subject is previously known to have LDL > 100 mg/dl, appropriate statin therapy should be started at baseline. At investigator's discretion, statin therapy can also be started at baseline even if this is the first known reading >100 mg/dl. If not, therapy must be started as soon as LDL elevation is confirmed and no later than the 3-month visit. If patient is already on statin, increase dose if LDL >100 mg/dl.

2. Triglycerides > 200 mg/dl - Fibrate at Investigator's Discretion
   If LDL <100 mg/dl (or patient on statin), investigator may elect to start fibrate therapy (or increase statin if patient already on statin) at baseline or wait 3 months for effect of

intensified glucose control. At 3 months, fibrate therapy (or increased statin dose or initiation of fish oil therapy) would be expected if triglycerides > 200 mg/dl and suggested for consideration if triglycerides are between 150 mg/dl and 200 mg/dl.

3. LDL > 100 mg/dl and Triglycerides >150 mg/dl
   Generally patients with LDL > 100 mg/dl would initially be started on statin therapy. However, subjects with minimal LDL elevation (e.g. ~ 120 mg/dl) and moderate triglyceride elevation (e.g. ~ 300 mg/dl) may initially be treated with a fibrate. If triglycerides are > 600, statin therapy is unlikely to be successful and fibrate therapy would be a preferable first choice.

II. THREE (3) MONTHS

A. Diet and, where appropriate, medication adherence will be reviewed and reinforced.

B. Fasting lipid profile drawn and sent locally unless LDLc and triglycerides are at goal at baseline. However, if the patient had an MI in the three months prior to baseline, a lipid profile should be repeated at the three month visit, even if baseline LDLc and triglycerides were at goal.

C. If LDL cholesterol >100 mg/dl, statin therapy will be initiated (if not already started) or increased. If maximum recommended dose is already being used, patient should be switched to simvastatin or atorvastatin in equivalent doses.

D. If triglycerides are >200 mg/dl, definitive therapy (fibrate or fish oil) should be initiated unless it is felt further improvement of glycemic control is likely to be achieved and will bring triglycerides down <200 mg/dl.

E. If triglycerides are 150-399 mg/dl, fish oil or fibrate therapy should be considered. However, if statin therapy is being initiated or increased (because LDLc >100 mg/dl), fibrate or fish oil therapy may not be needed and should generally be delayed.

F. Patients put on combined statin and fibrate therapy should be counseled as to increased risk of myositis and to report generalized muscle pain/ache promptly.

G. For all patients not at minimal goals (LDLc <100 mg/dl and triglycerides <150 mg/dl), a fasting lipid profile should be scheduled for the 6-month visit. If the triglyceride level is 150 mg/dl - 199 mg/dl and LDL < 100 mg/dl, schedule fasting profile at 6-months.

H. ALT should be measured if on statins or fibrates. CPK (CK) and ALT should be measured if on both statin and fibrate.

III. SIX (6) MONTHS AND SUBSEQUENT QUARTERLY VISITS

A. Repeat procedures as for 3 months, and continue intensification of therapy until goals of LDLc < 100 mg/dl and triglycerides <150 mg/dl (or <200 mg/dl) are reached.

B. Fasting lipid profiles will be done every three months until goals are achieved.

C. ALT will be measured every 3 months if on statins or fibrates. CPK (CK) and ALT will be done every 3 months if on both statin and fibrate.

D. When goals are reached, maintenance of appropriate drug and dietary intervention will be reviewed at each quarterly visit, but lipid profiles will be done annually. Should an annual lipid profile reveal values above goal, procedures G through I from baseline should be performed and protocol with quarterly fasting lipid profile and follow-up instigated until goals achieved.

IV. ANNUAL VISITS

A. A fasting lipid profile will be drawn and sent both locally and centrally. Adherence to diet and drug therapy should be assessed and reinforced.

B. Refractory Hypercholesterolemia
If LDLc remains >100 mg/dl despite maximum statin (i.e. atorvastatin 80 mg daily) therapy or if patient intolerant of statins, therapy with bile acid resins should be tried**.** Please consult Dr. Orchard if LDL remains > 100 mg/dl.

C. Refractory Hypertriglyceridemia
If triglycerides remain >200 mg/dl despite optimal fibrate and fish oil therapy and good glycemic control (HbA1c <7.0%), please consult Dr. Orchard.

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CHAPTER EIGHT : SECTION THREE LIPID MANAGEMENT OVERVIEW

OVERVIEW OF LIPIDS MANAGEMENT PROTOCOL

LDLc >100 mg/dl*
↓
statin Rx (↑ dose until LDL < 100 mg/dl)
↓
triglycerides remain >200
despite LDL <100 mg/dl)
↓
add fibrate or fish oil (both if needed)

However, if triglycerides moderately increased
(e.g.~ 300 mg/dl) and LDLc only minimally
increased (e.g.~ 120 mg/dl)
↓
fibrate therapy may be considered as initial therapy

If triglycerides very elevated (e.g.> 600 mg/dl),
statin therapy unlikely to be successful
↓
Fibrate therapy may be more appropriate
initial choice

LDLc <100 mg/dl + Triglycerides >200 mg/dl
↓
improve glycemic control
↓
if goal not reached
↓
Fish oil or fibrate therapy
↓
if goal not reached
↓
Fish oil plus fibrate therapy

* A goal LDL of 75 mg/dl may be appropraite for some participants

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CHAPTER EIGHT : SECTION FOUR LIPID MANAGEMENT CENTER (LMC) OPERATIONS

The BARI 2D Coordinating Center (CC) will forward data to the LMC to track all patients regarding their lipid measurements from baseline on. The CC will calculate and track both an overall BARI 2D average (and median) LDL and triglycerides and a center specific % of subjects at goal (100 and 150 mg/dl respectively). This will provide an overall and a contemporary updated lipid control profile for each patient. In addition, the CC will calculate the mean value of each of the above lipid profile parameters for every BARI 2D clinical site every three months by visit number (e.g. baseline, three month, etc.). All the above data will be provided to the LMC on a timely basis in the following fashion: As a single histogram of all BARI 2D subjects trial wide; as separate histograms of all the subjects within each clinical site; and as a single histogram of the mean/median LDL and triglyceride values of each clinical site. Accompanying these histograms will be tables of the distribution of each parameter that indicates the 10th, 25th, 50th, 75th, and 90th percentile values and the percentages of patients above and below goal. In addition the CC will provide a break down by site of the actions taken when goals are not achieved. All of the above analyses will be carried out separately for the two treatment strategies, IP and IS, and, within each treatment strategy, by whether patients were previously on insulin or not. The identity of each clinical site in these reports will remain anonymous unless the LMC considers it necessary to take some action regarding the performance of a particular clinical site.

A survey of the above lipid data will enable the LMC to judge the quality of lipid control being provided to all the BARI 2D patients, to the BARI 2D patients at each clinical site, and the comparative performance of each BARI 2D clinical site. Clinical sites with mean/median LDL and triglyceride values greater than suitable monitoring thresholds or with 50% of subjects above goal (100 and 150 respectively) will be prospects for investigation by the LMC with regard to the adequacy of treatment and treatment effects. The monitoring thresholds will be set equal to values somewhat larger than the corresponding goals of 100 for LDL and 150 for triglycerids (for instance, 130 for LDL and 400 for triglycerides), and will be gradually reduced as the lipid control improves during the course of BARI 2D.

To ascertain drug use, a standardized form will be used at each clinical site with a drug checkoff list; the form will be updated whenever a new drug for lowering LDL or triglyceride is introduced into the protocol. The study coordinator at each clinical site will record the start and discontinuation dates of each drug used for lipid control. These data will be sent to the CC, which will maintain in its database the drug use history of each BARI 2D subject from entry on and updated periodically.

In its report to the LMC, the CC will calculate the percentage of subjects using each drug for the entire BARI 2D subject population and the same percentages will be calculated for the subjects in each individual clinical site.

Lipid Management Group: The plan for monitoring lipid control and the implementation of treatment strategies will be carried out by Dr. Trevor Orchard, who will consult the Lipid Management Group (LMG) on an as needed basis. Twice a year reports from the CC will be made available to the LMC and will be circulated to the LMG and comments/advice sought along with general discussion. Though one of these reviews (the 6 monthly one) will be done via conference call, it is hoped the annual review would be face to face.

The LMC will have two other important responsibilities to fulfill. The first will be to help the CC prepare its reports to the NHLBI-appointed DSMB for BARI 2D. The second will be to give the entire BARI 2D Steering Committee a periodic progress report on the lipid control achieved and the implementation of the protocol at BARI 2D Steering Committee meetings. This feedback will afford all investigators an opportunity to discuss this critical aspect of BARI 2D and offer suggestions to the DMC director for improvement in its monitoring procedures or in the diabetes management techniques being employed. In addition, the LMC will arrange educational sessions at the annual BARI 2D meeting if needed, as new drugs or techniques for lipid management appear that would contribute to the success of lipid control in the IP and IS treatment groups.

CHAPTER NINE

CORE LABORATORIES

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CHAPTER NINE : SECTION ONE ANGIOGRAPHIC CORE LABORATORY

I. INTRODUCTION

A. Purpose of Angiographic Core Laboratory

Rationale for an Angiographic Core Laboratory is based on the following goals.

1. Characterize the extent and severity of coronary disease at study entry to assess comparability of patients randomized to the different treatment and revascularization strategies.

2. Provide data for relevant ancillary studies

    a. What is the correlation of HbA1c levels with progression of coronary disease?
    b. Retrospectively analyze the angiographic determinants that guided physician “choice” of PTCA or CABG in those patients randomized to "revascularization of choice".

B. Primary Goals

The primary goals of the Angiographic Core Laboratory are to support the primary BARI 2D study purpose by providing angiographic data that is objective, reproducible, and consistent with the study goal and provide additional information that may assist in understanding the unique pathobiology of vascular disease in patients with diabetes. The specific goals of the Angiographic Core Laboratory are to:

1. Provide uniform angiographic acquisition procedures for all participating clinical sites. At the same time a major goal is to minimize the imposition of extra effort to acquire the angiograms. Detailed collection and analysis of angiography interpretations performed at the clinical sites is not a requirement of the study.
2. Collaborate with clinical site investigators, coordinating center and other core laboratories to develop final clinical site protocols to include angiography data collection forms, core laboratory operations manual and procedures for electronic data transfer.
3. Provide expertise to the coordinating center to assist interpretation of complex data structures used to characterize coronary anatomy, disease and revascularization.
4. Provide quality control of diagnostic and therapeutic procedures performed on study patients.
5. Provide status reports, quality assurance information, reproducibility data and angiographic results to project directors, data policy board and steering committee.

C. Angiographic Interpretation

The Central Radiographic Laboratory at Stanford developed methods and quality control procedures for interpretation of BARI I angiograms. A coronary angiographic database supports anatomic characterization that was developed for BARI I and for other projects. Using quantitative measurements and anatomic coding of vessel distribution, we estimate the extent and severity of coronary disease. We use modified database formats for BARI 2D, which proved effective in BARI I. A myocardial jeopardy index was developed and validated that provides a

semi-quantitative measure of the extent of myocardial jeopardy and the degree to which revascularization procedures mitigate this jeopardy (Alderman and Stadius 1992).

To ensure the most accurate interpretation of angiograms, we require a catheter size larger than 5Fr. We strongly recommend the use of 6Fr or larger catheters because of somewhat better coronary ostia engagement and contrast delivery.

The Stanford Angiographic Laboratory has acted as core laboratory for multiple projects. Those requiring serial quantitation of coronary dimensions for anti-atherosclerosis trials include the Stanford Coronary Risk Intervention Project (SCRIP; Haskell 1994) and multiple studies of premature coronary disease in cardiac transplant recipients. Characterization of coronary anatomy and disease has been used in many studies of percutaneous coronary interventions including devices. BARI I along with the International Multicenter angiographic study of graft patency (IMAGE; Berger 1997) are examples of studies for which detailed coronary quantitation is unnecessary, but characterization of the coronary anatomy, the extent to which coronary lesions affect myocardium at risk and the effects of revascularization are of primary importance. The Laboratory is directed by Dr. E. Alderman who overreads all angiograms after preliminary readings by experienced research fellows or technicians.

In order to accomplish these goals the Angiographic Core Laboratory developed an angiographic operations manual. Of particular importance in characterizing patients prior to and following revascularization procedures is an accurate and reproducible assessment of the extent of myocardium jeopardized by coronary lesions jeopardized. To this end, we semi quantitatively assess the percent of LV myocardium jeopardized by lesions exceeding a 50% threshold (50% was used in BARI I) that was developed and its reproducibility evaluated (Botas 1996).

II. RESEARCH DESIGN AND METHODS

We propose that entry and revascularization procedure angiograms (for patients initially assigned to undergo revascularization) be sent to the Angiographic Core Laboratory after patients have completed consent and are randomized to the treatment groups. All procedure reports of angioplasties and bypass surgeries among patients initially assigned to revascularization will be accessible to the Core Laboratory for data entry into the angiographic database. The angiographic database provides a means for assessing the extent to which completeness of revascularization (reduction of myocardial jeopardy) is accomplished by surgery or angioplasty. Myocardial jeopardy measured as a percent of total LV myocardium at risk, is a measure of completeness of revascularization (Alderman 1992).

A. Angiographic Interpretation Logistics

For the purposes of BARI 2D, angiograms will be sent to the Core Laboratory where they will be read, interpreted and data entered for transfer to the Coordinating Center. Angiograms recorded on cine film will not be retained at the Core Laboratory, but promptly returned to the clinical sites. CDs will be retained. Clinical sites will not be asked to read and interpret angiograms for this study.

B. Entry Angiograms – Angiographic Interpretation

Analysis of entry angiograms will focus on characterizing coronary anatomy, myocardial distribution and location and severity of coronary disease. Left ventriculography will be assessed for the extent of LV dysfunction and any other major valvular or anatomic abnormalities. Coronary anatomy is entered into a graphic database which characterizes the size and distribution of the major coronary arteries and their branches. Details of the system and the associated algorithms are available (Alderman 1992). Lesions are located on a caricature of the coronary tree structure along with lesion

severity. If the lesion severity is thought to be near 50% or greater severity, the residual lumen and adjacent reference diameters are quantitated and the results automatically entered into the graphic database. The Coordinating Center statistical staff has considerable experience in working with this unique database structure and has explored several different hypotheses regarding coronary disease in diabetic patients.

Coronary anatomy will be characterized with respect to the size and distribution of the distal coronary vessels and coronary lesions will be characterized with regard to type, location and severity. Standard grading algorithms for coronary lesions (Type I, II, IIa, IIb and III) are employed. Semi-quantitative measures of myocardial jeopardy and the extent to which jeopardy is mitigated by revascularization procedures (among patients assigned to undergo revascularization), whether by percutaneous coronary intervention or coronary surgery, will be assessed.

Because BARI 2D is entirely a study of patients with diabetes, several new indices will be added to lesion characterization in recognition of the fact that diabetic coronary atherosclerosis tends to be more diffuse in extent with greater involvement of distal coronary branches. Despite the fact that coronary ultrasound is far more definitive and precise in assessing the extent to which subintimal disease is present and the extent to which concentric narrowing is present, it is too expensive, limited in coronary survey capability and logistically complex to pursue. However, it is possible to make semi-quantitative assessment of some aspects of diabetic coronary disease.

One approach is to make use of the normal coronary dimensions that have been previously defined in studies of normal healthy subjects (Leung 1991, Leung 1995). The dimensions obtained from right coronary, circumflex, left anterior descending and left main coronary arteries in normal subjects provide diameter standards that, to some extent, can be used for comparison with diabetic subjects. For this reason we will use electronic measurements on entry arteriograms of coronary dimensions of "normal" appearing segments within the left main, right main, mid-LAD and proximal left circumflex coronary arteries in a manner and location consistent with those measured in normal subjects. The "normal" appearing reference diameter in areas free of obvious discrete stenoses in diabetic subjects, vis-a-vis the reference diameter in normal subjects adjusted for gender, may provide indirect indication of the extent of concentric, intimal disease.

C. Assess Quality of Initial Percutaneous Revascularization Procedures in Randomized Patients Based on Direct Angiographic Review

It is important to assess the quality and extent of revascularization procedures performed by reading angiograms at the core laboratory. Half of all patients will be randomly assigned to revascularization of choice. We estimate 60% will have PCI and 40% coronary surgery.

D. Evaluate Completeness of Revascularization in all Patient Subsets

We believe that in a randomized study that compares a strategy of initial revascularization of choice vs. aggressive medical therapy alone, not only the type of initial revascularization procedure (PTCA, CABG), but also the extent to which myocardial jeopardy is potentially mitigated, needs to be recorded. Ideally one might wish routine protocol mandated follow-up angiography in all patients several years after entry, however, this is impractical because of cost, logistic complexity, potential adverse effects of contrast in diabetic patients and systematic bias towards restudy of surviving patients with symptoms.

For the purposes of this study, it is not practical to assess the extent to which arterial and saphenous vein grafts placed by surgeons are actually patent. It also is not practical to assess the extent to which percutaneous interventions remain functional post procedure. Multiple studies of coronary

angioplasty suggest that with the availability of stenting, the one-year results of angioplasty may be substantially improved over results for balloon angioplasty used almost exclusively in BARI I. However, the net effect of the adverse influence of diabetes on restenosis and the beneficial effect of stents on restenosis are uncertain with regard to patient survival.

For these reasons, we believe it is both feasible, albeit less exact, to use the clinical site PCI and surgery report forms as primary source documents. The key information from these procedure forms, which are routinely collected, will be entered into the angiographic database, specifying the distal insertion sites of venous grafts and arterial grafts for surgically treated patients and the lesions dilated and their initial outcome, for patients treated with percutaneous methods. This will be restricted to patients initially assigned to undergo coronary revascularization. Although not based on direct angiographic visualization, manual data entry into the graphic database provides a basis for estimating in any patient subset the extent to which myocardial jeopardy has potentially been mitigated by coronary revascularization. This approach is cost effective because it only involves interpretation of written reports by individuals with an excellent knowledge of coronary anatomy and nomenclature of interventional and surgical procedures.

E. Patient Confidentiality

The clinical sites should make every effort to remove patient names and all other identifying information other than the BARI 2D ID prior to transmission to the Angiographic Core Laboratory. All patients are identified by the BARI 2D ID. The data forms and data carry only these codes and do not carry the patient's name or other identifying information. The data files are restricted on computer systems that require password access. Data is transmitted electronically to the Coordinating Center at the University of Pittsburgh where similar measures to protect patient confidentially are in effect.

F. Angiography Quality Control at Clinical Sites

The Angiographic Core Laboratory assumes logistic responsibility for direct communication with clinical sites regarding issues such as image quality, completeness of angiography and prompt transferal of films or CDs for interpretation. We will provide quarterly feedback to clinical sites evaluating their performance in comparison with data from all other sites.

G. Quality Control of Angiographic Interpretation by CRL

All angiographic readers are blinded as to patient clinical and demographic features as well as randomization assignment (except for revascularization procedures performed which are angiographically evident). Quality control is assured by having the Coordinating Center recycle random angiograms in a blinded manner for reinterpretation by the Core Laboratory. This provides a method to assess the reproducibility of interpretation of angiograms, and associated composite measurements.

III. LITERATURE CITED

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CHAPTER NINE : SECTION TWO BIOCHEMISTRY AND FIBRINOLYSIS CORE LABORATORY

I. INTRODUCTION

A. Purpose of Biochemistry Core Laboratory

The Biochemistry Core Laboratory investigators will provide at a state-of-the-art level the assays utilized in the BARI 2D Study for the optimal measurement of hemoglobin A1c (HbA1c), lipids (cholesterol, HDL-cholesterol, triglycerides and either calculated or measured LDL-cholesterol), and urine albumin/creatinine ratio. The lab will also bank the baseline HbA1c sample for future genetic research from patients who have signed such consent.

Responsibilities of the Biochemistry Laboratory include assuring the optimal procurement, preparation and transportation of specimens for analysis from the clinical centers to the Biochemistry Laboratory. Measurements will be completed for each analyte in the most efficacious manner with state-of-the-art procedures. The lab will actively participate within the conduct of the study and will contribute suggestions for those tests or procedures that most efficaciously address the major questions of the study.

B. Purpose of Fibrinolysis Core Laboratory

Insulin, t-PA antigen, and PAI-1 activity will be measured in each of 13 samples to be obtained from each patient. The sequence of sample acquisition will be baseline, 1 month, 3 month, 6 month, and every six months thereafter for a total of 5 years (13 samples per patient). Samples will be drawn by peripheral venipuncture, placed on ice within 15 minutes, centrifuged for separation of plasma, frozen, and shipped in batches to the core laboratory. At each time of sample acquisition, a tube in addition to the citrate tube, will be obtained for banking of separated plasma in the core laboratory. This tube will be a sodium heparin tube. Insulin, t-PA antigen, and PAI-1 assays will be performed by ELIZA. PAI-1 activity will be assayed with a chromogenic substrate kinetic procedure. The banked blood sample will be retained for possible assay of fibrinopeptide A, prothrombin fragment 1.2, plasmin/antiplasmin complexes, and other moieties of potential interest.

At the time of sampling, a separate tube will be acquired without anticoagulant and sent to the Biochemistry Core Laboratory for determination of HgA1c. Other samples needed for lipid analyses will be forwarded from the Fibrinolysis Core Laboratory to the Biochemistry Core Laboratory and LipoScience, Inc. The lipid samples will be stored in aliquots from EDTA tubes.

C. Protocol for NMR Analysis of Lipids

Two blood samples will be obtained from each patient for the NMR analysis, a methodology for quantifying 16 subfractions of lipoproteins. One sample will be drawn at baseline and one at the one year follow-up visit. If a sample is not drawn at study entry, the one year follow-up sample should not be drawn.

Samples will be drawn by peripheral venipuncture and collected in a 3 ml lavender EDTA tube #2. After the draw, the sample should be mixed by gentle inversion and then placed on crushed ice and centrifuged within 15 minutes. The plasma sample should then be pipetted into 2 lavender microcentrifuge tubes prelabeled as NMR EDTA (EDTA tube #2), frozen and shipped in batches to the Fibrinolysis Core Lab with regular core blood samples. Here the samples will be stored frozen and shipped quarterly to LipoScience, Inc. LipoScience will measure the lipoprotein subfractions and will report the measurements back to the Coordinating Center on a regular basis.

In terms of BARI 2D, a number of hypotheses have been raised regarding the lipid effects of our two diabetes management arms, and whether these lipid effects will play a role in mediating any of the differential effects on outcome that may be observed. However, our lipid management protocol calls for optimal management across all groups for LDLc and triglycerides, so in terms of classic lipid levels, there should be little difference across groups. On the other hand, NMR has demonstrated considerable differences in particle number among individuals with similar lipid concentrations, differences that have been related to cardiovascular disease. Primarily this has been observed in the LDL fraction wherein overall LDLc differences were modest between disease, positive and negative, but major differences in the NMR L1 fraction were observed, with no differences for the other two LDL fractions. This has also been seen in a Type 1 diabetic population and is of particular relevance for BARI 2D as the "L1" sub-fraction contains smaller, denser particles, which are more artherogenic and a hallmark of insulin resistance, which our treatment arms are designed to differentially affect. While the NMR technique also yields mean particle size data, analyses to date suggest measurement of L1 itself may be more discriminating.

Increases in triglycerides and VLDL particles are also critically important in Type 2 Diabetes, especially those with heart disease. Previous studies have suggested NMR derived total VLDL particle number is a better marker than triglyceride concentration. Similarly, while HDLc is generally inversely related to coronary artery disease, NMR determined H1+2 and H4+5 show this inverse relationship while "H3" shows a positive and independently significant prediction of cardiovascular events in a Type 1 diabetic population. It thus seems likely that NMR measures may predict risk in the BARI 2D population and be differentially affected by our treatment regimens.

The hypotheses to be addressed in BARI 2D include:

1. Those treated in the IS arm will have a lower mean "L1" particle number compared to those in the IP group at one year and experience a greater fall in L1 particle number from baseline.

2. Those treated in the IS arm will have a lower mean "VLDL" particle number compared to those in the IP group at year one and experience a greater fall in VLDL particle number from baseline.

3. Those treated in the IS arm will have a higher mean H1+2 and H4+5, and lower mean H3 particle number compared to those in the IP group at one year and experience a greater fall in H3 particle number from baseline.

4. Each of the differences in NMR spectroscopy in hypotheses 1 – 3 above (i.e., lower L1, total VLDL and "H3" particle numbers) will attenuate any group differences between IS and IP observed in terms of mortality and cardiovascular outcomes.

D. VAP Analysis of Lipids/Lipoproteins

Samples: These analyses will be performed on plasma samples previously collected at baseline and 1 year for the above NMR analysis Unthawed samples will be used whenever possible; however, if the second (duplicate) sample is not available, the refrozen original sample from the NMR analysis will

be used. Identification of those samples which have been thawed and refrozen is critical and all subsequent data analyses will be repeated, excluding results from tests using thawed and refrozen samples, to verify robustness of the results. Frozen samples will be shipped on dry ice from LipoScience to the Diabetes and Lipid Research facility (3512 Fifth Avenue) in Pittsburgh on a periodic basis, starting April 05, and stored at -70°C until being forwarded in batches to Atherotech, Inc. for VAP analyses.

Vertical Auto Profile II and BARI 2D: The Vertical Auto Profile-II (VAP-II) method determines two key properties of lipoproteins: their relative densities and their cholesterol concentrations. After density gradient ultracentrifugation for lipoprotein separation, cholesterol (C) is directly measured in all five major lipoprotein classes: HDL, R-LDL, Lp(a), IDL and VLDL, where total LDL-C = R-LDL-C + Lp(a)-C + IDL-C (1). VLDL remnant lipoprotein cholesterol is expressed as the sum of IDL-C + $VLDL_3$-C (small, dense VLDL). Using proprietary deconvolution software, VAP-II also measures the cholesterol concentration in HDL_2 (large, buoyant), HDL_3 (small, dense), LDL4 (smallest, most atherogenic), LDL3, LDL2, LDL1 (largest, least atherogenic), $VLDL_3$ (small/dense) and $VLDL_{1+2}$ (large, buoyant) (2,3). As large, buoyant, very low density lipoprotein particles ($VLDL_{1+2}$) are not seen in plaque at biopsy, they are probably too large to penetrate the coronary endothelial barrier and are thus not intrinsically atherogenic (4). In addition, the density of R-LDL particles where the peak cholesterol load occurs is reported as the LDL Subclass Pattern. The VAP-II is performed at Atherotech, Inc., a CDC-NHLBI standardized lipid laboratory.

After ultracentrifugation each fraction is pumped at a continuous rate into a spectrophotometer where approximately 400 sequential spectrophotometric/enzymatic cholesterol measurements are made on each sample. In a typical VAP profile the y axis reflects the relative densities of the lipoproteins measured in seconds and the x axis reflects the cholesterol concentration at any given point in time (density).

The advantages of having the VAP-II analysis, in addition to the NMR, in BARI 2D are:

1. An additional, alternative measure of overall LDL density and quantification of real lipoprotein subclasses (HDL, LDL + VLDL).

2. A more specific determination of the subclasses of low density lipoprotein cholesterol, namely real LDL-C, Lp(a)-C and IDL-C which are either not well distinguished with NMR (i.e. IDL-C) or not determined at all (i.e. Lp(a)-C). IDL-C (8) has been correlated with insulin resistance and cardiovascular risk, while Lp(a) has been inconsistently (9,10) reported to be correlated with microvascular complications, particularly renal disease, in diabetes.

The hypotheses to be addressed in BARI 2D include:

1. Those treated in the IS arm will have a lower mean LDL_4-C + LDL_3 -C compared to those in the IP group at one year and will experience a greater fall in LDL_4-C + LDL_3 -C from baseline.

2. Those treated in the IS arm will have a lower mean VLDL remnant lipoprotein cholesterol [IDL-C + $VLDL_3$-C] compared to those in the IP group at year one and will experience a greater fall in VLDL remnant lipoprotein cholesterol from baseline.

3. Those treated in the IS arm will have higher HDL_2 cholesterol and lower HDL_3 cholesterol compared to those in the IP group at one year and will experience a greater fall in HDL3 cholesterol from baseline.

4. Each of the differences in VAP-II in hypotheses 1-3 above (i.e. lower small dense LDL, VLDL- and IDL cholesterol, and higher HDL_2 cholesterol) will attenuate any group differences between IS and IP observed in terms of mortality and cardiovascular outcomes.

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II. CONTACT INFORMATION

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III. BLOOD SPECIMEN COLLECTION

A. General

1. Venipuncture should be performed conventionally using a 21-gauge butterfly and vacutainer holder (such as the Holdex Tube Holder) to ensure optimal compliance with OSHA standards and to minimize trauma and allow for standardization of samples.
2. Tourniquets should be applied for less than 90 seconds

B. Procedure (see blood drawing diagram)

1. Arrange draw tubes within easy reach and in order of draw
2. Assemble blood collection supplies as well as crushed ice
3. Perform venipuncture
4. Fill tiger top SST tube first, then fill blue citrate tube #1, blue citrate tube #2, green sodium heparin tube, lavender EDTA tube # 1, and lavender EDTA tube # 2, in that order.
5. Fill each vacutainer tube as completely as possible; i.e., until the vacuum is exhausted and blood flow ceases
6. After each tube is filled, mix by gentle inversion, and then immediately put the 2 blue citrate tubes, the green sodium heparin tube, and the EDTA tube # 2 on crushed ice until centrifugation

7. The tiger top SST tube should remain at room temperature for at least 30 minutes, but no longer than 60 minutes, prior to centrifugation
8. The lavender EDTA tube # 1 should be labeled and refrigerated as is until shipment to Fairview-University Medical Center/University of Minnesota.

C. Genetic Specimen Collection

There is no additional collection of blood for the genetic sample. The genetic specimen will be obtained from the 10 ml Hemoglobin A1c specimen that is collected at baseline. If a patient has signed genetic consent this sample will be banked at the Biochemistry Core Laboratory at Fairview University in Minnesota, otherwise it will be destroyed.

IV. SEPARATION OF PLASMA

A. Centrifugation (5 tubes will need to be spun)

1. BLUE CITRATE TUBE #1, BLUE CITRATE TUBE #2, GREEN SODIUM HEPARIN TUBE, LAVENDER EDTA TUBE # 2

   After draw, place on crushed ice. Spin ***within 15 minutes*** using a refrigerated (4°C) centrifuge unless the spin duration is 2 minutes or less (see below) in which case centrifugation can be at room temperature.

2. TIGER TOP SST TUBE

   After draw, keep at room temperature for at least 30 minutes, but no longer than 1 hour. Then spin using a refrigerated (4°C) centrifuge unless the spin duration is 2 minutes or less (see below) in which case centrifugation can be at room temperature.

The total force of the centrifugation must be 30,000 g X minutes

Example: If 30,000 g, then spin x 1 minute
If 15,000 g, then spin x 2 minutes
If 2,000 g, then spin x 15 minutes

DO NOT centrifuge at a speed slower than 2,000 g

B. Aliquotting

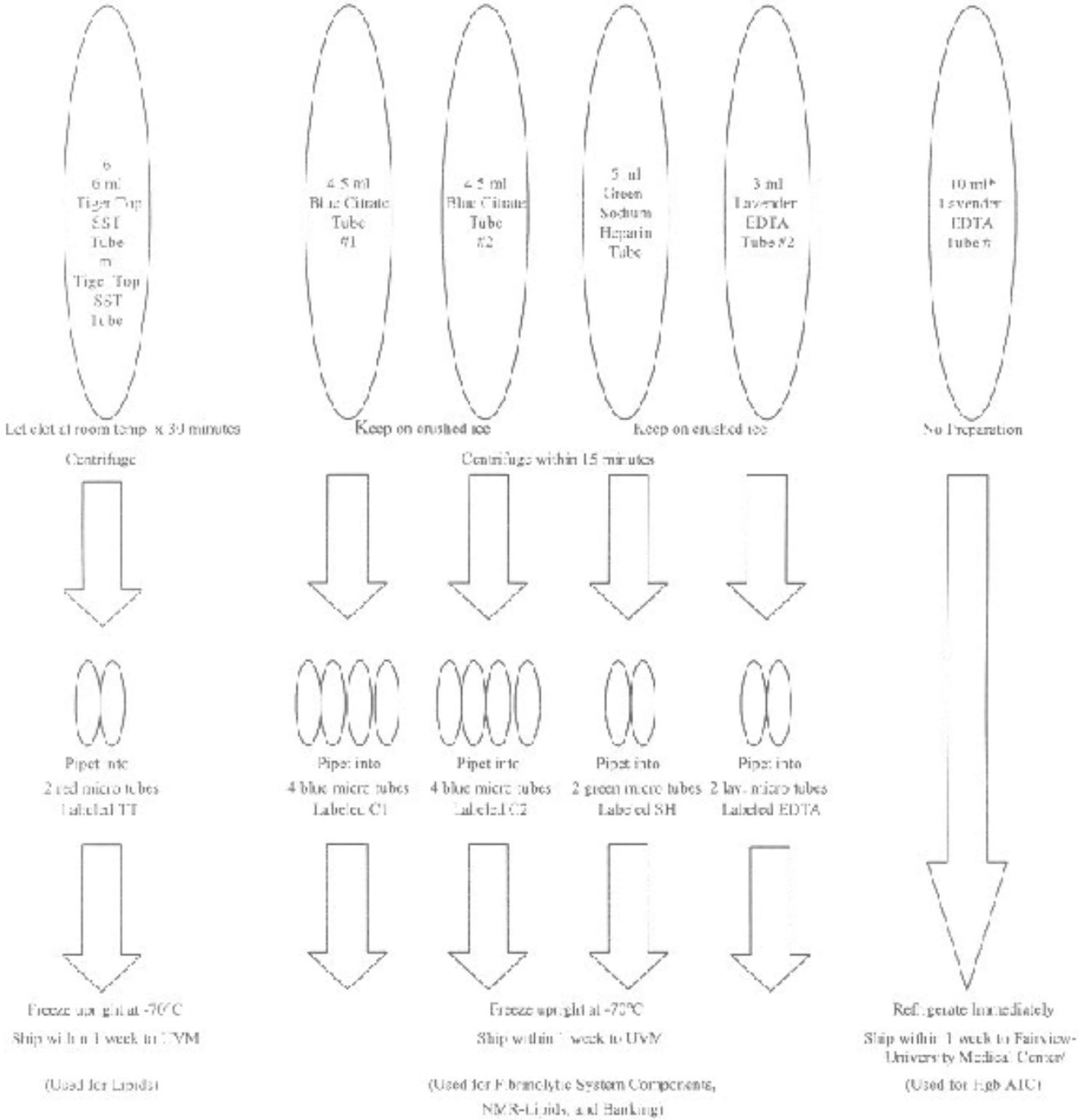
1. After centrifugation, the plasma from each tube should be removed with a pipet and placed in pre-labeled microcentrifuge tubes (eppendorfs), described below. Use a new disposable pipet for each sample tube
2. When pipeting, caution should be used to avoid drawing off plasma any closer than 1 cm from the cell layer
3. Do not fill microcentrifuge tubes completely; allow a 1 cm space at the top to allow for expansion when freezing
4. Plasma from the tiger top SST tube should be pipeted into 2 red microcentrifuge tubes prelabeled as TT (tiger top SST tube). Plasma from each blue citrate tube should be pipeted into 4 blue microcentrifuge tubes each. Each set of 4 blue microcentrifuge tubes will be prelabeled as C1 or C2 (blue citrate tube #1 or blue citrate tube #2). Plasma from the green sodium heparin tube should be pipeted into 2 green microcentrifuge tubes prelabeled as SH

(sodium heparin tube). Plasma from the lavender EDTA tube #2 should be pipeted into 2 lavender microcentrifuge tubes prelabeled as EDTA (EDTA tube #2).

5. At the end of this procedure, you should have 2 red, 8 blue, 2 green, and 2 lavender microcentrifuge tubes.
6. Each microcentrifuge tube will be pre-labeled. You will need to complete the labeling by adding patient ID and date of draw. A sharpie permanent marker will be provided as part of the start up supplies. Complete labeling before putting the tubes on ice or freezing the samples.
7. Immediately after aliquoting plasma, the microcentrifuge tubes must be frozen upright at -70°C.
8. All samples must be shipped to the reference lab at the University of Vermont within one week.

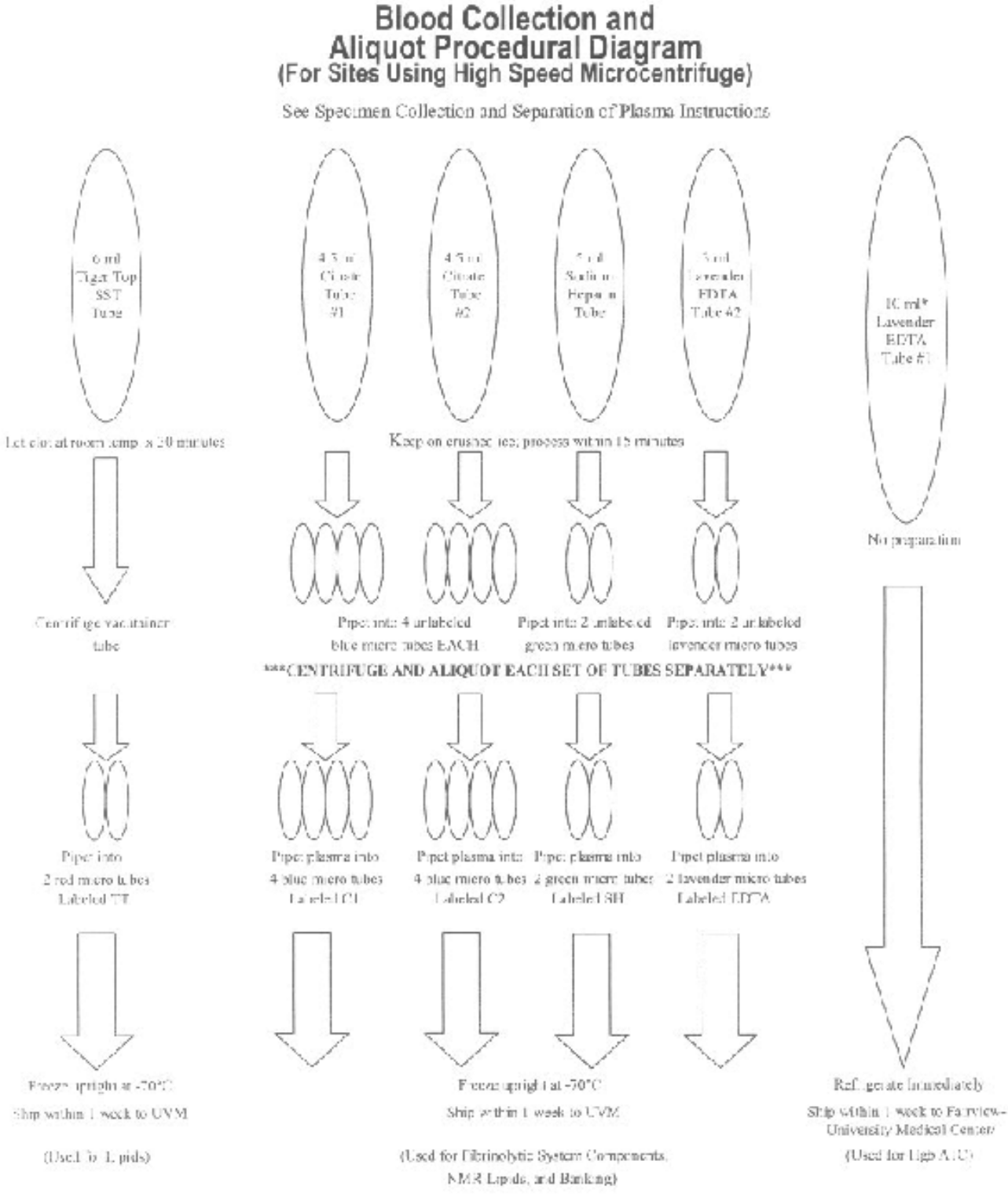
Blood Collection and Aliquot Procedural Diagram

See Specimen Collection and Separation of Plasma Instructions



Label each Microcentrifuge Tube with Patient ID and Date Using Black Permanent Marker

* 10 ml lavender EDTA #1 tube for baseline draw only. All other draws use 3 ml lavender EDTA tube # 1

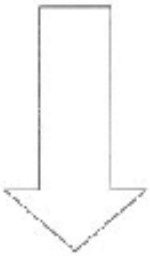

Blood Collection and
Aliquot Procedural Diagram
(For Sites Using High Speed Microcentrifuge)
See Specimen Collection and Separation of Plasma Instructions
6 ml Tiger Top SST Tube
4.5 ml Citrate Tube #1
4.5 ml Citrate Tube #2
5 ml Sodium Heparin Tube
5 ml Lavender EDTA Tube #2
10 ml* Lavender EDTA Tube #1
Let clot at room temp x 20 minutes
Keep on crushed ice; process within 15 minutes
No preparation
Centrifuge vacutainer tube
Pipet into: 4 unlabeled blue micro tubes EACH
Pipet into: 2 unlabeled green micro tubes
Pipet into: 2 unlabeled lavender micro tubes
CENTRIFUGE AND ALIQUOT EACH SET OF TUBES SEPARATELY
Pipet into 2 red micro tubes Labeled TT
Pipet plasma into 4 blue micro tubes Labeled C1
Pipet plasma into 4 blue micro tubes Labeled C2
Pipet plasma into 2 green micro tubes Labeled SH
Pipet plasma into 2 lavender micro tubes Labeled EDTA
Freeze upright at -70°C
Ship within 1 week to UVM
(Used to Lipids)
Freeze upright at -70°C
Ship within 1 week to UVM
(Used for Fibrinolytic System Components, NMR Lipids, and Banking)
Refrigerate immediately
Ship within 1 week to Fairview-University Medical Center
(Used for Lipo A-1)
Label each Microcentrifuge Tube with Patient ID and Date
Using Black Permanent Marker
* 10 ml lavender EDTA tube #1 for baseline draw only. All other draws use 3 ml lavender EDTA tube #1

V. URINE SPECIMEN COLLECTION (MICROALBUMINURIA)

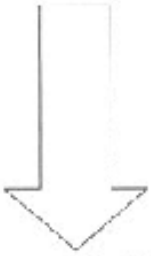
To be collected at baseline and yearly thereafter

1. Collect random urine in urine collection cup
2. Pipet urine equally into 2 clear micro tubes labeled "Urine"
3. Each micro tube will be pre-labeled. You will need to complete the labeling by adding patient ID and date of collection. A sharpie permanent marker will be provided as part of the start up supplies. Complete labeling before putting the tubes on ice or freezing the samples.
4. The micro tubes should then be frozen upright at -70°C.
5. Ship samples within one week on dry ice to the reference lab at the University of Vermont.

Urine Collection
Aliquot Procedural Diagram



2 Clear Micro Tubes



Freeze upright at -70°C
Ship within 1 week to
the University of Vermont

Label each Microcentrifuge Tube with Patient ID and Date Using Black Permanent Marker

For Samples Being Shipped to The University of Vermont (Urine, Lipids, & Fibrinolytic Samples)

1. Styrofoam shipping boxes have been provided
2. Use at least 5 kg of dry ice per box
3. Place each freezer storage container (with microcentrifuge tubes stored upright) in a 1 quart ziplock bag with absorber pack (Green Z)
4. Then place that 1 quart ziplock bag in a 1 gallon ziplock bag (the bag the tubes come in)
5. The double bagged samples can then be placed in the Styrofoam shipping box with dry ice (more than patient can be packed in the same box)
6. Complete and include "BARI 2D Sample Identification Log for Urine, Lipids, & Fibrinolytic Samples"
7. Samples must be shipped priority overnight on dry ice
8. Shipping should only be Monday-Wednesday to ensure delivery during the week
9. Complete Federal Express airbill (example provided)
10. Ship samples to:

Dagnija Neimane, Lab Administrator
The University of Vermont
Colchester Research Facility
208 South Park Drive, Suite 2
Colchester, VT 05446
(802) 656-8956

11. Fax completed "BARI 2D Sample Identification Log for Urine, Lipids, & Fibrinolytic Samples" prior to shipment to:

Michaelanne Rowen/Dagnija Neimane
Fax # (802) 656-8932

Date Entered _____
Initials_____

PLEASE COMPLETE FORM, ENTER INTO MATRIX, INCLUDE COPY IN EACH SHIPMENT, AND FAX COPY TO: MICHAELANNE ROWEN / DAGNIJA NEIMANE, (802) 656-8932

DATE OF SHIPMENT: _____ **SITE ID AND NAME: _____**

FEDEX AIRBILL NUMBER: _____ **SITE CONTACT NAME: _____**

SITE TELEPHONE: _____ FAX #: _____

MATRIX System will assign SAMPLE IDENTIFICATION LOG ID ___ ___ ___ ___ ___ ___ ___ ___ ___ __ _ _

BARI 2D ID	Draw Date*	Base-line	1 mo	3 mo	6 mo	1 yr	1.5 yr	2 yr	2.5 yr	3 yr	3.5 yr	4 yr	4.5 yr	5 yr	Partial sample	No sample	Reason **	
																	Code	Other Explanation

***If no sample provided, enter date of follow-up evaluation under "Draw Date", check the correct follow-up period for patient.**

**** Codes for Reason Partial Sample or No Sample:** **1.** Patient Died **2.** Patient Refused **3.** Physician Refused **4.** Venipuncture Unsuccessful **5.** Decompensated medical status precluded sampling **6.** Processing accident following collection 7. Other (write reason in space provided)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Packages up to 150 lbs.
X FedEx Priority Overnight
FedEx Standard Overnight
FedEx First Overnight
FedEx 2Day*
FedEx Express Saver*
4b Express Freight Service
Packages over 150 lbs.
FedEx 1Day Freight*
FedEx 2Day Freight
FedEx 3Day Freight
5 Packaging
FedEx Envelope/ Letter*
FedEx Pak*
X Other Pkg.
6 Special Handling
SATURDAY Delivery
SUNDAY Delivery
HOLD Weekday at FedEx Location
HOLD Saturday at FedEx Location
Does this shipment contain dangerous goods?
No
Yes
Dry Ice
Cargo Aircraft Only
7 Payment Bill to:
Sender
Recipient
X Third Party
Credit Card
Cash/Check
2555-3223-5
Total Packages
Total Weight
Total Declared Value
$ .00
FedEx Use Only
8 Release Signature
By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.
360

VII. PACKAGING AND SHIPPING

For Samples Being Shipped to Fairview-University Medical Center/University of Minnesota (Hemoglobin A1c sample)

1. Small styrofoam shipping boxes have been provided
2. The lavender EDTA tube #1 will be pre-labeled. You will need to complete the labeling by adding patient ID and date of draw
3. Place each lavender EDTA #1 tube in the foam insert (each box holds 4)
4. Place absorbent cloth and frozen cold pack on top of tubes (your kits will come with cold packs; when you receive them, place them in the freezer)
5. ***DO NOT SHIP SAMPLES ON DRY ICE***
6. Place styrofoam container in bag provided, seal with tie
7. Place in shipping box
8. Complete and include "BARI 2D Sample Identification Log for Hemoglobin A1c Sample"
9. Complete Federal Express airbill (example provided)
10. Samples must be shipped priority overnight
11. Shipping should only be Monday-Wednesday to ensure delivery during the week
12. Ship samples to:

Jean Bucksa
BARI 2D Lipid Biochemistry Core Lab Coordinator
Fairview University Medical Center
420 Delaware Street, SE L275
Minneapolis, MN 55455
(612) 273-3391

13. Fax completed "BARI 2D Sample Identification Log for Hemoglobin A1c Sample" prior to shipment to:

Jean Bucksa
Fax # (612) 273-3489

Date Entered _____
Initials_____

PLEASE COMPLETE FORM, ENTER INTO MATRIX, INCLUDE COPY IN EACH SHIPMENT, AND FAX COPY TO: JEAN BUCKSA, (612) 273-3489

DATE OF SHIPMENT: _____ **SITE ID AND NAME:** _____

FEDEX AIRBILL NUMBER: _____ **SITE CONTACT NAME:** _____

SITE TELEPHONE: _____ **FAX #:** _____

MATRIX System will assign SAMPLE IDENTIFICATION LOG ID ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

BARI 2D ID	Draw Date*	Base-line	1 mo	3 mo	6 mo	1 yr	1.5 yr	2 yr	2.5 yr	3 yr	3.5 yr	4 yr	4.5 yr	5 yr	No sample	Reason **	
																Code	Other Explanation

***If no sample provided, enter date of follow-up evaluation under "Draw Date", check the correct follow-up period for patient.**

****** Codes for Reason No Sample:** **1.** Patient Died **2.** Patient Refused **3.** Physician Refused **4**. Venipuncture Unsuccessful
5. Decompensated medical status precluded sampling **6.** Processing accident following collection **7.** Other (write reason in space provided)

FedEx USA Airbill 822637117248

1 From

Date

Sender's FedEx Account Number

Sender's Name

Phone ( )

Company

Preprinted with Site Information

Address

City State ZIP

2 Your Internal Billing Reference

3 To

Recipient's Name Jean Bucksa, BARI 2D Phone (612) 273-3391

Company Fairview University Medical Center

Address 420 Delaware Street, SE L275

City Minneapolis State MN ZIP 55455

Questions? Call 1-800-Go-FedEx® (800-463-3339)

Visit our Web site at www.fedex.com

By using this Airbill you agree to the service conditions on the back of this Airbill and in our current Service Guide, including terms that limit our liability.

0200 Sender's Copy

4a Express Package Service — Packages up to 150 lbs.

X FedEx Priority Overnight — Next business morning

FedEx Standard Overnight — Next business afternoon

FedEx First Overnight — Earliest next business morning delivery to select locations

FedEx 2Day® — Second business day

FedEx Express Saver® — Third business day

4b Express Freight Service — Packages over 150 lbs.

FedEx 1Day Freight® — Next business day

FedEx 2Day Freight — Second business day

FedEx 3Day Freight — Third business day

5 Packaging

FedEx Envelope/Letter®

FedEx Pak®

X Other Pkg.

6 Special Handling

SATURDAY Delivery

SUNDAY Delivery

HOLD Weekday at FedEx Location

HOLD Saturday at FedEx Location

Does this shipment contain dangerous goods?

One box must be checked.

No

Yes

Yes

Dry Ice

Cargo Aircraft Only

7 Payment Bill to:

Sender

Recipient

X Third Party

Credit Card

Cash/Check

2555-3223-5

Total Packages

Total Weight

Total Declared Value†

$ .00

8 Release Signature

360

VIII. RESUPPLY

Your initial supply will include:

1. Baseline Collection Kits (each containing)

    a. 2 blue citrate vacutainer tubes
    b. 1 green sodium heparin vacutainer tube
    c. 1 tiger top SST vacutainer tube
    d. 2 lavender EDTA vacutainer tubes (pre-labeled)
    e. 8 pre-labeled blue microcentrifuge tubes
    f. 2 pre-labeled green microcentrifuge tubes
    g. 2 pre-labeled red microcentrifuge tubes
    h. 2 pre-labeled lavender microcentrifuge tubes
    i. Disposable pipets

2. Baseline and Year kits will include supplies for urine collection
3. Bulk supplies (collection tubes, microcentrifuge tubes, pipets)
4. Storage containers for freezing/shipping samples
5. Preprinted Federal Express Airbills (for The University of Vermont and Fairview-University Medical Center)
6. Styrofoam shipping boxes
7. Cold packs (to be frozen upon delivery and then used to keep lavender EDTA tube #1 cold during shipment to Fairview-University Medical Center)
8. Marking pens for labeling microcentrifuge tubes

Upon enrollment of the first subject, Month 1 and Month 3 collection kits will be sent

Baseline, Month 1, and Month 3 collection kits will be replenished as necessary

Supplies for Month 6, Month 12, and every 6 month visits through Year 5 will be sent 2 months prior to expected visit

If you need additional specimen collection kits or shipping supplies, please complete the "Reorder Form" and fax to:

Michaelanne Rowen, Laboratory Coordinator
The University of Vermont
Fax #: (802) 656-8932

BARI 2D Fibrinolysis and Coagulation Core Lab

SUPPLY REORDER FORM

Fax to: (802) 656-8932
Attn: Michaelanne Rowen, Laboratory Coordinator
The University of Vermont

Requester's Name: _____
Investigator's Name: _____ Site Number: _____
Telephone Number: _____ Fax Number: _____

Specific Visit Kits:

Visit Name	# Kits Needed	Current Quantity on Hand
Baseline	_____	_____
Month 1	_____	_____
Month 3	_____	_____
Month 6	_____	_____
Month 12	_____	_____
Year 1.5	_____	_____
Year 2	_____	_____
Year 2.5	_____	_____
Year 3	_____	_____
Year 3.5	_____	_____
Year 4	_____	_____
Year 4.5	_____	_____
Year 5	_____	_____

Shipping Supplies	Order Quantity
Styrofoam Boxes	_____
Preprinted Fed Ex Airbills (for The University of Vermont)	_____
Preprinted Fed Ex Airbills (for Fairview University)	_____
Cardboard Storage Boxes	_____
Other_____	_____
Other_____	_____

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CHAPTER NINE: SECTION THREE ECG CORE LABORATORY

I. PURPOSE OF THE CORE ECG LABORATORY (CEL)

The purpose of the CEL is to classify myocardial infarction/ischemic events through analysis of resting ECGs, electrocardiographic data, cardiac enzyme findings, and clinical documentation. The information and the methods used to acquire it must be consistent across clinical units to ensure uniform analysis at the CEL. This manual of operations concerns acquisition and submission procedures of resting ECGs to the CEL.

II. DATA COLLECTION INTERVALS

A. Scheduled Resting ECG Collection

Standard 12 lead resting ECGs will be collected at the following time points:

1. Baseline (within seven days prior to randomization)
2. 3 months post-randomization
3. Annually at years 1, 2, 3, 4, 5, 6, and 7
4. Patients initially randomized to the immediate revascularization strategy (PCI or CABG) will have a resting ECG taken pre-procedure and post-procedure. The pre-procedure resting ECG should be acquired within seven days before the revascularization procedure. If the baseline and pre-procedure resting ECG are within 14 days**,** the same ECG may be used for both time points, providing that there is no intervening cardiac event.

    a. The post-procedure resting ECG for patients undergoing CABG should not be acquired during the first 48 hours since bandages on the patient's chest result in different lead placements. The post-procedure resting ECG should be acquired 48-96 hours post-CABG.
    b. The post-procedure resting ECG for patients undergoing PCI should be acquired before the patient goes home.

B. Unscheduled Resting ECG Collection

Additional standard 12 lead resting ECGs will be collected for patients hospitalized for acute coronary syndrome (myocardial infarction or unstable angina), admission for revascularization procedure, death or any patient discharged from hospital with a diagnosis of myocardial infarction.

- If the patient experiences ischemic cardiac pain, ECGs should be collected as close as possible to the time of pain and at 24 hours post-symptoms.

The ECG that shows the maximum new Q or QS wave or maximum change of an old Q or QS wave and the ECG that shows the maximum elevation of the ST segment should be selected whenever possible. If no ECG displays elevation of the ST segment, the ECG that displays maximum depression of the ST segment or maximum negativity of the T wave should be selected.

III. QUALITY, COMPLETENESS, AND ACQUISITION OF RESTING ECG DATA

A. Quality of Resting ECG Data

The following sections will review methods used to achieve good quality 12 lead resting ECGs. It is important that all clinical units adhere to uniform ECG electrode placement and acquisition procedures. The CEL monitors ECG quality within 48 hours of receipt at the CEL and reports inadequate ECG quality to the Coordinating Center (CC).

B. Completeness of Resting ECG Data

It is essential that all resting ECGs be obtained at their specified time points. The baseline resting ECG serves as the initial comparison with future ECGs. Omission of this ECG may invalidate serial ECG analysis because it is not possible to differentiate an abnormal ECG finding on a subsequent ECG from a pre-existing ECG abnormality. Omission of resting ECGs subsequent to baseline could miss the development of new ECG abnormalities.

C. Resting ECG Acquisition

1. GENERAL GUIDELINES

Resting ECGs will be acquired with the following general guidelines:

a. All resting ECGs will be 12 lead ECGs
b. 25mm/sec paper speed
c. Recorded calibration mark confirming calibration of 10 mm to 1 mV
d. Resting ECGs should be raw data and not obtained in "average" mode.
e. Uniform procedures for lead placement, skin preparation, and quality control which follow will ensure comparability of resting ECG data.

2. RESTING ECG LEAD PLACEMENT

a. The patient should be supine with upper body exposed, shoulders straight, and arms relaxed.
b. Ask the patient to avoid movements that may cause errors in marking the electrode locations or artifact in the 12 lead resting ECG recording.
c. Mark each electrode site with a felt tip pen using anatomical landmarks to determine lead placement (see Attachment A):

Lead V1: Fourth ICS space at the right of the sternal border
Lead V2: Fourth ICS space at the left of the sternal border
Lead V3: Position equidistant between lead V2 and V4
Lead V4: Fifth ICS space in the midclavicular line
Lead V5: Fifth ICS space at the level of the anterior axillary line
Lead V6: Fifth ICS space at the level of the midaxillary line
Lead RL: Right lower leg above the inner ankle or as close as the electrode will reach
Lead LL: Left lower leg above the inner ankle or as close as the electrode will reach
Lead RA: Right inner right arm above the wrist
Lead LA: Left inner right arm above the wrist

Note: Electrode positioning for women is determined with respect to anatomical landmarks. In women with large breasts, place the electrodes on top of the breast in their natural position when supine. Do not move the breast upwards or laterally to place the electrodes under the breast.

3. RESTING ECG SKIN PREPARATION

The skin should be prepared for electrode attachment by the following:

a. Shave hair from the electrode site. This will improve adhesion and conduction as well as electrode removal.
b. Rub each electrode site with alcohol or acetone to remove skin oils.
c. Rub in a single direction with gauze or a mildly abrasive pad to remove the epidermal layer at each site. This will remove dead skin and oils to enhance conduction. The skin should appear slightly red.

4. RESTING ECG ELECTRODE ATTACHMENT

a. Place an electrode at each prepared site.
b. Apply pressure around the perimeter of the electrode in a single motion if disposable electrodes are used. Do not press on the center gelled portion.
c. Suction cup electrodes are connected to electrode cables and their placement follows the same sequence as disposable electrodes.
d. Allow the gel to penetrate a minute or two to enhance conduction before recording the 12 lead resting ECG.

5. RESTING ECG ELECTRODE CABLE ATTACHMENT

The risk of wrong connections (lead reversals) can be minimized if a uniform sequence of electrode attachment is followed. The following sequence of connecting electrode cables is recommended:

a. Right Leg
b. Left Leg
c. Right Arm
d. Left Arm
e. V1
f. V2
g. V3
h. V4
i. V5
j. V6

Straighten the electrode cable wires prior to attaching the electrodes to decrease the possibility of lead reversals. After attaching the lead wires, verify one by one that the connections to all electrode sites are correct.

D. Recording the Resting ECG

The patient should be in the supine position. Ask the patient to relax, breathe normally, and refrain from talking or moving while the 12 lead resting ECG is being recorded. Specific directives for recording the resting ECG with Marquette electrocardiographic equipment are given in Attachment B. Record the 12 lead resting ECG and confirm good quality 12 lead printout using the post-recording quality check items listed below (E.).

E. Post-recording Quality Check of Resting ECG

Inspect the resting ECG recording immediately for quality and repeat the recording if problems are identified. Check for the following:

1. EXCESSIVE BASELINE WANDER

Excessive Baseline Wander is defined as 1.0 mm difference between the PQ baseline in three consecutive ECG complexes. The source of this artifact is usually inadequate skin preparation.

2. MOTION ARTIFACT OR LOOSE ELECTRODE CONTACT

These may cause sudden jumps in some ECG leads.

3. EXCESSIVE MUSCLE NOISE

This is random noise in excess of 5 mm. The source of this artifact may be inadequate skin preparation or a patient that is shivering or trembling.

4. EXCESSIVE 60 HZ NOISE

60Hz noise is visible on the 12 lead resting ECG. This noise is usually associated with A-C interference from nearby machines. Another source may be poor skin contact.

5. VALID CALIBRATION DOCUMENTATION

The calibration standard should be recorded on each resting ECG. Invalid calibration exceeds $\pm$ 1.0 mm of the standard 10 mm pulse. Equipment should be calibrated if outside of the acceptable range.

6. MISSING LEADS

Ensure all 12 leads are recorded. A flat line in one or more of the lead groups is an indication that one or more leads is not attached.

7. CHECK FOR LEAD REVERSAL

The 12 lead resting ECG should be inspected for possible lead reversals. Look for normal progression of chest lead patterns from V1 to V6. Inspect lead AVR for negativity, and lead I for mainly positive P, QRS, and T wave. If any condition is suggestive of lead reversal, re-check the electrode cable attachment.

8. SOURCES OF ARTIFACT

Sources of artifact may include the following:

a. Inadequate skin preparation (the most common cause of artifact)
b. Defective electrodes (check expiration dates, gel dries over time)
c. Fractured lead wires
d. Fractured wires in the acquisition cord interface
e. The patient not resting quietly and relaxed

F. Resting ECG Submission

The CEL is equipped to receive 12 lead resting ECGs electronically via a dedicated Marquette MUSE receiving unit. The unit has a validated noise reduction algorithm and because of the simultaneous 12 lead data transmission is economical in terms of phone transmission time. The aim of standardizing ECG recording equipment and transmission capabilities is to provide the highest quality document for ECG analysis and provide a repository of digitized ECGs which can be easily stored and retrieved for subsequent data analysis. Detailed instructions are included in Attachment B for programming and

transferring data via the phone line. It is imperative that electronic data be sent according to the parameters specified in Attachment B; resting ECGs that are not correctly identified will not be directed to reside in the BARI 2D ECG electronic folder and will not be logged in as received.

Attachment B is written for Marquette electrocardiographic equipment that is compatible with the Marquette MUSE receiving unit at the CEL. Clinical units may possess other ECG recording machines that have storage capacity of resting ECGs. Even though such machines would not be capable of electronic transmission of resting ECGs to the CEL, the stored resting ECGs should not be deleted from these machines until a confirmation of receipt of the hardcopy ECG has been received from the CEL.

All non-electronic transferred resting ECGs will be original paper copies and will be mailed to the CEL where they will be logged in and assessed for quality. Each original paper copy resting ECG will be labeled using study labels. A template for these labels will be available on the BARI 2D website. These labels should be meticulously completed to provide all necessary information (patient ID, ECG date and time, ECG category, digitalis usage, procedure date and time, myocardial infarction/ ischemic event, etc.) to route the resting ECG to the appropriate study. Resting ECG categories will include baseline, follow-up (3 months and 1, 2, 3, 4, 5, 6, and 7 years), pre-procedure, post-procedure, emergency room visit, and hospital discharge. More than one category may be checked if appropriate. Data should be submitted to the CEL with the patient's name either deleted or blocked out to ensure confidentiality.

IV. RECEIPT OF RESTING ECG DATA AT THE CEL

Electronically transmitted resting ECGs and original hardcopy resting ECGs will be sent from the clinical units daily to the CEL. All resting ECGs arriving at the CEL are logged into a computer database. Data for interim suspected myocardial ischemic events (emergency room notes, initial history and physical, discharge summary, resting ECG closest to admission and closest to discharge, and cardiac enzyme data) will be provided to the CEL by procedures established prior to the initiation of BARI 2D (electronic via the CC or hardcopy via the clinical unit).

V. RESTING ECG QUALITY CONTROL PROCEDURES AT THE CEL

Incoming data to the CEL will be logged into an inventory program for tracking purposes. All resting ECGs will be evaluated for the quality parameters listed below. See section C.5 for a detailed description of the parameters.

1. Excessive baseline wander
2. Motion artifact or loose electrode contact
3. Excessive muscle noise
4. Excessive 60 Hz noise
5. Valid calibration documentation
6. Missing leads
7. Lead reversal

VI. CONFIRMATION OF DATA RECEIPT FROM THE CEL

When resting ECGs are electronically transmitted (via the MUSE), clinical units are notified by fax within 24 hours of receipt. Monthly reports from the CEL are sent to all clinical units and are made available to the CC upon request. The CEL personnel will be available for consultation and questions regarding study operations (Attachment C).

VII. DEFINITION OF MI

The diagnosis of MI will be made on the basis of clinical information available from hospitalization (*[ER sheet]* discharge summary; laboratory data, ECG) and will require an appropriate clinical history consistent with acute MI.

QMI is defined as symptomatic or asymptomatic (discovered during routine follow-up). A symptomatic QMI is confirmed if the patient is admitted to hospital, has abnormal cardiac enzymes as defined below and develops a new 2-grade Q wave worsening (using adapted Novacode for serial comparison). New permanent LBBB will be confirmed as a QMI when enzymes are abnormal. An asymptomatic QMI is confirmed when ECG QMI criteria are detected during a routine follow-up visit and there is no intervening event from the prior scheduled visit that would explain the finding.

NonQMI is defined by the ACC/ESC MI consensus document. A nonQMI is confirmed if the patient is admitted with an abnormal cardiac enzyme profile (typical rise and fall) defined below and has either (1) new ST-T wave changes or (2) chest pain or clinical history consistent with MI or (3) a coronary revascularization procedure in the preceding 48 hrs with a subsequent increase in cardiac enzymes that meet criteria.

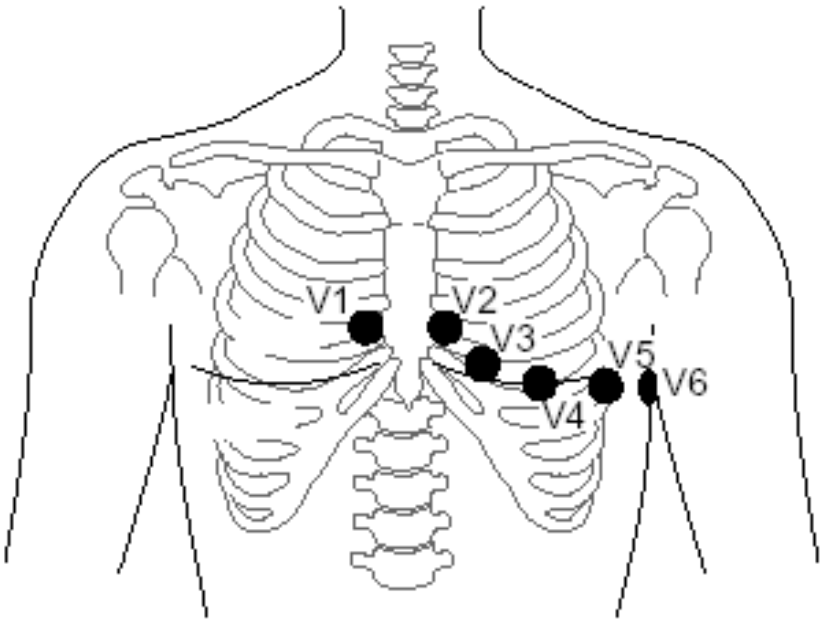
Criteria for Abnormal Cardiac Enzymes

1. The enzyme profile must exhibit a typical rise and fall and result from an ischemic event.
2. For CK-MB or CK, the elevation must be $\geq$ 2ULN for the local laboratory. CK-MB takes precedence over total CK
3. For cTn, the elevation must be $\geq$ 2ULN using local laboratory criteria established as diagnostic of MI. cTn takes precedence over CK-MB (i.e. when CK-MB is abnormal but cTn is normal, the enzyme profile will be considered normal)
4. When CK-MB is collected after a coronary revascularization procedure, the threshold for abnormality is increased to $\geq$3ULN for PCI procedures and $\geq$10ULN for CABG procedures. cTn post-procedure will not be used to diagnose post-procedure MI because of the lack of reliable long-term data at the current time, *except in the situation where there are no available CK MB data, in which case cTn will be used to establish a diagnosis.*
5. Isolated cardiac enzyme rise alone does not qualify as an MI event.

Notes: By requiring the cardiac enzymes to have a higher threshold (2ULN), the sensitivity to detect MI events is diminished to enhance specificity. If we lower it to just the ULN, we enhance sensitivity at the expense of specificity. *The Core Lab will code for* the more specific criteria but also code for the more sensitive criteria so we can examine the impact on treatment differences using both definitions although the latter would purely be for exploratory hypotheses.

ATTACHMENT A: PRECORDIAL RESTING ECG LEAD PLACEMENT

1 Electrode Placement for Standard Leads (I, II, III, aVR, aVL, aVF, V1...V6)



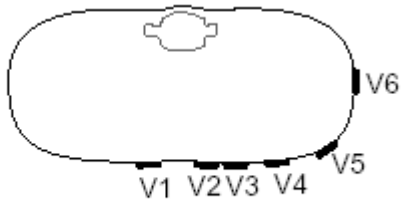


Figure 1-1. Chest electrode placement

For acquisition of the standard ECG leads four electrodes must be applied on the limbs and six on the chest. The limb electrodes should be placed distally on the inner aspect of the wrists and ankles (Figure 1-2). Figure 1-1 shows the chest electrode application points.

V1 4th intercostal space at the right border of the sternum

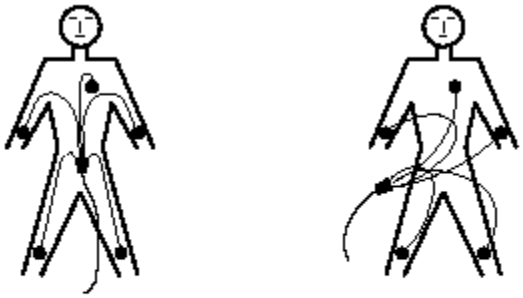
V2 4th intercostal space at the left border of the sternum

V3 midway between locations V2 and V4

V4 at the mid-clavicular line in the 5th intercostal space

V5 at the anterior axillary line on the same horizontal level as V4 and V6

V6 at the mid-axillary line on the same horizontal level as V4



correct wrong

Figure 1-2 Arranging the patient cable

- Arrange the leadwires and patient cable as shown in Figure 1-2.

ATTACHMENT B: RESTING ECG ACQUISITION: MARQUETTE EQUIPMENT SET-UP PROCEDURES

A. Equipment Information

Marquette manufactures several models of electronic resting ECG analysis systems that are capable of telephone transmission. The present description refers to a Marquette Mac PC (Part # MACPC-AAA-ABCA, Model: MACPC). The systems are similar with respect to setting up parameters specific to the study.

B. Equipment Support and Troubleshooting Information

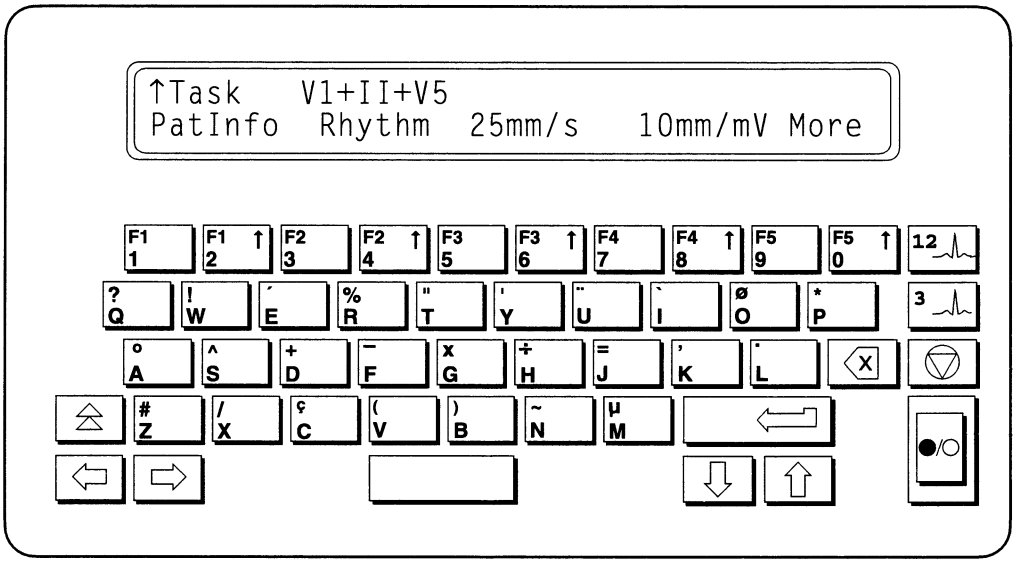
The Marquette Operator's Manual provides additional information and should be used in conjunction with the information provided here. It is an excellent resource and contains detailed information for troubleshooting equipment problems.

C. Marquette Equipment Set-up Procedures

The system set-up will be modified to the following specifications for the BARI 2D Study. The set-up will be stored for the duration of the study; only changes in time will need to be modified. (Refer to the Marquette Operator's Manual, Chapter 11: SETUP). *Once these details are set, the system will retain them until they are manually modified.*

D. Overview: MAC PC Keyboard

The following diagram is from the Marquette MAC PC Operator's Manual and provides a brief overview to the MAC PC keyboard.



Note: Each of the 10 numerical keys on the keyboard has a number from 1-5 on it preceded by the letter F. These keys have a dual purpose of either typing in numerical data or serving as function keys to select an item from the LCD.

E. Marquette Equipment Set-up for the BARI 2D Study

1. SETTING DATE AND TIME

To enter the setup menu:

a. Press the STOP key to display the main menu.
b. Hold the shift key down while pressing the 2 key for the system functions menu.
c. Select setup to enter the Cart Set up menu. Enter the date/time from this menu.
d. Select Date/Time
e. Select Date: type the day, a dash, the month, a dash, and the year. (Press enter)
f. Select Time: type the hour, a dash, and the minute. (Press enter)
g. Press the STOP key to return to the main menu.

***** ***Note: remember to edit when the time changes*** *****

2. SETTING RECEIVING UNIT (CEL) PHONE NUMBER

To enter the setup menu:

a. Press the STOP key to display the main menu.
b. Hold the shift key down while pressing the 2 key for the system functions menu.
c. Select setup to enter the Cart Set up menu. Enter phone numbers from this menu.
d. Select Phone

The CEL Marquette receiving unit phone number can be stored in the clinical unit Marquette machine. Entering and storing the CEL phone number will save time because the number will not have to be entered for each transmission. Store the CEL phone number with the following specifications:

Phone Numbers: Select Number 1
Phone Number 1 Description: Type in BARI 2D SLU CEL (press enter)
Phone Number 1: The CEL Marquette receiving unit phone number is (314) 725-2907

Refer to the Marquette Owner's Manual to enter the phone number; note special entry is required if you must dial 9 for an outside line.

Press the STOP key to return to the main menu.

3. ENTERING REMAINING SYSTEM SET-UP ITEMS

Step 1: Press the STOP key to display the main menu.
Step 2: Hold the shift key down while pressing the 2 key for the system functions menu.
Step 3: Select setup to enter the 1st Cart Set up menu.

Step	LCD display	Your Action
4	Cart Set up Dat/Tim Phone Ldgrps Reports More	Select More
5	Cart Set up Modem Passwds Misc Defaults More	Select Misc
6	Line Frequency: 60 Hz 50 Hz	Select 60 Hz
7	Cart ID: 0-255	To be determined

8	Site ID: 1-255	Type your site number
9	Default Location: 0-999	Type 30 (CEL code for BARI 2D ECG)
10	Institution Name: Up to 40 characters	Type your institution name and state
11	Number of Patient ID Digits: 1-12	To be determined
12	ID Required to Record an ECG: Yes No	Select Yes
13	Height/Weight: in/lb cm/kg	Select in/lbs to record height and weight in inches and pounds
14	Input Patient Age as: DOB Years	Select DOB to enter date of birth
15	Ask Blood Pressure Questions: Yes No	Select No
16	Ask Options Questions: Yes No	Select No
17	Ask Order Number Questions: Yes No	Select No
18	Confirmation Text: Unconf RevdBy	Select Unconf
19	Suppress Normal Statements: Yes No	Select Yes
20	Suppress Border + Abn Stmts: Yes No	Select Yes
21	ECGs to Store/Transmit: All Abnormal	Select All
22	Delete ECGs After Transmission: Save Delete	Select Save (ECGs will be deleted manually after transmission)
23	Store/Transmit Control: Store Transmit	Select Store (ECGs will be transmitted at scheduled intervals)
24	Power up Speed: 25 mm/s 50 mm/s	Select 25 mm/s
25	Power up Filter: 40 Hz 100 Hz	Select 100 Hz
26	Screening Criteria: Yes No	Select No
27	Baseline Roll Filter: .01 Hz .02 Hz .16 Hz .32 Hz	Select .16 Hz
28	QC Baseline Drift: Yes No	Select Yes
29	QC Muscle Tremor: Yes No	Select Yes
30	Disable Automatic Gain Check: Yes No	Select No
31	Pace Pulse Gain (AM - 3): Normal Enhance	Select Normal
32	Bad Lead Handling (AM - 3): Use Flatline	Select Flatline
33	Cart Set up Modem Passwds Misc Defaults More	Press the STOP key to return to the main menu

F. Equipment Set-up for Entering Patient Data

Patient information is entered **prior to acquiring the 12 lead resting ECG** for each resting ECG obtained. If the Main Menu is not already displayed, press the STOP key.

Step	LCD Display	Your Action
1 (main menu)	Task V1 + II + V5 PatInfo Rhythm 25 mm/s 10mm/mV 100Hz	Select PatInfo
2	New Patient: Yes No	Select Yes
3	Patient Last Name:	Enter participant's Study Acrostic (BARI 2D Name Code)
4	Patient First Name:	Type ECG category Type "baseline" or "f/u 1" (3 month follow-up) or "f/u 2" (1 year follow-up) or "f/u 3" (2 year follow-up) or "f/u 4" (3 year follow-up) or "f/u 5" (4 year follow-up) or "f/u 6" (5 year follow-up) or "f/u 7" (6 year follow-up) or "f/u 8" (7 year follow-up) or "admit" or "disch" or "pre-proc" or "post-proc" or "SMI" (suspect infarction/ischemia) (press enter)
5	Patient ID: Digits 0 to 9	Type the participant's BARI 2D Numerical Code (press enter)
6	Referred by: (physician name)	Type BARI 2D
7	Location Number: 0-99	Type your site number (press enter)
8	Room Number:	Type BARI 2D Staff # for the ECG technician acquiring the data
9	Patient Over 1 year Old: Yes No	Select Yes (press enter)
10	Age:	Enter date of birth
11	Height (in inches) 0 to 999	Enter height in inches
12	Weight (in lbs) 0 to 999	Enter weight in pounds
13	Sex Male Female	Select participant gender
14	Race Cauc Black Orietal Hisp More	Select participant race
15	Medication None Unknown Clear Add Scroll	Enter None if the patient is not taking digitalis (press enter) Select Add if the patient is taking

		digitalis (also known as Digoxin, Lanoxin, Lanoxicaps, Novodigoxin) Select D for first letter of medication name Select Digoxin for digitalis and press enter

After entering the patient information, the main menu will reappear. This completes the entry of patient information.

G. Recording the 12 Lead Resting ECG

1. Ask the participant to relax, breathe normally, and refrain from talking or moving while the 12 lead resting ECG is being recorded. Record the 12 lead resting ECG by pressing the record ECG key at the top right corner of the keyboard next to the numerical zero key.
2. A display will appear in the LCD window ** Acquiring Data **, followed by ** ECG Acquisition Complete**.
3. The Mac PC will process the data (LCD screen: ** Analyzing ECG **) and print reports (LCD screen: **Printing reports**).
4. The LCD screen will prompt for number of extra copies (0-9). One copy of each resting ECG should be retained as hardcopy in the participant's study chart at the clinical unit. Enter the number of additional copies. If you do not want additional copies, press enter.
5. The LCD screen will display ** Processing ECG ** then ** ECG Storage complete**.
6. Press enter to return to the main menu.

H. Recording the Resting ECG in the Resting ECG Log

Enter the resting ECG into the Resting ECG Log (next page). Each resting ECG with acceptable quality selected for submission to the CEL should be recorded in the Resting ECG Log. The purpose of the Resting ECG Log is to record each BARI 2D resting ECG that was performed, submitted to, and received by the CEL. The Resting ECG Log should be used for resting ECGs that are electronically transmitted to the CEL as well as paper copy resting ECGs that are mailed to the CEL. Use the Resting ECG Log as a guide for the following:

1. Record resting ECGs to be electronically transmitted to the CEL (and which resting ECGs need to be deleted before transmission).
2. Cross-check the directory of resting ECGs to be electronically transmitted to the CEL before transmission.
3. Confirm successful electronic transmission of the resting ECG from the confirmation of receipt report sent from the CEL.
4. Select resting ECGs to be deleted following verification of successful electronic transmission to the CEL.
5. Record paper copy resting ECGs to be mailed to the CEL. If they are stored on electrocardiographic equipment that is incompatible with the Marquette MUSE unit at the CEL, they may be deleted following confirmation of receipt from the CEL.

BARI 2D Resting ECG Log

The purpose of the Resting ECG Log is to record each BARI 2D Resting ECG that was performed, submitted to, and received by the CEL. The Resting ECG Log should be used for resting ECGs that are electronically transmitted to the CEL as well as paper copy resting ECGs that are mailed to the CEL. Use the Resting ECG Log as a guide for the following:

1. Select resting ECGs to be electronically transmitted to the CEL (and which resting ECGs need to be deleted before transmission).
2. Cross-check the directory of resting ECGs to be electronically transmitted to the CEL before transmission.
3. Confirm successful electronic transmission of the resting ECG from the confirmation of receipt report sent from the CEL.
4. Select resting ECGs to be deleted following verification of successful electronic transmission to the CEL.
5. Record paper copy resting ECGs to be mailed to the CEL. If they are stored on electrocardiographic equipment that is incompatible with the Marquette MUSE unit at the CEL, they may be deleted following confirmation of receipt from the CEL.

Date*	**Time***	**Patient Name Code**	**Patient ID Number**	**ECG Category**	**Was ECG Electronically Transmitted? (Y/N)**	**Date ECG Transmitted**	**Date CEL Confirmed Receipt**	**Delete ECG After Verify Receipt (Y/N)**	**Comments**

* Enter the **date and time of the resting ECG to be submitted**. If to improve quality, a 2nd resting ECG was obtained and the quality was acceptable, record only the 2nd resting ECG date and time. This will allow you to select out and delete the poor quality resting ECG prior to transmission to the CEL.

I. Procedure for Electronically Transmitting Resting ECGs by Telephone to the CEL

Select Resting ECGs for Transmission by Printing a Directory

1. Press the STOP key to display the main menu.
2. Hold the shift key down while pressing the 2 key for the system functions menu.
3. Select Storage
4. Select Directory

A directory will be printed. Compare it to the handwritten BARI 2D ECG Log to determine which resting ECGs to transmit to the CEL. You must print a directory before transmission so you can delete resting ECGs that are recorded twice due to poor quality.

Delete poor quality resting ECGs or resting ECGs not to be transmitted (see next section). Print a final directory of resting ECGs to be transmitted. Initial the directory, the date will be stamped by the machine, and attach the directory to your daily log for later verification of receipt by the CEL.

J. Deleting Resting ECGs

The Marquette Operator's Manual chapter on deleting an ECG is an excellent resource. A resting ECG is deleted if it is a duplicate record or when the resting ECG has been successfully transmitted to the CEL. If more than one resting ECG was acquired in an attempt to improve the quality of the tracing, the recording time will provide a clue as to which resting ECG to keep and which to delete. To delete one or more resting ECGs:

1. Press the STOP key to display the main menu.
2. Hold the shift key down while pressing the 2 key for the system functions menu.
3. Select Storage
4. Select More
5. Select Delete
6. "Select by Patient ID?" Select No
7. The patient data for each stored resting ECG will appear in the LCD display. The following options are available:

    a. Yes (selects this resting ECG for deletion)
    b. No (bypasses this resting ECG for deletion)
    c. No… (bypasses this and all subsequent resting ECGs for deletion)
    d. Yes… (selects this and all subsequent resting ECGs for deletion)
    e. Expand (provides additional information such as date and time of resting ECG which may be required in the decision to select the resting ECG for deletion)

8. After the resting ECGs are selected for deletion, you have a chance to change your mind. The LCD will display the number of resting ECGs selected for deletion and you select Yes to perform the deletion and No to cancel the deletion.

K. Electronically Transmitting Resting ECGs

Transmit Resting ECGs at the end of each day.

1. Connect a telephone cable from a telephone wall outlet to the telephone connector on the back of the system (cable PN 80159-014).
2. Press the STOP key to display the main menu.
3. Hold the shift key down while pressing the 2 key for the system functions menu.
4. Select Storage
5. Select Transmit

6. Select Phone
7. The machine was set up with one location for transmission. The telephone number of the CEL will appear in the LCD. Press enter.
8. The LCD will display: Select by Patient ID? Select No.
9. The patient data is displayed for a single resting ECG with an LCD display such as:

123456 HANJO, baseline
Yes No No...

Select Yes... to include all stored resting ECGs in the file transmission (the resting ECGs were selected in the previous section).

10. The LCD will display ** Batch Transmission**
11. After the last resting ECG is transmitted, a message will appear displaying the number of resting ECGs transmitted (should equal the number of resting ECGs on the directory printed prior to transmission).
12. Press the STOP key to return to the main menu.
13. Record the transmission date on the BARI 2D ECG Log.

Do not delete the resting ECGs from storage until a confirmation of receipt report is obtained from the CEL. Clinical units will be notified by fax within 24 hours of receipt when ECGs are electronically transmitted (via the MUSE).

Quality Control Checklist for Resting ECG Transmission

- ☐ Print a directory
- ☐ Cross check the directory with the BARI 2D Resting ECG Log for selection of resting ECGs for transmission
- ☐ Delete resting ECGs that do not need to be transmitted
- ☐ Transmit the resting ECGs
- ☐ Document the date transmitted on the BARI 2D Resting ECG Log

Quality Control Checklist for Resting ECG Deletion

- ☐ Print a directory
- ☐ Cross check the confirmation report from the CEL with the directory print out
- ☐ Document the date the CEL confirmed receipt on the BARI 2D Resting ECG Log
- ☐ Delete resting ECG's successfully transmitted to the CEL
- ☐ Document the resting ECG deleted on the BARI 2D Resting ECG Log

ATTACHMENT C: CORE ECG LABORATORY DIRECTORY

St. Louis University Core ECG Laboratory
1034 South Brentwood, Suite 1550
St. Louis, Missouri 63117-1215

Phone: (314) 725-4668
Fax: (314) 725-2171

PRINCIPAL INVESTIGATOR

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Assistant Professor

email ksstock@ecglab.org

NURSE COORDINATOR

Jane Eckstein, R.N.

email jfeckst@ecglab.org

For questions regarding protocol requirements, receipt of data, and confirmation reports contact Jane Eckstein at (314) 725-4668.

CHAPTER NINE : SECTION FOUR ECONOMICS CORE LABORATORY

I. ROLE OF ECONOMICS CORE LABORATORY

Patients enrolled in BARI 2D will be contacted every three months by a trained interviewer at the Stanford University Central Economic Laboratory. The interview will be conducted at a time the patient indicates will be convenient for him or her, and will focus on utilization of both outpatient and inpatient medical services. The number of outpatient and home health visits, specific outpatient tests and procedures (e.g., stress tests, coronary angiograms, ventricular function studies) and medication will be ascertained at each interview. Hospital admissions will be a prime focus of data collection efforts, as they represent the highest cost component of medical care. The interviewer will note the hospital name and location using a national reference guide as necessary during the interview to assure accuracy, dates of admission and discharge, and reason for admission. The Central Economic Laboratory will then contact the hospital to obtain a copy of the standard hospital bill (UB92 format), including ICD-9 codes for diagnosis and procedures, diagnosis-related group assignment, and charges by hospital department. When a hospital admission is identified with the patient, The Central Economics Laboratory will use a release authorization form signed by the patient, and will obtain a copy of the UB92 hospital bill from the hospital.

II. DOCUMENTS

A. Introduction Letter

This letter will be provided by the site coordinator to the participant at time of enrollment and randomization. The letter introduces the role of the Economics Core Lab to the participant and briefly outlines the schedule for follow-up contact from the Economics Core Lab at Stanford University by a trained interviewer. The nature of the questionnaire that will be administered is reviewed. The Economics follow-up questionnaire is available on the BARI 2D website. Site coordinators will provide the questionnaire to patients at the time of enrollment as needed. The letter also informs the participant that we will request an authorized Release of Information form in order to request bills associated with hospitalizations. **See Attachment A.**

B. Patient Information Sheet

Site coordinators will complete the Patient Information form at the time of enrollment/randomization. The patient information form is faxed to the Economics Core Lab within 2 weeks of randomization. **See Attachment B.**

C. Release of Information

This document allows the Economics Core Lab to obtain hospital bills when BARI2D patients are hospitalized. The purpose of collecting the hospital bills is to compare long-term all-cause costs between the BARI 2D treatment arms. Once the bills are received at the Economic Core Lab, all identifying information is removed and the patient's BARI 2D identification number and namecode are applied to keep track of the bills. All of the information we receive is confidential and we will not release it to anyone without written permission from the patient. If the patient ever has any questions or concerns about the consent form, they can contact the project manager directly. This document is available in English and Spanish. **See Attachments C and D**.

D. Sending Information to the Economics Core Lab

Coordinators will FAX the following information to (650)-723-3786:

1). Patient Information Form
2). Release Authorization
3). Copy of the main BARI2D consent

Coordinators will MAIL the following information to:

Cheryl Kallmann
BARI2D Economics Core Lab
HRP/Redwood Building T259
Stanford, CA 94305-5405

1). Original Release Authorization

ATTACHMENT A

Dear BARI 2D Participant:

Thank you for agreeing to participate in the BARI 2D Economics Study. We would like to explain what your participation will involve and introduce the goals of the Economics Core Laboratory.

Your hospital is participating in the BARI 2D clinical trial to learn about the best ways to treat patients with diabetes and heart disease. As a part of that goal, the Economics Core Lab will evaluate the long-terms costs of different ways of managing diabetes, and the different ways of treating heart disease that are being studied in BARI 2D.

We would like to contact you by telephone every three months to complete a short questionnaire lasting about 3 to 5 minutes. A trained interviewer from our offices at Stanford University in Palo Alto, California, will call you at a time that is most convenient for you. The interviewer will ask you about any doctor or clinic visits, outpatient procedures or hospitalizations you have had in the past few months. You will also be asked about your work status and the medications that you are taking.

To compare long-term costs, we would need to obtain a copy of the bill from the hospital anytime you are admitted for treatment.

Enclosed is a release of information form that will allow us to request a copy of your hospital bill. Please read and sign it and give it to your site coordinator who will mail it to us. If you would like to wait to sign this form until after we've called you, we will be happy to answer any questions and address any concerns you may have at that time. All of the information that we collect will remain confidential and none of the information will be released to anyone without your written permission.

We will be calling you in about 3 months to introduce ourselves and to answer any questions you may have about your participation in the BARI 2D Economics study. Feel free to call us anytime at (650) 723-6427.

We look forward to talking with you. Thank you for you cooperation and participation in this very important study.

Sincerely,

Kathryn Melsop, MS
BARI 2D Economics Core Laboratory
Project Manager

Mark Hlatky, MD
BARI 2D Economics Core Laboratory
Prinicipal Investigator

ATTACHMENT B

FAX FORM TO:
KATHRYN MELSOP
650-723-3786

BARI2D ECONOMICS CORE LAB
PATIENT INFORMATION FORM
·CONFIDENTIAL·

BARI2D ID ___ ___ ___ ___ ___ ___ **Name Code** ___ ___ ___ ___ ___

Date of Randomization: ____/____/____ **Site Coordinator Name:** _____

PATIENT DEMOGRAPHIC INFORMATION

Name (first, middle, last) _____

If female, please check here: _____ **Maiden Name:** _____

Social Security Number: ___ ___ ___- ___ ___ - ___ ___ ___ ___

Medicare Number: _____

Site Hospital Record Number: _____

Date of Birth: ____/____/____ **Place of Birth (City, State):** _____

PATIENT CONTACT INFORMATION

_____
ADDRESS **CITY** **STATE** **ZIP**

_____ _____
HOME PHONE **WORK PHONE**

BEST TIME TO CALL: _____ **OKAY TO CALL AT WORK? (YES OR NO)** _____

PLEASE LIST ANY ADDITIONAL INFORMATION OR COMMENTS THAT THE ECONOMICS CORE LAB SHOULD KNOW:

ATTACHMENT C

Release Authorization

I am a participant in the Bypass Angioplasty Revascularization Investigation 2-Diabetes (BARI 2D) Study. The Economics Core Lab at Stanford University is evaluating the economic impact of the health care I have received. As part of this study, I authorize you to release copies of my hospital, physician bills or Medicare claims to Dr. Mark Hlatky, the Principal Investigator of the Economics Core Laboratory until the end of the study. Please do not hesitate to call him at (650) 723-6427 if you have any questions regarding this study.

_____

Signature of Patient Date Signed

_____

Printed Name of Patient

ATTACHMENT D

Autorización de Entrega de Información

Soy un/a participante en el estudio de Investigación 2-Diabetes Bypass Angioplasty Revascularization (BARI2D). El Laboratorio Economics Core en la Universidad de Stanford está evaluando el impacto económico del cuidado médico que he recibido. Como parte del estudio, yo le autorizo a que le entregue copias de mis recibos de hospitalización, de doctor o reclamos del Medicare al Dr. Mark Hlatky, el investigador principal del Laboratorio Economics Core hasta el final del studio. Por favor, no dude en llamarle por teléfono al (650) 723-6427 si usted tiene alguna pregunta sobre este estudio.

_____ _____

Firma del o de la paciente Fecha

_____

Nombre impreso del o de la paciente

Release Authorization

I am a participant in the Bypass Angioplasty Revascularization Investigation 2-Diabetes (BARI 2D) Study. The Economics Core Lab at Stanford University is evaluating the economic impact of the health care I have received. As part of this study, I authorize you to release copies of my hospital, physician bills or Medicare claims to Dr. Mark Hlatky, the Principal Investigator of the Economics Core Laboratory until the end of the study. Please do not hesitate to call him at (650) 723-6427 if you have any questions regarding this study.

CHAPTER NINE : SECTION FIVE NUCLEAR CARDIOLOGY CORE LABORATORY

I. INTRODUCTION AND RATIONALE

Stress SPECT myocardial perfusion imaging is widely used for detection of CAD and risk assessment. Most patients with physiologically significant coronary stenoses develop reversible perfusion defects. Patients with myocardial infarction have scar. Factors that lower the sensitivity of the test include: submaximal exercise, limited CAD [such as 1-vessel or branch disease, distal stenosis and mild stenosis], anti-ischemic medications, poor images and lack of experience. Abnormal images in the absence of coronary stenosis may be of two broad categories: technique- related [false positives] or due to micro-vascular disorders. In addition to its ability to detect ischemia and scar, the use of gated SPECT provides measurement of LV EF, regional wall motion/thickening and volumes. The EF by gated SPECT correlates well with EF derived by other methods such as contrast angiography, radionuclide angiography, 2DE and MRI. The measurement is also reproducible. The majority of nuclear cardiology laboratories now gate the perfusion images. Gating improves accuracy and enhances prognostic power.

Several studies show considerable variability in the size of ischemic burden by perfusion imaging and coronary angiographic findings. Thus, though in general patients with multi-vessel CAD have larger defects than patients with 1-vessel CAD, and patients with left anterior descending stenoses have larger defects than patients with right or circumflex stenoses, considerable scatter is observed. This observation may help explain why stress perfusion imaging provides independent and incremental prognostic information to clinical, non-imaging stress data and even to coronary angiographic data.

II. PURPOSE OF THE CORE NUCLEAR CARDIOLOGY LABORATORY (NCCL)

The purpose of the BARI 2D NCCL is to determine the impact of therapy on ejection fraction, extent of ischemia and scar [measured by adenosine sestamibi gated SPECT images] as well as on the progression /regression of ischemia/scar and changes in left ventricular function over the study period in relation to glycemic control and micro-vascular complications. The data will also determine the prognostic value of ischemia, scar and ejection fraction for death, myocardial infarction in the entire patient population and specified subgroups.

Key NCCL Personnel and contact information are listed in Attachment A.

III. PROTOCOL FOR ACQUISITION OF NUCLEAR CARDIOLOGY IMAGING

A. Documentation of Site-specific Quality Control Procedures

The NCCL requires submission of a sample SPECT study from each site. The NCCL in collaboration with clinical specialists from Bristol-Meyers Squibb (formerly DuPont Pharma) will have a continued dialogue with clinical sites to maintain high quality studies.

B. Data Collection Intervals

Annual stress SPECT imaging [years 1, 2, 3, 4 and 5 after randomization] will be done on all patients recruited in BARI 2D. It is anticipated that a proportion of patients will have studies completed upon entry if stress SPECT is used as the screen for ischemia and serves as qualifiers to study entry. Baseline studies should be submitted to the NCCL. Interim studies done for clinical reasons should also be submitted. Whenever possible, the attached protocol should be used for entry and interim (non-protocol mandated) studies. Please fax the *Form #1* with all SPECT studies.

C. Patient Study Protocols (see attachment B)

To facilitate completing the nuclear studies, several protocols are acceptable as these mimic those used in routine patient care. The image transfer to NCCL is also set up to be as user-friendly as possible. Possible study sequences to be performed in BARI 2D include the following:

Rest/stress [adenosine] 1-day sestamibi
Stress [adenosine]/rest 1-day sestamibi
Stress [adenosine]/rest 2-day sestamibi
Rest thallium/stress [adenosine] sestamibi

Note: The same protocol should be used in a given patient throughout the study period.

Adenosine stress testing is contraindicated in patients with bronchospasm, second degree or greater AV block in the absence of a pace-maker, or those who are taking oral dipyridamole at the time of testing.

Note: Dobutamine stress will be used in patients with contraindications to adenosine.

A 2-day protocol is recommended in patients whose body weight >220 lbs. or BMI >30 [BMI=Body Mass Index =weight (Kg)/Height(M^2).
Tracer Preparations for these studies are as follows:

Low dose MIBI: 10-14 mCi
High dose MIBI: 25-35 mCi
2-day: 25-35 mCi per study.
Rest thallium: 3-4 mCi in dual isotope protocol

Note: Dipyridamole stress will be used in the Canadian sites (see Attachment B).

For technical specifications for nuclear studies, including guidelines for patient preparation, electrode placement, and quality control guidelines, please review imaging guidelines in J Nucl Cardiol 2001, 8:G1-58.

D. Ordering 99m Tc Sestamibi (Cardiolite®)

The following is the procedure by which the BARI 2D Trial's Nurse Coordinator/Nuclear personnel will utilize to obtain the nuclear imaging study drug, Tc-99m Sestamibi (Cardiolite®), for those patients enrolled in the BARI 2D Trial having their annual nuclear imaging procedure:
The Nurse Coordinator shall contact their institution's Nuclear Imaging laboratory to schedule the annual nuclear imaging procedure, identifiying the scheduled patient as a BARI 2D Trial participant

The Nurse Coordinator will schedule the BARI 2D patient for a Stress (Adenosine) Cardiolite® Gated SPECT myocardial perfusion study. The Nuclear Imaging laboratory personnel at the clinical site will contact their local Syncor radiopharmacy to order the appropriate doses of Cardiolite® by providing the patient's name and identifying the patient as a BARI 2D Trial participant. All study drug, Cardiolite®, ordered from the Syncor radiopharmacy in this manner will be provided free of charge. For issues related to the supply of Cardiolite®, contact your regional Bristol-Meyers Squibb Imaging's Clinical Specialist.

All BARI 2D Trial sites will exclusively utilize and obtain the study drug,Tc-99m Sestamibi (Cardiolite®), from their local Syncor radiopharmacy. Bristol-Myers Squibb Medical Imaging (formerly DuPont Pharmaceuticals Company) has entered into a nationwide agreement with Syncor to provide free (reconstitution and delivery) Cardiolite® to identified BARI 2D Trial participants. The utilization of any radiopharmacuetical service provider other than Syncor will not be reimbursed for the acquisition or replacement costs of Cardiolite® by Bristol-Myers Squibb Medical Imaging.

IV. TRANSFER OF STUDY DATA FROM CLINICAL CENTERS TO NCCL

A. Site SPECT reports: Each site is required to fax to NCCL a copy of stress SPECT report (using code names). The NCCL will extract the relevant data. These include the hemodynamics and ECG response during the stress test as well as site specific interpretation of SPECT images.

B. Image data, in virtually all formats, may be transmitted to the laboratory via FTP, floppy disk, CD ROM or tape and FTP by IP address with sites specific user names and passwords. Data may also be shipped by Fed Ex. In order to send data via FTP, clinical centers will be given a username and password to access the NCCL FTP server. When data is sent via FTP, sites should notify the NCCL by phone, fax, or email that the study has been placed on the server. This will cue the core laboratory staff to retrieve the image data from either the FTP or modem folder. The file lengths will be compared to reference source files.

C. Raw projection images should be submitted to the NCCL after completion of the study. All data sets should be coded for patient confidentiality, corrected for uniformity and center of rotation. All data should be archived at the clinical center prior to transfer.

D. Methods of image transfer. The NCCL prefers the following methods for sending data. If the site is unable to send data in any of the following ways, please contact the core laboratory for more information.

ADAC	SIEMENS	PICKER	All other cameras
¼" Streamer Tape	3 ½" Floppy Disk	¼" Streamer Tape	FTP Data **must be corrected for**
3 ½" Floppy Disk	Zip Disk	3 ½" Floppy Disk	Uniformity and C.O.R.(Center of Rotation)
Optical Disk	Optical Disk	Optical Disk	
FTP		FTP	

Each study should be sent with a completed Core Laboratory SPECT Worksheet (*Form # 1*); for studies sent by FTP, this worksheet should be sent by FAX to the NCCL.

E. Back-up

A three tiered back-up system is in place:

Level I – All data received (Raw & Processed) in native format, will be merged with DTF information and stored on the office management PC in a site-specific folder. This information is backed up nightly on an optical disk.

Level II – All image data, once translated to the ADAC are archived on the ADAC Tracker Optical Disk System. The patient's code name is then indexed to the paper file containing the DTF and all other site communications.

Level III – On a monthly basis, all data including images, electronic text, and forms are recorded on a CD-ROM, which is then added to the site record.

F. Patient Confidentiality

Patient names and any other identifying information **must be removed from the imaging studies prior to transmission to the NCCL.** Each site should substitute the BARI 2D ID for the patient name and medical record number on all imaging studies submitted to the NCCL. The conversion may be implemented at the time the actual imaging procedure is performed, or after the fact as an editing function. In either case, **the imaging study is coded at the site prior to transfer to the NCCL.** The core lab will be contacting participating sites regularly once IRB approvals have been secured.

G. Confirmation of Data Receipt from the NCCL

All sites will receive notification of completed image transfer by email to the site coordinator.

V. INVENTORIES OF STUDIES AT CLINICAL CENTERS

Each site will have a log, which will contain all communications with the core laboratory. The site information form, data transmission forms, and hard copy images of every patient will be submitted from that site. These notebooks will be filed in lockable file cabinets and will contain an entry log to document all additions or edits to the notebook. In addition to the site notebook, which serves as the master record, the sites will have files containing copies of DTFs, image hard copy, and image QC data. An electronic version of this file will be in a password-protected database.

The QC data fields will contain more specific information regarding data transmission, image formatting/ translation, and image quality.

VI. IMAGE INTERPRETATION AT THE NCCL

A. Image Transfer

To validate completeness, the image data will then be checked for format type and converted to the sun file structure used by the ADAC Pegasys system. File headers will be checked to insure proper file naming conventions. Any residual information relating to patient's actual identity will be purged. Conversions will be accomplished by using the latest Numa ® Translation System, then transferred to the ADAC system. Once on the ADAC system, the data will undergo quality assurance check for acquisition/processing accuracy, and technical quality. Any communications between site and NCCL can be accomplished by telephone 205-975-0655, Fax 1-800-513-0656 or e-mail at GSPECT@uab.edu. Beginning January 1, 2002 a toll free fax number will be activated and the number distributed to all sites.

B. Image Interpretation

The images will be interpreted jointly by readers with extensive experience in the field. The images will be reviewed on the computer screen in color and gray scales. The interpretation will be visual and aided with quantitative analysis. A model of 17 segments, accepted by the imaging community, will be used. There will be 1 apical, 4 distal, 6 mid and 6 basal LV segments. The 4 distal segments are anterior, septum, inferior and lateral. The 6 mid and basal segments are anterior, antero-septal, infero-septal, inferior, infero-lateral and antero-lateral. The 17 segments will be re-grouped to correspond to the 3 vascular territories [LAD, LCX and RCA] as outlined in the core laboratory report form *(Form #2)*. Each vascular territory will be assigned as normal, ischemia, scar or both scar and ischemia.

C. Quantitation

Each of the segments will be scored [to assess severity of abnormality] and a global score will be calculated to reflect extent of scar + ischemia [# abnormal segments] and extent of ischemia [# of segments with reversible defects]. In addition, global scores [SSS, SRS and SDS in report form] that reflect extent and severity of abnormality will be measured for scar + ischemia [SSS], scar alone [SRS] and ischemia alone [SDS]. The extent of total [scar +ischemia] and ischemia abnormality may also be measured by a quantitative method, using a reliable polar maps method (optional). The results are expressed as % LV abnormality. Other data will be measured, including the presence of transient ischemic dilatation [TID] and lung tracer uptake. The TID means a larger LV cavity size on stress compared to rest images and in general its presence suggests a large amount of ischemia.

D. Wall Motion/Thickening

It is anticipated that the sites will acquire the perfusion images using gated acquisition [gated SPECT]. The gating allows, in addition to that above, assessment of LV function [wall motion, wall thickening and EF]. The regional data on motion and thickening will use the same model of 17 segments. The wall motion will be graded as normal to dyskinesia and the wall thickening from normal to absent (*Form # 2*). A global score will again be obtained. These data reflect resting LV function.

E. LV EF

In addition, the EF will be measured. Many prior studies have shown that gated SPECT-EF correlates well with other methods and is quite reproducible. LV size and RV size and function will also be assessed.

F. Variability

The NCCL reproducibility data obtained by blinded joint reading of random clinical images [n=10] reflect a high degree of agreement, as demonstrated in many prior studies, summarized in Attachment C. Prior studies suggest a change in perfusion defect size of up to 10% could be technique-related. The same may be true for EF, although the method-related difference is less pronounced in patients with more depressed EF than patients with high normal EF. Agreement in image interpretations in reading sessions #1 and #2 has been very high (*Attachment C*) The NCCL interpretation report is shown (*Form # 2*).

The NCCL will obtain copies of site-generated clinical interpretation of the images and stress test using fax number 1-800-513-0656 and will extract the data in special forms (*Forms #3 and #4*). Each transmission of BARI 2D studies require completion of *Form # 4*. All tabulated data will be transformed to a spreadsheet and transferred to the Coordinating Center. A copy will be maintained at the NCCL.

ATTACHMENT A: NCCL CONTACT INFORMATION AND DIRECTORY

A. Contact Information

Questions, comments, or concerns at any time throughout the study should be directed to the NCCL. The staff are generally available Monday – Friday, 8:30am – 5:30pm (Central Time).

Principal Investigator:	Ami E. Iskandrian, MD	Aiskand@uab.edu
Study Coordinator:	E. Lindsey Tauxe, MEd. CNMT	ltauxe@uab.edu
Nurse Coordinator:	Mary Elizabeth Hall, RN	mhall@uab.edu
Staff Physicist:	Michael V. Yester, PhD	myester@uabmc.edu

B. Mailing Address

BARI 2D Nuclear Cardiology Core Laboratory
The University of Alabama at Birmingham
314 LHT
701 South 19th Street
Birmingham Al 35294-0007
Tel: (205) 975-0655
Fax: (205) 975-0656
e-mail: gspect@uab.edu

C. NCCL Personnel

Ami E. Iskandrian, M.D. – Principal Investigator and Medical Director
Dr. Iskandrian will oversee all laboratory functions with particular attention to image interpretation. He will be in direct contact with sites to provide feedback on image quality and study protocols and to answer questions regarding nuclear cardiology issues related to the study. Dr. Iskandrian has distinguished himself in the field of nuclear cardiology, with many years of experiences.

E. Lindsey Tauxe, CNMT MEd --Technical Director
Mr. Tauxe will provide overall oversight for the operational aspects of the laboratory, especially image transmission, processing, database administration, and management. He is the Nuclear Technologists' Representative on the Board of the American Society of Nuclear Cardiology and is well respected for his knowledge and expertise in image processing.

Robert C. Bourge, M.D. – Chief of Cardiology
Dr. Bourge is Director of the Division of Cardiovascular Disease at UAB and has extensive experience in congestive heart failure, cardiac transplantation and nuclear cardiology. He is board certified in cardiovascular disease and nuclear medicine. Dr. Bourge will supervise the overall operation of the core laboratory and is a valuable asset to the success of the program.

Eva V. Dubovsky, M.D., Ph.D. – Nuclear Medicine Physician
Dr. Dubovsky is a highly experienced Nuclear Medicine Physician with extensive experience in Nuclear Cardiology. She will be involved in image interpretation and quality control.

Jaekyeong Heo, M.D. – Faculty member
Dr. Heo is board certified in nuclear medicine and has extensive experience in the field of Nuclear Cardiology.

Michael V. Yester, Ph.D. – Medical Physicist
Dr. Yester is a highly accomplished medical physicist with extensive experience in all aspects of nuclear imaging and instrumentation. He will provide support in image quality control, troubleshooting, and computer services support.

Mary Elizabeth Hall – B.S.N., RN
Ms Hall has extensive experience in nuclear cardiology research and will provide all research-related support including any necessary interacting with recruiting sites and with the coordinating center.

Bruce McMurray, BS – Information Technology Specialist
Mr. McMurray holds a BS Degree in Computer Science and is highly skilled in workstation support, networking, and hardware/ software management. He will provide computer and network support.

Rose S. Perry – Office Assistant
Mrs. Perry has many years of experienced in administrative secretarial support with emphasis in medical administration. She will be responsible for all clerical aspects of the core laboratory and communication between the core laboratory, coordinating center and the other sites.

Anita Kelly, RT – Nuclear Cardiology Applications Specialist
Ms. Kelly will process studies and prepare them for interpretation. She has extensive database management experience and will administer all database functions for the laboratory.

ATTACHMENT B: CLINICAL CENTER GUIDELINES FOR BARI 2D NUCLEAR STUDIES

Note: Please call us between 8:30am-5:30pm(central time) for any question regarding imaging protocol.

A. Patient Preparation

The patient should discontinue use of any caffeine-containing compounds 24 hours prior to the adenosine stress SPECT study. Patients should be NPO for at least 4 hours prior to stress SPECT studies. Patients should not smoke for at least 4 hours prior to both rest and stress SPECT studies. Cardiac medications may be discontinued the morning of the test.

Prior to the beginning of the imaging, the weight and height of each patient should be measured. Height and weight and other patient information (BARI 2D ID, age, and sex) should be recorded on the SPECT worksheet.

B. Electrode Placement

Prepare skin for optimal contact with electrodes using an alcohol prep and abrasive pad. Use 3 electrodes; 2 subclavicular (1 on each side) and 1 below left ribcage.

If small R wave: 1) Switch lead output on the gating box
2) Move left ribcage electrode to right side
3) Move subclavicular electrodes closer together

C. Image Acquisition

Use 100% acceptance window for gating.
Gating should be set for 8 or 16 frames per cardiac cycle.

Note: Both rest and stress images should be gated.

- Using standard tracer injection techniques inject the tracer into an appropriate arm vein. If there is excessive infiltration of the tracer the study should be re-scheduled for another day. For patients with poor veins, an intravenous catheter may need to be inserted and used to inject the tracer.

- Begin imaging 30-90 minutes after tracer injection for mibi and 15-30 minutes for thallium

Patients should be imaged supine with arms extended over the head, out of the field of view of the camera. Patients should be instructed to relax and breathe normally (no talking, sleeping, heavy breathing, or coughing). Inform them that the scan may need to be repeated if there is excessive motion. Use pillows and blankets to make patients comfortable.

The imaging characteristics for Tc-99m: 20% window over the 140 keV photo-peak, and 2 windows for thallium: one over 69-83 keV and another (optional) over 167 keV +-10%.

D. Computer Set-Up

Matrix size 64 x 64; number of projections 30-64 ; For 64 projections, time per projection 25 second for low dose and 20 second for high dose ; For 32 projections, time per projection 40 seconds ; total imaging time ~30 minutes for low dose and ~25 minutes for high dose (~50% less when using dual detector system) (J Nucl Cardiol 2001 ; 8 :G1-58).

Acquisition Parameters

Matrix :	64 x 64
Collimator:	Low energy, high resolution
Orbit:	180^0 (45^0 RAO - 45^0 LPO) ,Circular or Elliptical
Acquisition type:	Continuous or step-and-shoot

Note:
These are minimum requirements. For excessively large patients (>220 lbs.), time/projection may be increased by 5 seconds.

At the conclusion of the acquisition, the projection data should be corrected for non-uniformity,center of rotation, and patient motion according to camera manufacturer guidelines. In most cases this is done automatically by the camera system.

E. Post-Acquisition Quality Assurance

All projection data should be reviewed immediately post-acquisition for quality assurance.

Look for:	**Solve by:**
Excessive Motion	Repeat scan
Incorrect gating (flashing)	Adjust gate, then repeat scan
Poor counts	Check for infiltration. If no, repeat with longer acquisition times.
Hot liver activity	Repeat 1 hour later
Bowel activity too close to heart	Repeat 1 hour later

F. Adenosine Stress Testing Guidelines

- Adenosine stress testing is contraindicated in patients with bronchospasm, second degree or greater AV block in the absence of a pace-maker, or who are taking oral dipyridamole at the time of testing.
  Place an IV catheter.
  Connect ECG electrodes to patient.
  Using an adenosine pump, infuse 140 micrograms/kg/min of adenosine over 5 or 6 minutes.
  The injection of ^{99m} Tc- sestamibi should occur at 3 minutes.
  Obtain ECG, blood pressure and heart rate at rest and at every minute during the infusion.
- Myocardial ischemia is unusual with adenosine stress testing, but can occur. With definitive signs of ischemia, the ^{99m} Tc sestamibi injection may be made prior to the 3-minute time during adenosine infusion and then if possible, adenosine infusion should continue for at least 1 minute following tracer injection. The rate of the infusion may also be decreased if symptoms persist. Due to the short half-life of adenosine, pharmacologic reversal is usually not required. Occasionally, patients may benefit from intravenous aminophylline and/or sublingual nitroglycerin.
- In patients with contraindications to adenosine, use dobutomine up to a dose of 40 microgm/kg/min with or without atropine depending on heart rate response and side effects. Use the same stress test (adenosine or dobutamine) and same protocol each time on each patient.
- At the Canadian sites, where adenosine is not yet approved, dipyridamole will be used. A dose of 0.56 mg/Kg body weight will be infused IV over 4 minutes and the MIBI will be injected 3 minutes after the completion of infusion. Sites that use handgrip or upright exercise with dipyridamole should use same modification in each patient throughout the study period. The hemodynamic and EKG changes should monitored and recorded as with adenosine.

ATTACHMENT C: REPRODUCIBILITY (#1 VS #2)

1. SSS : 57±8 Vs 57±8 (mean ± SD)
2. SRS : 58±8 Vs 58±8
3. SDR : 1± 1 Vs 1± 1
4. # abnormal segments : 5± 2 Vs 5± 2
5. LV-EF (%) : 45± 7Vs 45± 7
6. WM score : 52±7 Vs 52± 7
7. WT score : 55±7 Vs 55± 7
8. TID : 100% agreement
9. Increased Lung uptake : 100% agreement
10. LV dilatation : 100% agreement
11. Enlarged RV : 100% agreement
12. Abnormal RV function : 100% agreement
13. Nature of Abnormality* : 100% agreement
14. Size of Abnormaility+ : 100% agreement

Abbreviations: *= Scar, ischemia or both, += Small, intermediate or large abnormality ;WM = wall motion; WT = wall thickening

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701 South 19th Street
Birmingham, AL 35294-0007

BARI-2D Transfer Image Acquisition DATA to be filled at site ***NCCL Form #1***

Fax to 1-800-513-0656

ID number: _____ **Date of Study:** _____

Name Code: _____ **Date received*:** _____

Site:_____ **Height:**____ **Weight:**____

Date of Randomization:_____ **Age:**_____ **Sex:**_____

Scheduled Test (Year 1, 2, 3, 4, 5, 6):_____
Unscheduled Test: Date_____

Please check the appropriate response.

1. TYPE OF STRESS ☐ 1. ADENOSINE ☐ 2. DIPRYDAMOLE **[CANADIAN SITES ONLY]**

___Alone
___With Handgrip Exercise
___With Treadmill Exercise

2. TRACER (Stress/Rest): ☐ 1. MIBI/MIBI ☐ 2. MIBI/thallium (dual isotope)

3. PROTOCOL: ☐ 1. Stress-Rest,1-day ☐ 2. Rest-Stress,1-day
☐ 3. Stress-rest, 2-day

4. ACQUISITION: ☐ 1. 180 deg. ☐ 2. 360 deg.

5. DOSE MIBI/MIBI: Rest _____ mCi Stress_____ mCi

6. DOSE (Dual Isotope): MIBI _____ mCi Thallium _____ mCi

Was the study performed according to protocol: YES ☐ NO ☐

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Birmingham, AL 35294-0007

NCCL Form #2

NCCL Interpretation Form

ID Number:_____ **Date of Study:**_____

Name Code:_____ **Date Received:**_____

Site:_____ **Height:**_____ **Weight:**_____

Randomization Date:_____ **Age:**_____ **Sex:**_____

	Stress	Rest	Motion	Thickening
Distal SA	0 - 3	0 - 3	0 - 3	0 - 3
1. Ant	☐	☐	☐	☐
2. Sep	☐	☐	☐	☐
3. Inf	☐	☐	☐	☐
4. Lat	☐	☐	☐	☐
Mid SA				
5. Ant	☐	☐	☐	☐
6. AS	☐	☐	☐	☐
7. IS	☐	☐	☐	☐
8. Inf	☐	☐	☐	☐
9. IL	☐	☐	☐	☐
10. AL	☐	☐	☐	☐
Basal SA				
11. Ant	☐	☐	☐	☐
12. AS	☐	☐	☐	☐
13. IS	☐	☐	☐	☐
14. Inf	☐	☐	☐	☐
15. IL	☐	☐	☐	☐
16. AL	☐	☐	☐	☐
17. Apx	☐	☐	☐	☐

Post-stress stunning

☐ 1 - None
☐ 2 - Anterior Wall
☐ 3 - Septal Wall
☐ 4 - Inferior Wall
☐ 5 - Lateral Wall
☐ 6 - Apex

Type of Study
☐ 1 Stress/Rest
☐ 2 Stress Only
☐ 3 Rest Only

Image Quality
☐ 1 Uninterpretable
☐ 2 Poor – Fair
☐ 3 Good - Excellent

Regional Image Interpretation

	Normal	Scar	Ischemia	Scar+Isc
1.LAD	☐	☐	☐	☐
2.RCA	☐	☐	☐	☐
3.LCX	☐	☐	☐	☐

- LAD=Segments:1,2,5,6,7,11,12,13,17
- RCA=Segments:3,8,14,7
- LCX=Segments: 4,9,10,15,16,17

Regional Perfusion:
1- Normal
2- Scar
3- Ischemia
4- Ischemia + Scar

Polar Maps

	Apex	Anterior	Septum	Inferior	Lateral	Total
Ischemia	☐	☐	☐	☐	☐	☐
Scar	☐	☐	☐	☐	☐	☐
Total	☐	☐	☐	☐	☐	☐

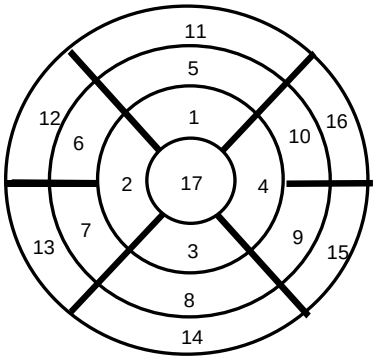
Size of abnormality: ☐ 1- Small (1,2 segments) ☐ 2- Intermediate (3-5 segments) ☐ 3- Large (≥ 6 segments)

LVEF: 1- Post Stress: ☐ % 2-Rest: ☐ % ☐ 3- could not be measured

LV Size: ☐ 4- Normal ☐ 3- Mildly Enlarged ☐ 2-Moderately Enlarged ☐ 1-Markedly Enlarged

Scores:
1- Extent of scar + ischemia [# abnormal segments] = ☐
2- Extent of Ischemia [# reversible segments] = ☐
3- (SSS): Summed Stress Score = ☐
4- (SRS): Summed Rest Score = ☐
5- (SDS): Summed Difference (Reversibility)Score= ☐

TID:	☐ 1-Yes	☐ 2 - No
L/H ratio:	☐ 1- Normal	☐ 2 - Increased
RV function :	☐ 1- Normal	☐ 2- Abnormal
RV size:	☐ 1- Normal	☐ 2- Abnormal



Initials ☐ **Date** ☐

Form 2:
Revised 8-30-01

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University of Alabama at Birmingham
LHRB 314
701 South 19th Street
Birmingham, AL 35294-0007

NCCL Form #3

BARI - 2D: SPECT Transfer Data

ID number:_____

Name Code:_____

Date of Study:_____

Date send:_____

Site:_____

Adenosine SPECT Perfusion Imaging

	Perfusion			
	Normal	Reversible	Partially reversible	Fixed
1- Anterior wall	☐	☐	☐	☐
2. Septum	☐	☐	☐	☐
3. Inferior wall	☐	☐	☐	☐
4. Lateral wall	☐	☐	☐	☐
5. Apex	☐	☐	☐	☐

LVEF: 1-Post Stress: _____ % 2-Rest:_____ %

Form 3

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LHRB 314
701 South 19th Street
Birmingham, AL 35294-0007

NCCL Form #4

BARI - 2D: Transfer data

ID Number: _____

Name Code:_____

Site **:** _____

Date of Study:_____

Date received_____

Response to Adenosine Infusion

I. Heart Rate:

a) Rest = _____bpm
b) Stress= _____bpm

II. Blood Pressure:

a) Rest = _____mmHg
b) Stress= _____mmHg

III Resting ECG:

- ☐ a) Normal
- ☐ b) NS ST/T
- ☐ c) AFIB
- ☐ d) ANT MI
- ☐ e) INF MI
- ☐ f) ANT MI/I MI
- ☐ g) LVH
- ☐ h)Pace-maker
- ☐ I) LBBB
- ☐ j) Other

IV. Chest Pain:

- ☐ a) Yes
- ☐ b) No

V. Ischemic ST Response:

- ☐ a) Yes
- ☐ b) No
- ☐ c) Non- Diagnostic

Form 4

CHAPTER TEN

REVASCULARIZATION STRATEGIES

SECTION ONE: GENERAL REVASCULARIZATION GUIDELINES

SECTION TWO: BYPASS SURGERY GUIDELINES

SECTION THREE: PCI GUIDELINES

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CHAPTER TEN : SECTION ONE GENERAL REVASCULARIZATION GUIDELINES

I. SELECTION OF REVASCULARIZATION STRATEGY

Prior to randomization, all patients will be evaluated for suitability for percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG). Determination of the more appropriate revascularization strategy will be based on clinical and angiographic criteria including:

1. safety of performing either procedure
2. expectation of providing relief to the major areas of ischemia
3. expected durability of the procedure.

Investigators and clinicians, in consultation with the patient, will have discretion in selecting PCI or CABG, as well as a 'hybrid' approach involving both approaches if appropriate, thereby reflecting contemporary clinical practice. To assist in this determination, prior experience from the BARI, EAST, New York State, Emory University, and Duke University registries can be considered, as well as recent guidelines from the ACC/AHA Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures. Clinicians should recognize that findings and guidelines derived from the above sources are not restricted to patients with diabetes mellitus, but rather are based on the universe of patients with coronary artery disease at large. Listed below is a synopsis of the most usual recommendations:

Patient Characteristic	Usual/Preferred Procedure
Single vessel disease	PCI
Three vessel disease	CABG
Two vessel disease:	
With severe proximal LAD stenosis	CABG or PCI
With multiple chronic total occlusions	CABG
With ejection fraction < 40%	CABG
With diffusely diseased arteries with distal vessels suitable for bypass grafting	CABG
With multiple anatomic characteristics associated with sub-optimal success rate of dilation (i.e. bifurcation, ostial, excessively long lesions, severe calcification, etc.)	CABG
Without any of the above characteristics	PCI
Two or three vessel disease with advanced age and comorbidity	PCI

II. PATIENT CONSULTATION

Prior to randomization, the patient will be informed as to the strategy of revascularization that will be performed if the subsequent randomization is to the invasive intervention arm of the trial. This intended revascularization strategy will be recorded in the BARI 2D database prior to randomization assignment, and randomization will be stratified by intended treatment within each clinical center.

III. INTENDED PROCEDURAL STRATEGY

Once the strategy of revascularization has been determined, the operator will declare characteristics of the intended procedural strategy. This includes the following:

1. The number and anatomic location of lesions planned for treatment
2. Whether or not complete "anatomic" revascularization is technically feasible and planned (defined as all lesions with stenoses ≥50% in vessels ≥2.0 mm that can and will be treated)
3. Whether or not complete "functional" revascularization is technically feasible and planned (whether all "high-priority" lesions, defined as lesions with stenoses ≥70% in large or proximal vessels that supply viable myocardium, [as defined in Zhao et al, "Effectiveness of Revascularization in EAST, Circulation 1996], can and will be treated).

CHAPTER TEN : SECTION TWO BYPASS SURGERY GUIDELINES

I. SURGEON CERTIFICATION

All CABG procedures on BARI 2D patients should be performed by a certified BARI 2D surgeon, and the randomized procedure must be performed by a certified BARI 2D surgeon. Certification requirements are:

1. Has practiced as an attending staff surgeon for ≥ 3 years
2. Has performed ≥ 100 CABG procedures during the last 3 years.
3. Has performed ≥ 100 CABG procedures with LIMA-LAD internal mammary artery grafts.
4. Results of most recent 100 consecutive, primary, elective, isolated CABG operations have a mortality rate of no more than 2% and a MI rate (new Q-waves) of no more than 4%.
5. The principal BARI 2D cardiac surgeon at the participating BARI 2D clinical unit is satisfied that the judgment, technical performance, results, and after-care meet current standards of the institution's Department of surgery.

For certification in BARI 2D, each participating surgeon is responsible for documenting the above certification criteria on a form signed by the surgeon and the Cardiology Principal Investigator of the clinical center. This information will be reviewed and approved by the BARI 2D Revascularization Working Group chairs (see Attachment A).

In addition to the above, surgeons must have demonstrated additional experience in order to perform procedures off-pump or procedures using alternative conduits in BARI 2D, as defined below:

A. Certification for Use of Non-IMA/Vein Grafts

In BARI 2D, use of conduits other than the internal mammary artery or saphenous vein (e.g., radial, gastroepiploic artery) is restricted to BARI 2D certified surgeons who in addition have as principal surgeon performed ≥ 50 procedures with each particular conduit.

B. Certification for Use of Off-Pump Procedures

In BARI 2D, off-pump CABG is to be performed only by BARI 2D certified surgeons who in addition have performed ≥ 50 off-pump surgery procedures as principal surgeon.

II. GOALS OF CABG

The primary goal of the CABG procedure is to provide adequate relief to the major area(s) of ischemia, while minimizing the risk of procedure-related untoward events. Based on the demonstrated long-term clinical benefit of a LIMA-LAD bypass, it is strongly recommended to use at least one IMA conduit if at all possible.

III. TIME TO PERFORM CABG

Once a patient is randomized to revascularization (with CABG as the pre-determined strategy), the procedure must be performed within 4 weeks.

IV. USE OF MEDICATIONS

While each BARI 2D site will treat CABG patients according to individual protocol, careful attention is warranted to maintenance of tight glycemic control during the post procedure. Suggested guidelines for implementation of insulin therapy prior to CABG and postsurgical insulin regimens are described in the BARI 2D protocol section on management of glucose during acute hospitalizations.

V. PROCEDURAL GUIDELINES

A. Degree of Revascularization

Incomplete or partial revascularization can be a planned therapeutic strategy because of morphological features that preclude successful bypass of all lesions. However, surgeons should strive to bypass all stenoses that significantly contribute to patient's clinical symptoms and ischemia.

B. Off-pump CABG

Off-pump CABG is permissible for appropriate patients when this procedure is carried out by a surgeon certified for this procedure, per the guidelines above.

C. Non-traditional Conduits

These may be used as appropriate by surgeons meeting criteria for minimum experience with these conduits, as indicated in the guidelines above.

VI. RECORDING COMPLICATIONS

All surgical complications must be documented on the Surgery Procedure Form. This is paramount given the overall high-risk status of the patient with diabetes mellitus, and the wide range of available treatment devices and technologies. The most frequent expected complications may include:

1. Chest tubes in place >5 days post surgery
2. Bleeding requiring reoperation
3. Wound dehiscence or infection
4. Mediastinitis
5. Post thoracotomy Syndrome
6. Neurologic event
7. Redo CABG

VII. REDO CABG

For patients who initially undergo CABG, reasons for undergoing redo CABG include:

1. Graft closure not amenable to revascularization by PCI
2. Development of new CAD that is more amenable to intervention with CABG.

VIII. SUBSEQUENT PCI

For patients who initially undergo CABG, reasons for undergoing subsequent PCI include:

1. Stenosis in Bypass Grafts: For patients who experience stenosis in bypass grafts, repeat PCI should be considered if feasible.
2. Development of new CAD that may be more amenable to PCI.

ATTACHMENT A

BARI 2D Study

Certification for Coronary Artery Bypass Surgery

(Please return to the BARI Coordinating Center)

Surgeon Name: _____
Please Print

Clinical Site Name: _____
Please Print

The above surgeon is certified to perform coronary artery bypass surgery in the BARI 2D study having met the following criteria:

1. Has practiced as an attending staff surgeon for _____ years (must be at least 3 years).

2. Has / has not (circle one) performed at least 100 CABG procedures during the last 3 years.

3. Has performed _____ CABG procedures with LIMA-LAD internal mammary artery grafts (must be 100 or more).

4. Results of the most recent 100 consecutive, primary, elective, isolated CABG procedures have a mortality rate of _____ % (must be no more than 2%) and a MI rate (new Q-waves) of _____ % (must be no more than 4%).

5. (Optional) Specify if surgeon has sufficient additional experience to perform the following procedures in BARI 2D:
   a. Off-pump procedures: has performed _____ off-pump surgery procedures (must be at least 50) as principal surgeon.
   b. Alternate conduits (e.g. radial, gastroepiploic artery): has performed as principal surgeon _____ procedures (must be at least 50) employing alternative conduits.

6. By the signature below, the Chief of Cardiothoracic Surgery at this participating BARI 2D clinical site is satisfied that this surgeon's judgment, technical performance, results, and after-care meet current standards set forth by this department.

The signatures below confirm that all criteria for BARI 2D surgeon certification have been met by this surgeon.

_____	_____
Signature (Chief of Cardiothoracic Surgery)	Signature (Surgeon to be Certified)
_____	_____
Print Name	Print Name
_____	_____
Date Signed	Date Signed

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CHAPTER TEN : SECTION THREE PCI GUIDELINES

I. OPERATOR CERTIFICATION

All PCI procedures associated with randomization must be performed by a certified BARI 2D operator. To be certified, operators should devote a substantial portion of their practice to performing PCI. This includes having performed ≥300 PCI procedures as primary operators with a current case volume of ≥75 cases per year as the primary operator. Operators must also provide documentation of the following criteria for their most recent 100 cases treated outside of the setting of evolving MI:

a. Overall lesion dilation success rate of > 90%
b. Procedural mortality rate of < 1.5%
c. Procedural Q-wave MI rate of < 4.0%
d. Procedural emergency CABG rate of < 2.0%

For certification in BARI 2D, each participating PCI operator is responsible for documenting the above certification criteria on a form signed by the surgeon and the Cardiology Principal Investigator of the clinical center. This information will be reviewed and approved by the BARI 2D Revascularization Working Group chairs (see Attachment B).

II. GOALS OF PCI

The primary goal of the PCI procedure is to provide adequate relief to the major area(s) of ischemia, while minimizing the risk of procedure-related untoward events. For some patients, this may be accomplished by the pre-planned use of partial revascularization. While there are no specific anatomic requirements, it is conventional to aim to reduce most treated lesions to a final-diameter stenosis of <30%.

III. TIME TO PERFORM PCI

Once a patient is randomized to revascularization (with PCI as the pre-determined strategy), the procedure must be performed within 4 weeks. If the procedure is to be a staged procedure, all additional stages should be performed within 2 weeks of the first stage.

IV. PRE-PROCEDURAL MEDICATIONS

Prior to the procedure, the patient should be treated with the following:

1. aspirin 325 mg
2. Plavix 300 mg or Ticlid 250 mg b.i.d.
3. Heparin – weight-adjusted dose unless contraindicated.

The use of ReoPro during PCI is recommended in all BARI 2D patients undergoing PCI, including those assigned to initial intervention as well as patients randomized to medical therapy undergoing subsequent PCI, unless contraindicated in the operator's judgment. ReoPro will be available without cost for on-label use in BARI 2D patients, under the stipulation that all product insert information will be adhered to during use.

V. POST-PROCEDURE MEDICATIONS

Following the procedure, the patient should be treated with the following:

1. aspirin 325 mg
2. if bare metal stent(s) only was(were) implanted, Plavix 75 mg qd for at least 30 days
3. if a drug-eluting stent was implanted, continued antiplatelet therapy for 3 months post-stenting

Other medications should be given as appropriate for secondary prevention. Anti-ischemic medications should be used as appropriate, according to local practice.

VI. PROCEDURAL GUIDELINES

A. Degree of Revascularization

Incomplete or partial revascularization can be a planned therapeutic strategy because of morphological features that preclude successful dilation of all severe lesions, as well as planned avoidance of non-flow-limiting lesions. However, PCI operators should strive to successfully and safely dilate all lesions that significantly contribute to patient's clinical symptoms and ischemia.

B. New Devices

Although it is expected that most lesions will be treated with stents, the use of new devices and evolving technologies (e.g., radiation, drug-eluting stents) will be at the discretion of the PCI operator, thereby reflecting contemporary clinical practice. However, use of new devices and technologies in BARI 2D is limited to devices approved by the U.S. FDA, Canadian HPB, or the appropriate entity in other countries. Consistent with then use of bare-metal stents, the early experience with DES indicates that its use should be in strict accordance with the Indications for Use and procedures contained in the package insert. In particular, adherence to the following guidelines is paramount:

(i) The size of the DES selected should match the reference vessel diameter as closely as possible. Caution: Use of a DES in a vessel larger than the nominal stent diameter could adversely affect the stent's performance.

(ii) The primary indicated lesion types for use of DES include discrete de novo lesions < 30mm in native coronary arteries with reference vessel diameters of > 2.5mm to < 3.5mm. Note: At present, use of DES is not indicated for patients presenting with acute myocardial infarction, for treatment of restenosis, or for treatment of sapheneous vein graft or bifurcation lesions.

(iii) All patients should receive a fully effective anti-platelet regimen, including an adequate pre-medication period or optimal loading dose. In addition, administration of anti-platelet therapy should continue for 3 months post-stenting.

(iv) Each lesion to be stented should be pre-dilated with a PTCA catheter using limited longitidunal length to avoid creating a region of vessel injury. Note: DES should not be used in the setting of direct stenting only.

(v) The DES should be fully deployed and in contact with the vessel wall. Caution: Poor stent apposition due to under-deployment is a factor that can increase the risk of stent thrombosis.

C. Surgical Backup

An experienced cardiovascular surgical team must be available within the attending institution.

VII. RECORDING COMPLICATIONS

All PCI procedural complications must be documented on the PCI Procedure Form. This is paramount given the overall high-risk status of the patient with diabetes mellitus, and the wide range of available treatment devices and technologies. The most frequent expected complications may include:

1. Abrupt vessel closure
2. Coronary artery dissection with or without thrombus
3. Stent thrombosis
4. Slow-flow or no-flow phenomenon
5. Hypotension requiring inotropic or mechanical support
6. Peripheral vascular complications
7. Hemodynamic and renal dysfunction secondary to doses of contrast material
8. Arrhythmias requiring cardioversion

VIII. REPEAT PCI

Repeat PCI may be performed on patients with initially successful PCI procedures (both clinical and angiographic improvement) if the lesions to be treated are suitable for PCI and major ischemia is expected to be eliminated after treatment of PCI-suitable lesions. This may occur in the settings of:

1. Restenosis of previously dilated coronary artery, associated with either recurrent angina or ischemia
2. New significant CAD indicated by recurrent ischemia and verified by angiography.

IX. SUBSEQUENT BYPASS SURGERY

For patients who initially undergo PCI, reasons for triage to subsequent CABG include:

1. Procedural complications from PCI that necessitate emergency CABG to prevent severe MI or death
2. Inadequate or unsatisfactory PCI result that requires use of elective CABG to relieve ischemia.
3. Restenosis: For patients who experience restenosis, repeat PCI should be considered, however, CABG is preferred if there is evidence that repeat PCI is likely to be ineffective or associated with increased risk of untoward events.

Development of new CAD that may be more amenable to CABG

ATTACHMENT B

BARI 2D Study

Certification for Percutaneous Coronary Intervention Operator

(Please return to the BARI Coordinating Center)

Operator Name: _____
Please Print

Clinical Site Name: _____
Please Print

The above PCI operator is certified to perform percutaneous coronary intervention (PCI) in the BARI 2D study having met the following criteria:

1. Has performed _____ PCI procedures (must be 300 or more) as primary operator with a current case volume of _____ cases per year (must be 75 or more) as the primary operator.

   Answer questions 2 through 5 in relation to your most recent 100 cases treated outside of the setting of evolving MI.

2. Has an overall lesion dilation success rate of _____ % (must be greater than 90).

3. Has a procedural mortality rate of _____ % (must be less than 1.5).

4. Has a procedural Q-wave MI rate of _____ % (must be less than 4.0).

5. Has a procedural emergency CABG rate of _____ % (must be less than 2.0).

6. By the signature below, the Chief of Cardiology at this participating BARI 2D clinical site is satisfied that this operator's judgment, technical performance, results, and after-care meet current standards set forth by this department.

The signatures below confirm that all criteria for BARI 2D PCI operator certification have been met by this operator.

_____	_____
Signature (Chief of Cardiology)	Signature (Operator to be Certified)
_____	_____
Print Name	Print Name
_____	_____
Date Signed	Date Signed

CHAPTER ELEVEN

NON-PHARMACOLOGIC INTERVENTION PROTOCOLS

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CHAPTER ELEVEN : SECTION ONE NON-PHARMACOLOGIC PROTOCOLS INTRODUCTION

I. INTRODUCTION

The interrelationship between type 2 diabetes mellitus and coronary artery disease (CAD) is complex. The causes of increased risk of CAD in type 2 diabetes are multifactorial. Smoking, an independent CAD risk factor in type 2 diabetes mellitus, low levels of physical activity, and central obesity further interact with the traditional risk factors, such as hypertension and hyperlipidemia, to compound the increased risk for cardiovascular mortality in type 2 diabetes mellitus.

An important aspect of the BARI 2D trial is the uniform management of all CAD risk factors in all randomized patients, enabling assessment of the efficacy of a revascularization and glycemic management strategy over and above maximal management of other factors and without confounding due to variable management of such factors. All patients in the BARI 2D trial receive intensive management of the key CAD risk factors, such as dyslipidemia and hypertension, in addition to intensive management of the CAD and attaining optimum glycemic control. Smoking, low levels of physical activity and obesity are also targeted because of their potential as CAD risk factors.

II. RATIONALE FOR NON-PHARMACOLOGIC/LIFESTYLE INTERVENTION

Smoking, obesity and sedentary lifestyle worsen blood glucose, complications of type 2 diabetes and cardiovascular disease. Tobacco addiction treatment, medical nutritional therapy (MNT) and increased physical activity imply beneficial lifestyle changes in persons with type 2 diabetes and cardiovascular disease.

A Lifestyle Intervention Management Center (LIMC) has been established to ensure that lifestyle changes, a central component of treatment for these patients, will be closely monitored. A BARI 2D Lifestyle Balance Weight Control Program will be available for weight management after the initial 6 month intensive intervention period. Use of a pedometer and the BARI 2D Food and Activity Record will be encouraged as part of a biofeedback intervention aimed at increasing physical activity.

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CHAPTER ELEVEN : SECTION TWO EXERCISE PROTOCOL

I. EXERCISE PROTOCOL

E. Exercise Prescription

All BARI 2D patients will have an exercise protocol prescribed at baseline by the cardiologist or his/her designee according to the guidelines outlined below. In addition, the exercise prescription (see Attachment A) should be reviewed and updated every year as well as following any serious clinical event, such as a myocardial infarction. The exercise prescription should be individualized and, when possible, the patient should be referred to formal cardiac rehabilitation. All BARI 2D patients, as appropriate, will receive a pedometer along with instructions for use (see Attachment B).

In accordance with each institution's standard of care, an exercise stress test may be performed after medical therapy is instituted or revascularization performed. This test will be repeated as recommended by each institution's protocol, and the exercise prescription will be individualized accordingly. The patient will be referred to formal cardiac rehabilitation when possible; otherwise, the following will be used as general guidelines for the exercise prescription:

1. All patients will be informed of the beneficial effect of exercise on diabetes control and cardiac function.
2. The exercise sessions will be prescribed to have a frequency of 3 to 5 days/week for endurance training and 2 to 3 days/week for flexibility and resistance training. Written examples of flexibility and resistance training will be given to the patient.
3. The format of exercise sessions will be as follows: warm-up period (approximately 10 minutes); endurance phase (20-60 minutes); cool-down period (5-10 minutes).
4. The intensity of the exercise prescribed must be such as to achieve 55-90% Maximum Predicted Heart Rate (MPHR = 220 - age). Chronotropic drugs may require specifically tailored heart rate goals. The intensity should be modified according to the ischemic threshold determined during the stress test. The Borg scale rating (see Attachment C) will be used to assess physical activity intensity. An exercise test performed by BARI 2D personnel is strongly encouraged to determine the intensity of exercise necessary to achieve the target heart rate. Patient education of the Borg scale rating of perceived exertion should be implemented during this test.

B. Pedometer Protocol

Pedometers and instructions for pedometer use (see Attachment B) will be made available to all BARI 2D clinical centers. Pedometer use will be encouraged, as appropriate, for all patients in the study as a biofeedback tool to increase physical activity. This can be initiated at any time during the study. All patients will be encouraged to record their physical activity, including the daily number of steps recorded by the pedometer, using the BARI 2D Food and Activity Record (see Attachment D).

The Food and Activity Record should be brought to each of the quarterly visits. For the two visits following the initiation of the pedometer protocol, coordinators should contact the patients and remind them to record their physical activity and steps for the week prior to the next clinic visit and to bring this one week record with them to the visit.

II. CONTRAINDICATIONS TO EXERCISE

The following will be contraindications to exercise as defined above and patients will be advised to refrain from exercise in the presence of:

1. Unstable angina
2. Resting SBP > 200 mmHg or DBP > 110 mmHg
3. Orthostatic blood pressure drop of > 20 mmHg with symptoms
4. Severe aortic stenosis
5. Acute systemic illnesses or fever
6. Uncontrolled tachyarrhythmias
7. Complete heart block without pacemaker
8. Uncompensated heart failure
9. Active pericarditis or myocarditis
10. Thrombophlebitis
11. Uncontrolled diabetes (resting blood glucose > 300 mg/dl)
12. Orthopedic conditions prohibiting exercise
13. Other acute metabolic conditions such as thyroiditis, hypokalemia, hyperkalemia, hypovolemia, etc.

III. GLYCEMIC CONTROL

The following general guidelines, which may prove helpful in regulating the glycemic response to exercise, particularly for individuals using insulin, will be provided to patients:

1. A diabetes identification bracelet should be worn.
2. Avoid exercise until resting glucose levels are <300 mg/dl.
3. Ingest food prior to exercise if glucose levels are <100 mg/dl.
4. Identify when changes in insulin or food intake are necessary before and during exercise.
5. Learn the glycemic response to different exercise conditions.
6. Avoid exercise during periods of peak insulin activity.
7. Consume added carbohydrate as needed to avoid hypoglycemia.
8. Carbohydrate-based foods should be readily available during and after exercise.

IV. SPECIAL CONSIDERATIONS

A. Peripheral Vascular Disease

The patient must be evaluated to determine the presence of peripheral vascular disease (by clinical examination and/or Doppler exam) and the exercise prescription modified, as needed, although peripheral vascular disease is not a contraindication to exercise.

B. Diabetic Retinopathy

	Acceptable Activities	Discouraged Activities
No NPDR	Dictated by medical status	Same
Mild NPDR	As above	Same
Moderate NPDR	As above	Activities that dramatically elevated blood pressure such as power lifting, heavy Valsalva
Severe NPDR	As above	Activities that substantially increase blood pressure, Valsalva, weight lifting, boxing, heavy competitive sports
PDR	Low-impact cardiovascular, low impact aerobics, stationary cycling, endurance exercise	Strenuous activities, Valsalva, pounding or jarring, weight lifting, jogging, racquet sports, high impact aerobics, trumpet playing

C. Diabetic Peripheral Neuropathy

The presence of neuropathy must be assessed and the individuals with loss of protective sensation (insensitive feet) must be identified. These patients must be informed of the risk of doing weight-bearing exercise on insensitive feet.

Acceptable Activities	Discouraged Activities
Swimming	Treadmill
Bicycling	Prolonged Walking
Rowing	Jogging
Chair Exercises	Step Exercises
	Arm exercises and other non-weight bearing exercises

Proper footwear (shoes with silica gel or air insoles and polyester and cotton blend socks) should be used and the feet kept dry and examined before and after each exercise session.

D. Autonomic Neuropathy

The exercise stress test should reveal any problems with cardiac autonomic neuropathy. Otherwise, the patient should be advised to exercise in an adequate thermo-regulated environment and to avoid dehydration.

ATTACHMENT A

BARI 2D EXERCISE PRESCRIPTION WORKSHEET

Patient Name _____ BARI 2D ID __ __ __ __ __ __ __ __ __ __ __ __

Date Randomized _____

BARI 2D Assignment: CAD group: _____ DM group:_____

Pertinent History _____ **Meds** _____

_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____

BORG SCALE

1 Very Light	Sedentary, Rest to Moderate ADL every day
2 Light	Heavy ADL to Gentle Walking, at least 3 days/wk
3 Moderate	Walking >5 days to Gentle Exercise Routine, 3-5 days/wk
4 Hard	35 - 59 min Serious Exercise Routine, 3-5 days/wk
5 Very Hard	60 to 90 min Serious Exercise Routine, 5-7 days/wk
6 Maximum	> Level 5 – the individual's maximum every day

Patient's current BORG level of exercise without problem _____

MD recommended BORG level of exercise _____

PERMITTED EXERCISES:

____ Walking
_____Pedometer: # Steps/Day

____ Flexibility Exercises

____ Aerobic Routine

____ Resistance Training

____ Upper body ____ lb weight

____ Lower body ____ lb weight

MD Name _____ Date of Authorization _____

MD Signature_____

ATTACHMENT B

THE BARI 2D PEDOMETER

What is a pedometer?

A pedometer is an activity monitor that counts the number of steps that you take in a day. We are asking you to wear this monitor every day from the time you get up in the morning until the time you go to bed at night.

HOW DO YOU USE THE PEDOMETER?

1. Every morning when you get up, push the **yellow** reset button and make sure that the pedometer reads zero - "0".

2. Clip the pedometer on your dominant hip (right hip, if you are right handed; left hip, if you are left handed). It should slide down over the waistband of your pants, shorts or skirt. In it's correct position, a person facing you should be able to read "BARI 2D" in an upright position on the front cover. See picture below for proper placement.

3. Keep the cover closed at all times while you are wearing it. Steps will not be recorded if the cover is left open.

4. Make sure that the pedometer is worn SNUG against your body and that it does NOT move around.

5. DO NOT wear the pedometer sideways. DO NOT clip the pedometer to a belt loop. The pedometer will only work if in the correct UPRIGHT position.

6. Wear the pedometer all day, except when bathing, showering, swimming, in the rain, or during any activity that will cause the pedometer to get wet. **DO NOT GET THE PEDOMETER WET!**

7. Take the pedometer off at night just before you go to bed and write down the number of steps on the pedometer in your **BARI 2D Food & Nutrition Record**.

8. PLEASE DO NOT TOUCH THE **YELLOW** BUTTON ON THE PEDOMETER, except when you reset the pedometer in the morning.

9. Please DO NOT keep the pedometer in a pants, shirt, or coat pocket. In order for the pedometer to work properly, it needs to be tightly fitted against your body.

If you have any questions, please call the BARI 2D study office at _____ and ask for _____.

ATTACHMENT C

Classification of physical activity intensity, based on physical activity lasting up to 60 minutes.

Endurance-Type Activity	Relative Intensity		
Intensity	VO2 max (%)*	maximal heart rate reserve (MHR %)**	RPE†
Very light	<20	<35	<10
Light	20-39	35-54	10-11
Moderate	40-59	55-69	12-13
Hard	60-84	70-89	14-16
Very hard	>80	>90	17-19
Maximal	100	100	20

* Maximal rate of oxygen consumption by the body during maximal exertion.

** Result of subtracting the resting heart rate from the maximal heart rate.

† Borg Rating of Perceived Exertion 6-20 scale.

ATTACHMENT D

My Daily Goals

	Cals (C)	Fat (F)	CHO (Cb)	Pedometer Steps
Daily				

My Daily and Weekly Totals

Day	Cals (C)	Fat (F)	CHO (Cb)	Pedometer Steps
Monday				
Tuesday				
Wednesday				
Thursday				
Friday				
Saturday				
Sunday				
Totals				
Average				

Weight: _____ lbs.

Monday Food and Drink Record

Time	Amount/Food	Cals (C)	Fat (F)	CHO (Cb)

BARI 2D Lifestyle Balance

Food & Activity Record

Name _____

Date _____ _____
From To

Sample Entry:

Monday Food and Drink Record

Time	Amount/Name	Cals (C)	Fat (F)	CHO (Cb)
8:00 AM	½ cup oatmeal	73	1	13
	1 cup skim milk	90	.5	13

Daily Physical Activity

Type of Activity	Minutes
Total	

Total Pedometer Steps: _____

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CHAPTER ELEVEN : SECTION THREE NUTRITION PROTOCOL

I. NUTRITION PROTOCOL

"Medical Nutrition Therapy (MNT) is integral to total diabetes care and management" (the American Diabetes Association position statement on "Nutrition Recommendations and Principles for People with Diabetes Mellitus," *Diabetes Care*, 2000). The overall goal of the Medical Nutrition Therapy is to help individuals with diabetes to make changes in dietary habits to facilitate improved metabolic control.

The BARI 2D study seeks to achieve four specific nutrition goals:

1. To achieve near-normal blood glucose levels;
2. To achieve optimal lipid levels;
3. To provide adequate calories to maintain or attain reasonable body weight; and
4. To achieve and maintain optimal blood pressure level.

The following guidelines will be implemented at all BARI 2D Centers:

1. All patients will be provided with uniform nutrition therapy aimed at achieving the goals stated above.
2. Each patient will receive a nutrition assessment and a dietary consult at baseline. A registered dietitian (RD) will provide these. The patient will also receive an educational brochure supplemented with specific and individualized guidelines.
3. Follow-up visits with the RD will occur at the first 3 month follow up visit and annually thereafter to assess compliance and reinforce dietary principles and guidelines.

The following will prompt reinforcement of the nutrition guidelines by the study personnel and may indicate need for further dietary consult:

1. The patient gains 5% of original body weight.
2. HbA1C is not <7.0 after maximum pharmacological treatment; for two months in the IS arm and for one month in the IP arm.
3. The patient exhibits worsened glycemic, lipid or blood pressure control since the previous measurement.

II. SPECIFIC NUTRITION GUIDELINES

1. Patients who are overweight (BMI more than 25 kg/m^2) will be advised to lose 10% of their initial weight (10-20 lbs [5-9 kg]) over a 6-month period. A moderate calorie restriction (250-500 calories less than the total energy expenditure (TEE) [TEE - Resting Energy Expenditure (REE as calculated by the Harris-Benedict equation) x 1.3 (factor for light activity)] and a nutritionally adequate meal plan will be encouraged. The use of the weight loss drug Xenical will be permitted in the absence of contraindications.
2. The BARI 2D Lifestyle Balance Weight Control Program will be recommended for patients with a BMI >25 kg/m^2 (see Section Five).

3. Patients who are not overweight (BMI equal or less than 25 kg/m^2) will be counseled on an appropriate meal plan to maintain weight (total calorie level to be determined by the Harris-Benedict equation which includes a factor for light activity).
4. All patients will be instructed to consume three balanced meals per day at consistent times. Snacks will be incorporated into an individual's meal plan based on the individualized calorie level and typical daily intake.
5. The patients will be instructed that hypoglycemia may result from a delayed or missed meal, decreased carbohydrate (CHO) content of a meal or increased physical activity (exercise). Symptoms of hypoglycemia will be reviewed. The patients receiving IP treatment will be instructed to ingest at least 15 gm CHO to be eaten or taken in liquid form in the event of a hypoglycemic reaction.
6. The carbohydrate content of the diet will be 50-60% of total calories. The exact percent will vary based patient's eating habits and glucose and lipid goals (for example, carbohydrate calories will be decreased if triglyceride levels are over 400 mg/dl).
7. The American Heart Association Step One diet will be recommended for the total fat content (total fat <30% of total calories, saturated fat limited to <10%, polyunsaturated fat <10%, monounsaturated fat 10-15%, dietary cholesterol should be less than 300 mg per day). If LDL cholesterol is persistently elevated after maximum other treatment (more than 100 mg/dl), the AHA Step Two diet can be implemented (saturated fat to <7% of total calories and dietary cholesterol <200 mg per day).
8. The recommended fiber content of the diet should be 25-35 gm per day.
9. The protein content of the diet will be 10-20% of total calories. For patients with nephrotic syndrome, supplemental protein for continuing losses will be provided. For patients with overt nephropathy, the recommended protein intake is 0.8 gm/Kg body weight.
10. A reduced sodium intake of 2,400-3000 mg/day is recommended for all patients. Additional reduction is recommended for mild-moderate hypertension (<2,400 mg/day), for the presence of hypertension and nephropathy (<2,000 mg/day) and for the presence of nephrotic syndrome (800-1,600 mg/day).
11. It is recommended that alcohol intake should not exceed moderate amounts. One ounce of ethanol/day for men and half an ounce for women are defined as moderate. One ounce of ethanol is equal to 24 ounces of beer, 10 ounces of wine or three ounces of 80-proof whiskey.

III. DATA COLLECTION

The following measurements will be used as end-points for nutrition intervention:

1. **Weight/BMI:** Weight will be measured initially and at each visit. Height will be measured at the first visit and BMI calculated. A repeat height measurement will be done at the end of the study. The goal is to maintain the BMI less than 25 or, if BMI is more than 25, to lose weight until BMI is less than 25 or to lose a minimum of 10% of initial body weight even if this amount does not normalize BMI.

   BMI is calculated as kg/(m^2): $\frac{\text{weight in kg}}{\text{height}^2 \text{ (in meters)}}$

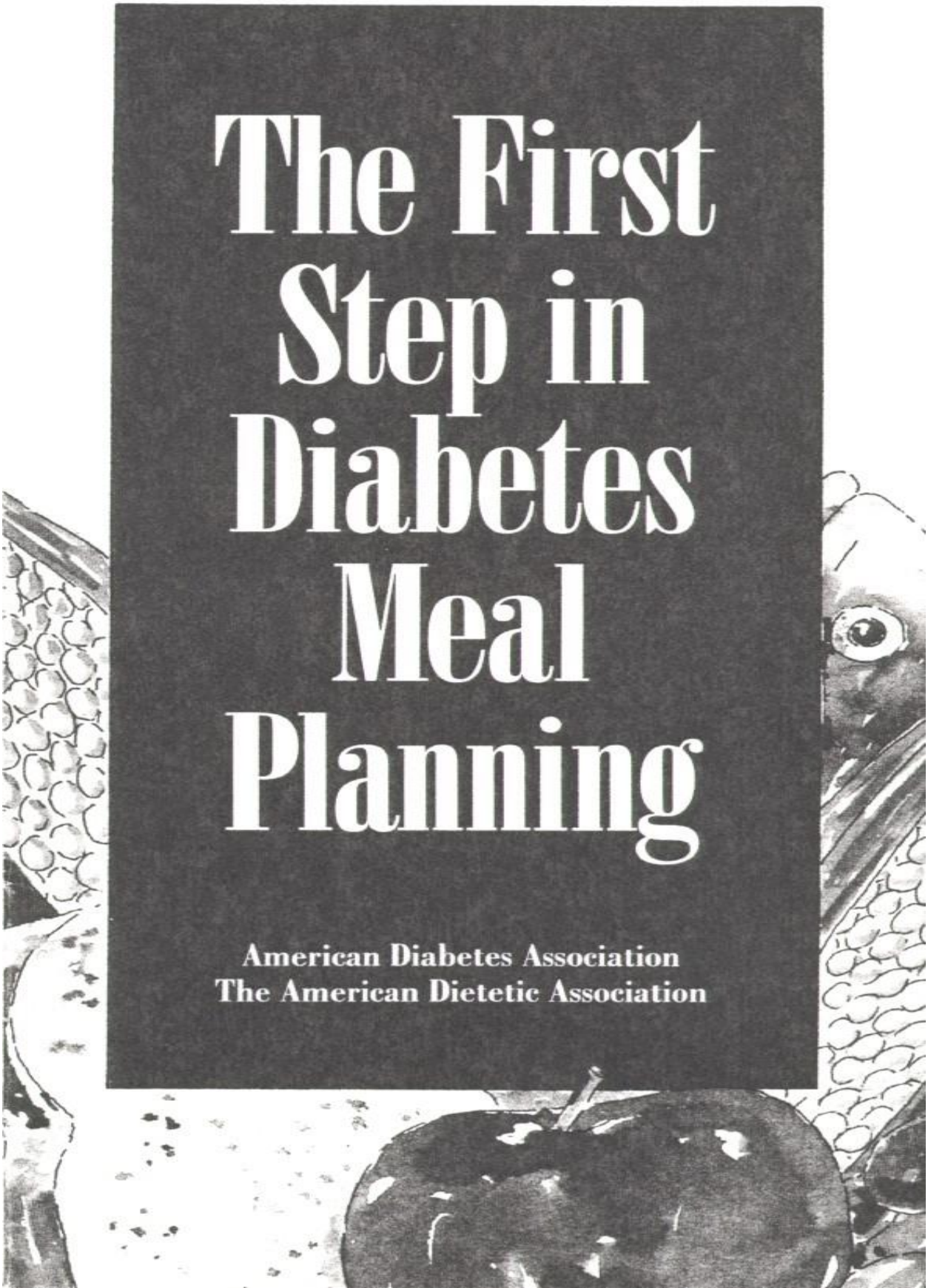
   Multiply the height (in meters) by itself (height²), then divide the weight (in kg) by the answer. The measurement is not recorded on the BARI 2D forms. It is to be used in the clinical management of the patient.

2. **Waist circumference**: This will be measured initially and annually. The goal is to have a waist circumference less than 40 inches in men and less than 35 inches in women.

3. **HbA1C:** This will be measured initially and at each visit. The goal is <7.0%.

4. **Lipid levels:** These will be measured initially and periodically, as per the lipid management protocol. The goal is LDL-cholesterol <100 and triglyceride level <200 mg/dl.

5. **Blood pressure:** This will be measured initially and at each visit. The goal is 130/80 mm of mercury.


The First Step in Diabetes Meal Planning
American Diabetes Association
The American Dietetic Association

Healthy Eating Is the First Step in Taking Care of Your Diabetes

You can make a difference in your blood glucose control through your food choices.

You do not need special or diet foods.

The food that is good for you is good for your whole family.

Developed by:
Madelyn Wheeler, MS, RD, CDE
Carolyn Leontos, MS, RD, CDE
Nancy Cooper, RD, CDE
Eva Brzezinski, MS, RD
Brenda A. Broussard, RD, MPH, MBA, CDE

Here's How You Do It

Eat a wide variety of foods every day. Try new foods.

Eat high-fiber foods, such as fruits, vegetables, grains, and beans.

Use less added fat, sugar, and salt.

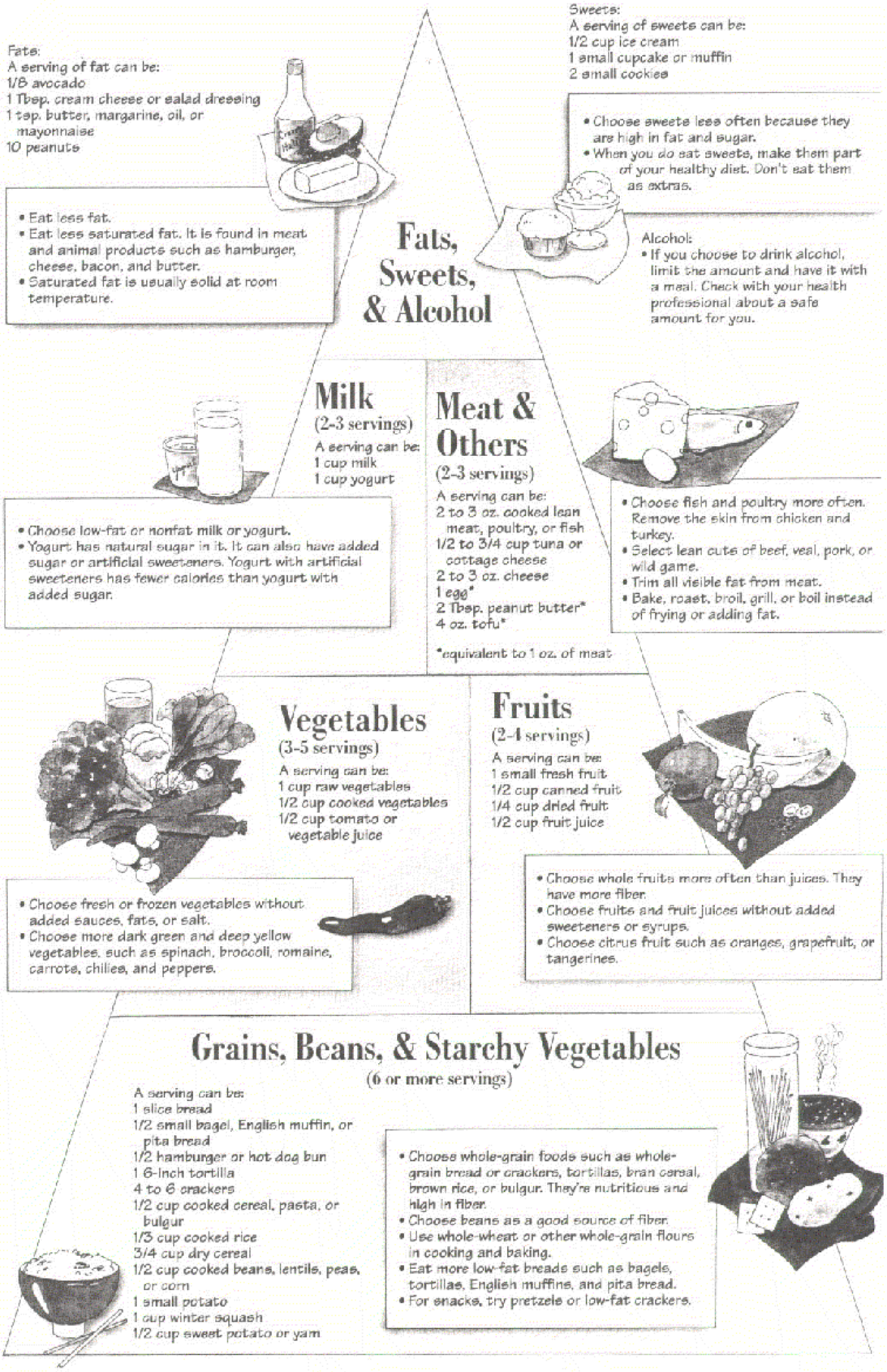
Changes You Can Make

Eat meals and snacks at regular times every day.

Eat about the same amount of food each day.

Try not to skip meals.

If you want to lose weight, cut down on your portion size. If you skip a meal, you may eat too much at your next meal.


Fats:
A serving of fat can be:
1/8 avocado
1 Tbsp. cream cheese or salad dressing
1 tsp. butter, margarine, oil, or mayonnaise
10 peanuts
• Eat less fat.
• Eat less saturated fat. It is found in meat and animal products such as hamburger, cheese, bacon, and butter.
• Saturated fat is usually solid at room temperature.
Sweets:
A serving of sweets can be:
1/2 cup ice cream
1 small cupcake or muffin
2 small cookies
• Choose sweets less often because they are high in fat and sugar.
• When you do eat sweets, make them part of your healthy diet. Don't eat them as extras.
Fats, Sweets, & Alcohol
Alcohol:
• If you choose to drink alcohol, limit the amount and have it with a meal. Check with your health professional about a safe amount for you.
Milk
(2-3 servings)
A serving can be:
1 cup milk
1 cup yogurt
• Choose low-fat or nonfat milk or yogurt.
• Yogurt has natural sugar in it. It can also have added sugar or artificial sweeteners. Yogurt with artificial sweeteners has fewer calories than yogurt with added sugar.
Meat & Others
(2-3 servings)
A serving can be:
2 to 3 oz. cooked lean meat, poultry, or fish
1/2 to 3/4 cup tuna or cottage cheese
2 to 3 oz. cheese
1 egg*
2 Tbsp. peanut butter*
4 oz. tofu*
*equivalent to 1 oz. of meat
• Choose fish and poultry more often. Remove the skin from chicken and turkey.
• Select lean cuts of beef, veal, pork, or wild game.
• Trim all visible fat from meat.
• Bake, roast, broil, grill, or boil instead of frying or adding fat.
Vegetables
(3-5 servings)
A serving can be:
1 cup raw vegetables
1/2 cup cooked vegetables
1/2 cup tomato or vegetable juice
• Choose fresh or frozen vegetables without added sauces, fats, or salt.
• Choose more dark green and deep yellow vegetables, such as spinach, broccoli, romaine, carrots, chilies, and peppers.
Fruits
(2-4 servings)
A serving can be:
1 small fresh fruit
1/2 cup canned fruit
1/4 cup dried fruit
1/2 cup fruit juice
• Choose whole fruits more often than juices. They have more fiber.
• Choose fruits and fruit juices without added sweeteners or syrups.
• Choose citrus fruit such as oranges, grapefruit, or tangerines.
Grains, Beans, & Starchy Vegetables
(6 or more servings)
A serving can be:
1 slice bread
1/2 small bagel, English muffin, or pita bread
1/2 hamburger or hot dog bun
1 6-inch tortilla
4 to 6 crackers
1/2 cup cooked cereal, pasta, or bulgur
1/3 cup cooked rice
3/4 cup dry cereal
1/2 cup cooked beans, lentils, peas, or corn
1 small potato
1 cup winter squash
1/2 cup sweet potato or yam
• Choose whole-grain foods such as whole-grain bread or crackers, tortillas, bran cereal, brown rice, or bulgur. They're nutritious and high in fiber.
• Choose beans as a good source of fiber.
• Use whole-wheat or other whole-grain flours in cooking and baking.
• Eat more low-fat breads such as bagels, tortillas, English muffins, and pita bread.
• For snacks, try pretzels or low-fat crackers.

Meal or Snack Time				
				Number of Servings
Grains, Beans, & Starchy Vegetables				
Vegetables				
Fruits				
Milk				
Meat & Others				
Fats, Sweets, & Alcohol				

Meal Plan for: _____

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CHAPTER ELEVEN : SECTION FOUR SMOKING PROTOCOL

I. PROTOCOL FOR TREATING TOBACCO USE AND DEPENDENCE (SPECIFICALLY SMOKING)

(Adapted from US Public Health Service Report - June 27, 2000, *JAMA* 2000; 283:3244-3254)

The following principles should be applied in the treatment of patients enrolled in BARI 2D:

1. Tobacco dependence (smoking) is a chronic condition that warrants treatment.
2. Effective treatments for smoking cessation exist and should be offered.
3. BARI 2D investigators should identify, document, and treat every smoker at every visit.
4. Brief smoking cessation treatment is effective and should be offered at a minimum.
5. Five first-line pharmacological therapies to aid in smoking cessation are effective, and at least one of these medications should be prescribed in the absence of contraindications.

The diabetology investigator will initiate this protocol at the time of initiation of the intensive pharmacological treatment and nutrition protocol.

II. BRIEF STRATEGIES TO HELP QUIT: 5 "A'S"

The following strategies should be used and their use documented:

1. **A**sk: identify tobacco user (smoker).
2. **A**dvise: give clear, strong, personalized recommendation to stop.
3. **A**ssess: assess the patient's willingness to intervene with intensive stop use program.
4. **A**ssist: help develop a Quit plan (a short practical counseling speech should be given, a hand-out will be given adapted from the *JAMA* article, and a list of local programs is provided).
5. **A**rrange: arrange follow-up.

All BARI 2D enrollees are queried on tobacco use, specifically smoking cigarettes. If the answer is yes, the patient is further questioned on his/her willingness to quit. If the patient is not willing to quit, motivation to quit should be promoted.

If the patient is willing to quit, practical counseling is provided, the patient is provided with a local list of quit smoking programs and information hand-out (adapted *JAMA* page). Practical counseling includes setting a quit date, encouraging total abstinence, enrollment of family members/friends/co-workers' support, anticipating removing challenges (i.e. removal of tobacco products, eliminating or dealing with known triggers), etc. Resource materials, including a list of local comprehensive stop-smoking centers, are provided. Pharmacological therapy is initiated. The patient is contacted by phone within one week and then monthly regarding implementation of plan. Success is applauded and drug therapy is re-assessed. The patient is referred to an intensive stop-smoking support group in area if needed and willing.

III. PHARMACOLOGICAL THERAPY GUIDELINES

1. All smokers willing to quit should receive pharmacological therapy.
2. Any of the five FDA approved first line drugs could be used

3. The treatment is individualized to patient and provider preference; bupropion and nicotine gum may be used in obese patients as these show least weight gain in short term studies while for patients with depression bupropion may be most appropriate drug.
4. Second line agents (clonidine or nortriptyline) are contraindicated for BARI 2D patients.
5. It is safe to prescribe nicotine for BARI 2D patients except in the presence of recent MI or unstable angina.

First Line Agents

Drug	Precaution	Side-effect	Dosage	Duration	Availability
Bupropion	hx seizures hx eating disorder	insomnia dry mouth	150mg qd x 3d 150mg bid treat 1-2 week prequit	7-12 weeks to 6 months	Rx only
Nicotine gum		mouth soreness dyspepsia	< 2ppd: 2mg gum > 2ppd: 4mg gum up to 24/day	up to 12 weeks	OTC
Nicotine inhaler		mouth/ throat irritation	6-16 cartridges/d	up to 6 months	OTC
Nicotine nasal spray		nasal irritation	8-40 doses/d	3-6 months	Rx only
Nicotine patch		skin reaction insomnia	21mg/ 24 hr 14mg/ 24 hr 7mg/ 24 hr or 15mg/ 16 hr	4 weeks then 2 wks then 2 wks 8 weeks	Rx and OTC

IV. RELAPSE PREVENTION

The following could be used to prevent relapse:

1. At every visit congratulate success, review benefits of success and encourage continued abstinence.
2. Promptly identify mood disorders and refer patients for treatment.
3. Refer to the nutrition and exercise protocols for weight gain prevention strategies.
4. Extend pharmacological therapy for prolonged withdrawal symptoms.

V. ENHANCING MOTIVATION FOR UNWILLING PATIENT

The following could be used to enhance motivation to quit:

1. Relevance: relate quitting tobacco to improvement in cardiac disease.
2. Risks: explain relationship of tobacco use to angina, MI, stroke, cancers, lung disease and harm to others.
3. Rewards: explain the effect of stop smoking to improved health, social and financial status.

4. Roadblocks: identify roadblocks and explain strategies to deal wit these (treatment of withdrawal symptoms, weight gain, depression, dealing with failure).
5. Repetition: repeat motivational intervention at each visit and explain that successful quitting may take several attempts

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CHAPTER ELEVEN : SECTION FIVE LIFESTYLE BALANCE WEIGHT CONTROL PROGRAM

I. ACKNOWLEDGEMENTS

The BARI 2D Lifestyle Balance Weight Control Program was developed by Laurey R. Simkin-Silverman, PhD, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh. Materials were adapted from the Diabetes Prevention Program (DPP), the National Diabetes Education Program, the Primary Care Weight Control Project (Simkin-Silverman & Wing, 1997), the Woman on the Move Through Activity and Nutrition Study (Lewis H. Kuller, MD, DrPH, Andrea Kriska, PhD and Laurey Simkin-Silverman, PhD, University of Pittsburgh), and through the valuable contributions from the BARI 2D Non-Pharmacologic Intervention Working Group and the BARI 2D Coordinating Center.

II. INTRODUCTION

A. Description

The Lifestyle Balance Weight Control Program materials were designed to enhance uniformity in weight control counseling tools and to provide resources for study coordinator and patient use across the BARI 2D clinical sites. While these materials provide for consistency across clinical sites, it is critical that weight control counseling be tailored to the patient's lifestyle, health status, learning style and culture.

B. Guidelines

The Lifestyle Balance Weight Control Program is designed to help BARI 2D study patients achieve a 10% weight loss in approximately 6 months (as per the nutrition protocol). It is recommended that it be initiated after the six month follow-up clinic visit if the patient has a BMI over 25 and:

1. There has been less than 5% weight loss since the beginning of the study and glycemic control is not on target; or
2. There has been 0-5% weight gain since the inception of the study and glycemic control is not on target; or
3. There has been more than 5% weight gain since the inception of the study.

In addition, any BARI 2D patient with a BMI over 25 may be offered this program at the discretion of the study investigators.

The Lifestyle Balance Weight Control Program is designed for patients to follow at home in between follow-up clinic visits, with appropriate telephone contact over a 6 month period. The program includes print materials along with routine telephone contact and brief counseling at clinic visits. It includes 14 chapters on key nutritional, behavioral and physical activity topics for weight control, with a primary emphasis on reducing fat (saturated) and calories. It is written in a structured, easy to read format, including self-management assignments for patients to complete at home.

a. During the initial visit, before the program is initiated:

1. Assess motivational readiness along with weight, BMI and waist circumference.
2. Offer the patient brief weight control counseling and provide the Lifestyle Balance Weight Control Program materials.
3. Ensure that the patient has enough information to begin the program. At a minimum, discuss dietary goals (see Chapter 1 of Lifestyle Balance Program manual) and provide a brief review of Chapters 1-3.
4. File a copy of the patient's dietary goals for future reference.
5. Instruct the patients to record their food and beverage intake and physical activity daily, including pedometer steps, as appropriate, using the *BARI 2D Food and Activity Record* and the Calorie, Fat and Carbohydrate Counter provided by the study.

b. For the first 3 months of the program:

1. Patients are expected to read and complete one chapter each week.
2. The patients are asked to complete the *BARI 2D Food and Activity Record* daily and to bring a completed record to their next clinic visit from the week prior to their visit for review with the study coordinator.
3. A brief telephone contact should be made from the coordinator within 2 weeks after the patient begins the Lifestyle Balance Program. The coordinator should assess the patient's understanding of the program, adherence to dietary/exercise goals, reinforce progress, and conduct brief problem-solving as needed.
4. Telephone contact on a monthly basis is recommended to review progress and conduct brief problem-solving. More frequent contact could prove more beneficial.
5. Instructions can be modified at the discretion of the coordinator, based on the patient's level of motivational readiness or learning style. For example, a patient could be asked to self-monitor in between clinic visits, and the coordinator could review selected Lifestyle Balance chapters or action plans at follow-up clinic visits. Alternatively, a committed patient who is struggling with the program may be asked to come for weight control counseling in between the quarterly visits.

c. At subsequent quarterly clinic visits:

1. The patient should be encouraged to self-monitor the week prior to the next clinic visit and to bring in the record for the coordinator to review during the visit. Ideally, the *BARI 2D Food and Activity Record* should be reviewed and verbal feedback provided to the patient.
2. The coordinator should continue to review the patient's weight loss within the context of available behavioral data (the *BARI 2D Food and Activity Record*) and medical data (e.g. change in glucose, lipids and blood pressure). The positive effects of even modest weight loss (5-7%) on glucose, blood pressure and lipids can be a strong motivator for patients.
3. Focus on adherence to both dietary and physical activity goals is important for weight maintenance.
4. The coordinator can review the handout "Staying Motivated" during the clinic visit and give the patient a copy.

d. For patients who are not losing weight:

1. A reassessment of dietary goals is suggested. Use of time-limited individually-tailored meal plans in accordance with the BARI 2D nutrition protocol may be helpful for certain patients who are not losing weight by monitoring fat and calories alone.
2. A referral to the study RD (if available) should also be considered.
3. All patients should be encouraged to continue to self-monitor daily using the *BARI 2D Food and Activity Record* and to bring their record from the week prior to their clinic visits to the visit for review with the study coordinator.

III. ADDITIONAL TOOLS

Additional counseling tools are available for coordinator use. An alternative self-monitoring tool (see Attachment A) is available for patients who find self-monitoring using the *BARI 2D Food and Activity* Record either too difficult, too time consuming, or for those patients who have been successful and now want a more streamlined method of self-monitoring.

IV. STUDY GOALS FOR WEIGHT CONTROL

A. Weight Loss

Patients who are overweight (BMI more than 25 kg/m^2) are advised to lose 10% of their initial weight over a 6 month period (as per nutrition protocol). After the initial 6 months, in patients with BMI over 25, the Lifestyle Balance Weight Control Program will be strongly recommended if: a) there has been less than 5% weight loss since the beginning of the study and glycemic control is not on target; or b) there has been 0-5% weight gain since the inception of the study and glycemic control is not on target; or c) there has been more than 5% weight gain since the inception of the study.

B. Calories

As per the nutrition protocol, a moderate caloric restriction goal of 250–500 calories less than the patient's estimated total energy expenditure (TEE) will be given [TEE – Resting Energy Expenditure (REE calculated by the Harris-Benedict equation) x 1.3 (factor for light activity). All patients are instructed to consume three balanced meals per day at consistent times. Snacks are incorporated into an individual's meal plan based on the individualized calorie level and typical daily intake.

C. Dietary Fat

As per the nutrition protocol, patients are advised to follow the American Heart Association Step One diet (<30% of total calories, saturated fat limited to <10%, polyunsaturated fat < 10%, monounsaturated fat 10-15% and dietary cholesterol < 300 mg per day).

D. Carbohydrates

The carbohydrate content of the diet is 50–60% of total calories (as per the nutrition protocol).

E. Exercise/Physical Activity

As per the study protocol, patients must be medically cleared by the study cardiologist for exercise/physical activity on an annual basis or after any clinical event. All patients are given a specific exercise prescription and guidelines to follow.

F. Self-Monitoring Plan

Patients are advised to self-monitor food, beverage and physical activity daily using the *BARI 2D Food and Activity Record*. Alternative self-monitoring tools (see Attachment A) can be used for patients who find self-monitoring too difficult or for patients who have met their weight goal and want a more streamlined method of self-monitoring.

G. Blood Glucose Monitoring

Patients receiving insulin or insulin-providing agents will be advised that calorie restriction may increase the risk of hypoglycemia. The need for close blood glucose monitoring will be reinforced by the study coordinator. The guidelines for detecting and managing hypoglycemia will be reviewed again at the time the Lifestyle Balance Weight Control Program is instituted and this will be documented in the patients' charts.

ATTACHMENT A

BARI 2D Lifestyle Balance Weight Control Program Alternative Self-Monitoring Tool: Quick Track

Quick Track is an alternative self-monitoring tool for BARI 2D patients. It has been designed for:

- Patients who find traditional self-monitoring using the *BARI 2D Food and Activity Record* and Calorie Counter too difficult (for example, because of very limited reading or math skills) or too time consuming.

- Patients who have been successful using traditional self-monitoring and now want a streamlined method for maintenance.

The first page of Quick Track lists certain "targeted" foods that are high in total and saturated fat and common in the American diet. The second page lists lower-fat foods that may be eaten instead of those high-fat foods.

Give patients both pages (you may want to print them back to back). Instruct patients to complete one column for each day by placing a check mark in the appropriate row **every time they eat any of the foods listed in that row *in any amount***, including in mixed dishes.

Feel free to modify the targeted foods on either the front or back of the form. For example, you may want to add a specific food to one of the rows that contains similar foods (or to the row labeled "other") if that food is a significant source of fat and/or calories for the patient at this time. Or, you may want to cross out certain rows to focus or simplify self-monitoring for a period of time.

Quick Track is a record of the ***number of times*** certain foods are eaten. Amounts are not recorded. Care must be taken, therefore, to educate patients about the importance of appropriate serving sizes and overall caloric intake. For some patients, you may want to write in what a "serving" should be for some of the foods and instruct them to check the row every time they eat one serving and to check the row twice or even three times for larger servings. For others, Quick Track may not be suitable because of the need to self-monitor portion sizes closely.

BARI 2D
Quick Track

Name _____Week of _____

Check every time you eat ANY AMOUNT of these high-fat foods, including in mixed **Dishes. Try to LIMIT these foods**

CAUTION! High-fat foods	M	Tu	W	Th	Fri	Sat	Sun
Added Fats							
Butter, regular or reduced-fat cream cheese							
Regular or reduced-fat sour cream, gravy							
Oil, lard, bacon fat, shortening							
Regular salad dressing or mayonnaise (including on sandwiches, in potato salad, tuna salad, coleslaw)							
Dairy Foods							
Whole or 2% milk							
Regular coffee creamer, cream, half and half							
Regular cheese, cheese or cream sauces							
Meats, Main Dishes							
Hamburger, cheeseburger, ground beef (except super lean), meat loaf, beef burritos, tacos							
Pizza							
Hot dogs, bologna, salami, ham (except extra lean), other lunch meats							
Bacon, sausage							
Most red meats (except lean cuts, trimmed of fat)							
Fried fish or fried fish sandwich							
Fried chicken, fried chicken sandwich, skin on chicken							
Side Dishes, Breads							
French fries, fried potatoes							
Pastry, doughnut, croissant							
Snacks, Desserts							
Regular potato chips, corn chips, tortilla chips							
Regular cookies, cake, pie, ice cream, chocolate candy							
Other:							

BARI 2D
Quick Track

Name _____Week of _____

Check every time you eat these lower-fat foods ***instead*** *of* a high-fat food, including in mixed dishes. **Remember:** These foods still contain calories, so be careful about the amounts you eat.

GO! Lower-fat heart healthy foods	M	Tu	W	Th	Fri	Sat	Sun
Fat Substitutes							
Low-fat or fat-free margarine (0 trans fats)							
Fat-free cream cheese or sour cream							
Jelly, jam							
Vegetable cooking spray (olive or canola oil)							
Low-fat or fat-free mayonnaise, mustard, catsup							
Dairy Foods							
Skim or 1% milk							
Low-fat or fat-free creamer							
Low-fat or fat-free cheese							
Meats, Main Dishes							
Grilled or roast chicken sandwich, without mayonnaise-based sauce							
Sliced turkey, chicken or water-packed tuna, with low-fat mayonnaise or mustard							
Lean red meats (round or loin cuts, lean ham), with fat trimmed							
Fish, baked, broiled or grilled							
Chicken or turkey, without skin, broiled, baked or grilled							
Side Dishes, Breads							
Baked or boiled potato							
Whole-grain bagels, English muffins, whole-grain breads							
Vegetables, raw or cooked, without added fat							
Snacks, Desserts							
Pretzels; plain, air-popped popcorn; low-fat chips							
Sherbet, ice milk, fruit ice, low-fat frozen yogurt, fruit							
Nuts (walnuts, cashews, pecans, almonds) or sesame seeds							
Other:							

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CHAPTER ELEVEN : SECTION SIX HYPOGLYCEMIA MANAGEMENT COUNSELING GUIDELINES

I. INTRODUCTION

Any person with diabetes who takes an oral hypoglycemic agent or insulin may experience low blood glucose. Severe hypoglycemia occurs more often in patients who are following an intensified treatment regimen with the target glucose level near normal range. Patient education and monitoring of blood glucose are the best approaches to preventing hypoglycemia.

II. GENERAL PRINCIPLES OF MANAGEMENT

A. Patients in the insulin sensitizing treatment arm will be asked to do self-blood glucose testing before breakfast and medication administration at least 3 days a week.
B. Patients in the insulin providing treatment arm will be asked to monitor more frequently as needed to guide insulin therapy in particular.
C. Patients on multiple daily injections will be asked to monitor glucose 4 times per day before meals and at bedtime with an initial fasting target 80–120 mg/dl.
D. Home blood glucose monitoring will be reviewed at the Diabetology visits and medications will be adjusted accordingly. Patients will be urged to report low blood glucose levels promptly.
E. Educational material should be provided to each patient and practical counseling should be provided including:

1. Recognition of Symptoms
   Instruct patients of the following:

   a. They may feel sweaty, shaky, faint, dizzy, weak, nervous, extra hungry, irritable or confused.
   b. Their heart may pound, their head may ache, or their lips or tongue may tingle.
   c. Other people may notice that their mood has changed, they cannot be awakened, or their speech is slurred.
   d. They may wake up with a headache or have damp sheets. These are signs they may have low blood sugar during sleep.
   e. It is possible to have a low blood sugar and not know it. This may happen more often to people who have diabetes for a long time.

2. Prevention of Low Blood Glucose
   Instruct patients of the following:

   a. Try to have meals and snacks at the same time each day.
   b. Carry foods to treat low blood glucose and snacks for emergencies.
   c. Eat an extra snack or use less insulin or pills if they plan to exercise.
   d. If they are eating out, inject their insulin or take their pills after they get to the restaurant in case their meal is delayed.
   e. Check their blood glucose as recommended.
   f. If they drink alcohol, drink it with a meal or snack.
   g. Get to know how they feel when their blood glucose is low.

h. Make sure their family and friends know what signs to look for when their blood glucose is low so they can help when necessary.

3. Self Treatment of Low Blood Glucose
Instruct patients of the following:

a. Step 1 – Test their blood glucose if they suspect it is low.
b. Step 2 – If their blood glucose is below 70 mg/dl OR if they have feelings or signs of hypoglycemia and cannot test, eat a treatment food (see below).
c. Step 3 – Rest for 15 minutes.
d. Step 4 – Retest their blood glucose.
e. Step 5 – If their blood glucose is still low, repeat Steps 2, 3 and 4. If their blood glucose is normal, go to Step 6.
f. Step 6 – If they missed a meal or snack or if one is due in the next hour, eat it now. If they are not due to eat a meal or snack, eat an extra snack with about 15 gm carbohydrate and some protein and fat. Here are some ideas:

A cup of milk or sugar-free yogurt
A small piece of fruit and an ounce of low-fat cheese
Half a sandwich
Three cheese or peanut butter sandwich crackers
Half a burrito or quesadilla

g. Step 7 – Get medical help immediately (dial 911) if their blood glucose is still low after 30 minutes and two treatments. If they pass out, they may need a glucagon injection or intravenous glucose.

Examples of Low Blood Glucose Treatments (10-15 grams carbohydrate):

2-3 tsp honey
3-4 tsp white sugar
4-5 small hard candies
5-6 large jelly beans
4-5 small gumdrops
4-6 oz (1/2-3/4 cup) regular soft drink
4 oz (1/2 cup) orange or apple juice
Glucose or dextrose tablets or gel (check label for amount)

4. After Low Blood Glucose
Instruct patients of the following:

a. Try to learn why their blood glucose was low.
b. Check their blood glucose again in 2 to 4 hours.

Call their health care team if they do not know why they had a low blood glucose reaction or if they have a low blood glucose reaction 2 or 3 days in a row.

CHAPTER ELEVEN : SECTION SEVEN FOOT CARE COUNSELING GUIDELINES

I. INTRODUCTION

The majority of non-traumatic amputations in the United States occur in diabetic patients. It has been estimated that more than half of these amputations could have been prevented with proper care. Therefore, the clinician and patient who are conscientious about prevention, early detection and prompt treatment of diabetic foot problems can make a significant impact on this problem (Medical Management of Non-Insulin Dependent (Type 2) Diabetes, Third Edition, American Diabetes Association).

The following guidelines should be applied by BARI 2D clinical personnel in the treatment of patients enrolled in BARI 2D:

1. Recommendation of a referral for a visual exam during the initial clinical visit. Follow-up visual exams are recommended to be done quarterly. Patients with a high risk for developing foot ulcers may need to be seen more frequently or referred to a specialist for particular problems.
2. Provide foot care counseling during the initial clinical visit with follow-up reinforcement as needed.

II. PRINCIPLES OF FOOT CARE COUNSELING

Patients should be instructed on the importance of regular foot care which should include:

1. Inspection of the feet daily; if vision impaired, instruct patient to have someone check feet for him/her. Check for scratches, cuts, blisters (with special care to check between toes).
2. Wash feet daily; dry carefully especially between toes.
3. If feet are dry apply a thin coat of cream after bathing and drying. Do not place cream between toes.
4. Never go barefoot.
5. Wear well fitting shoes. Try running or walking shoes for everyday wear.
6. Shake shoes out and inspect them before wear for areas that might cause blistering or rubbing.
7. Break new shoes in slowly.
8. Trim nails with a slightly rounded edge.
9. Don't cut calluses. Don't use astringents and over the counter preparations for corns, calluses, etc.
10. Don't use foot soaks.
11. Avoid extreme temperatures, test water with a hand before bathing. Don't walk on hot surfaces, such as sand at the beach or cement around swimming pools. Don't apply hot water bottles or heating pads.
12. Instruct patients to report the following to a doctor at once:
    a. Cuts or breaks in the skin
    b. Ingrown nails
    c. Changes in color or discoloration of the feet
    d. Changes in sensation or development of pain
    e. Changes in the architecture of the foot.
13. Patients should be informed about the relationship between neuropathy, peripheral vascular disease (PVD) and foot ulcers.

14. Patients should be urged not to smoke, particularly if they have PVD.
15. Inform patients about special shoes for preventing or treating foot problems.
16. Refer patients to a certified pedorthist if they have a deformity or otherwise need special shoes.
17. Refer patients to a podiatrist if it appears that they would benefit from podiatric services.

CHAPTER ELEVEN : SECTION EIGHT LIFESTYLE INTERVENTION MANAGEMENT CENTER

To ensure compliance with the Non-Pharmacologic (NP) Intervention Protocol and to oversee the attainment of trial goals, a Lifestyle Intervention Management Center (LIMC) has been established. The co-directors of this Center are Jeanine Albu, MD, St. Luke's Roosevelt Hospital, College of Physicians & Surgeons, Columbia University, and Sheldon H. Gottlieb, MD, Johns Hopkins Bayview Medical Center, Johns Hopkins University School of Medicine.

Just as the Lipid and Hypertension Management Centers oversee the uniform management of aspects of CAD risk factors, the LIMC will:

1. Oversee the design and current update of the protocols for smoking cessation, nutrition/weight loss and exercise interventions.
2. Oversee the implementation of these protocols by working with the Coordinating Center (CC) on educational materials and training of clinical site coordinators.
3. Monitor the actual implementation of the protocol by reviewing data on smoking, weight gain and physical activity provided by the CC with regard to individual sites in relation to the overall study mean.
4. Intervene by keeping in contact with those sites which are outliers (>1 SD above the study mean).

The following additions to the NP protocol will be implemented with the establishment of the LIMC:

1. A worksheet (see Section Two, Attachment A) to be used as the individual exercise prescription given by a cardiologist and revised annually or any time there is a change in cardiac status.
2. Pedometers, including instructions for their use (see Section Two, Attachment B), and physical activity records (see Section Two, Attachment D) as biofeedback interventions to increase physical activity.
3. The Lifestyle Balance Weight Control Program (see Lifestyle Balance manual) to be instituted at any time after the first 6 months of the study to reinforce the goals of weight control.

The LIMC will review data provided by the CC on a quarterly basis for clinical sites and individual patients. The LIMC will facilitate intensive and uniform lifestyle intervention by providing direct feedback to the clinical sites every 6 months.

The following data will be monitored by the LIMC:

1. BMI, weight and waist circumference at baseline and annual changes.
2. Physical activity, smoking and dietary information at baseline.
3. Compliance with the exercise protocol: exercise counseling, use of the exercise prescription and pedometer data.
4. Compliance with the smoking cessation protocol: smokers provided counseling, who quit, who quit and restarted, new smokers.
5. Compliance with the nutrition protocol: dietary counseling provided, use of the Lifestyle Balance Weight Control Program.

Data will be provided as mean values and proportions for both the study as a whole as well as the individual clinical centers. In addition, obesity and exercise data will be provided by gender, by quartiles of age, in relation to HbA1c, triglyceride levels, systolic blood pressure and hypoglycemia episodes.

The data above will include both the trend for the action taken by the clinical centers for each subject and the goal attained for these subjects. This information will be used to trigger further follow-up with the clinical sites. The individual follow-up with investigators responsible for participants who have not met the LIMC goals will consist of contact by an e-mail letter seeking further information and offering advice as appropriate. Advice may consist of help with exercise and diet prescriptions for the individual patients, assessing the need for registered dietitian intervention and/or implementation of the Lifestyle Balance Weight Control Program. The identity of individual patients in the reports will remain anonymous.

CHAPTER TWELVE

STANDARD CLINICAL MEASUREMENT PROTOCOLS

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CHAPTER TWELVE : SECTION ONE STANDARD HEIGHT PROTOCOL

I. EQUIPMENT:

The same measuring device should be used for all study participants. If possible a stadiometer should be used and should be calibrated daily.

II. PROCEDURE:

Measure the patient's height using the following procedure:

1. Instruct the patient to remove his/her shoes.
2. Ask him/her to stand with back erect with weight evenly distributed across both feet and feet flat on the floor with heels together. If possible have the patient stand against a wall with both shoulder blades touching the wall. Instruct him/her to look straight ahead and keep chin level.
3. Check that the participant is in the correct position.
4. Instruct him/her to look straight ahead keeping arms relaxed and hanging loosely at his/her side.
5. Bring the measuring bar down firmly, but not tightly, on top of the head.
6. Instruct the patient to inhale deeply and record the reading before he/she exhales.
7. Measurement can be done in inches and converted to centimeters. (1 inch = 2.54 cm)
8. Measurements should be taken twice until 2 consecutive measurements are within 1 cm of each other. Both measurements will be recorded.

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CHAPTER TWELVE : SECTION TWO STANDARD WEIGHT PROTOCOL

I. EQUIPMENT:

Standard balance beam scale. The same scale should be used at each visit.

II. MAINTENANCE:

1. When not in use, rest the counterweight (larger weight) in the far right position.
2. The top weight should rest in the left or zero position.
3. The counterweight should always be lifted carefully before it is moved across the beam. This prevents wear on the notches which could lead to erroneous readings.
4. Keep the scale on a level surface and move it as little as possible.
5. Scale calibration should be checked monthly against known weights. Each center should have a 50 kg weight for this purpose. If the beam does not "float" at zero with no weight on the platform, or if the measurement of the known weight is off by more than 1 kg, the scale may need to be repaired or replaced.

III. PROCEDURE:

Measure body weight using the following procedures:

1. Weights should be done in a fasting state and the participant should be encouraged to empty his/her bladder and bowels prior to the measurement.
2. Instruct the patient to remove any jacket or heavy sweater and empty his/her pockets. If possible the participant should be placed into a hospital gown.
3. Instruct him/her to remove shoes.
4. Zero scale before asking him/her to step onto the scale.
5. Ask the participant to step onto the scale, facing the measurement beam.
6. Instruct him/her to stand in the middle of the platform on the scale with the head erect and eyes looking straight ahead.
7. Ask him/her to distribute weight evenly on both feet.
8. Lift the counter weight and slide it to the right until the beam approaches balance with the participant standing in the proper position. Adjust the top poise until the beam approaches balance with the participant standing in the proper position.
9. Read the scale with your eyes level at the point of measurement.
10. Ask the participant to step off of the scale.
11. Measurement can be done in pounds and converted to kg. Record the measurement in kg, round to the nearest tenth of a kg. (2.2 pounds = 1 kg).

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CHAPTER TWELVE : SECTION THREE STANDARD WAIST CIRCUMFERENCE PROTOCOL

I. EQUIPMENT:

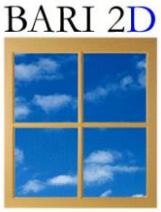
Non-stretch tape measure that is marked in centimeters.

II. PROCEDURE:

1. Instruct the participant to remove any extra layers of clothing or belts (only non-binding undergarments can be worn). Ask the patient to remove girdles, binding pantyhose, and all outer clothing.
2. Instruct him/her to stand with weight distributed evenly on both feet, abdomen relaxed, arms at sides and feet together.
3. Facing the participant, place the tape measure at the level of the natural waist, which is the narrowest part of the torso between the ribs and the iliac crest. An assistant may be needed to help positioning the tape in the horizontal position. For those participants in whom it is difficult to identify a waist narrowing, measure the smallest horizontal circumference in the area between the ribs and the iliac crest.
4. Ensure that the zero end of the tape is below the measurement value.
5. Verify that the participant is standing erect and that the tape measure is horizontal.
6. Take the measurement of the waist at the end of a normal expiration, without the tape measure compressing the skin.
7. Measurements should be taken twice until two consecutive measurements are within 1 cm of each other. Record the each of the two measurements, rounding to the nearest half centimeter (e.g, 35.5).

Standard Waist Circumference Observation Form

	Trainee	Trainer	Difference
First waist circumference (cm)	_____	_____	_____
Second waist circumference (cm)	_____	_____	_____
Third waist circumference (cm)	_____	_____	_____



Certification for Waist Circumference Measurement

_____ has successfully completed the BARI 2D Waist Circumference Training Program and is now certified to perform waist circumference measurements for the next two years. Recertification should be obtained after this time period.

_____

Trainee Signature and Date (mm/dd/yyyy)

_____

Certifying Signature and Date (mm/dd/yyyy)

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CHAPTER TWELVE : SECTION FOUR STANDARD BLOOD PRESSURE PROTOCOL

I. EQUIPMENT

1. Conventional mercury sphygmomanometer
2. Manual blood pressure cuffs (small, regular, large and thigh cuffs). Do not substitute automatic blood pressure devices.
3. Standard stethoscope and ear pieces with bell, tubing to be a maximum 14 inches long
4. Tape measure (non-stretch)

II. MAINTENANCE

Blood pressure sphygmomanometers will be checked daily to establish that the resting mercury level is at zero with maintenance as needed by the manufacturer.

III. PROCEDURE

Establish that the patient has not eaten, taken in caffeine (from coffee, tea or soda), participated in heavy physical activity, smoked and/or used alcohol 30 minutes prior to the recording of the blood pressure.

Measure the participant's right arm to determine the appropriate cuff size before allowing the participant to rest. If the person's right arm is injured or missing, is the site of dialysis access or the person has had a prior right mastectomy, use the left arm for arm circumference and blood pressure measurement.

Use the following procedures to measure the participant's arm and determine the appropriate cuff size:

1. Proper measurement requires that the participant's arm be bare to the shoulder. The participant will be wearing a gown or short-sleeved shirt.
2. Request the participant to stand, bend the elbow, and put the forearm across the abdomen. The upper arm should be at a 90° angle to the lower arm.
3. Measure the arm length from the bony prominence of the shoulder girdle to the tip of the elbow using a tape measure.
4. Mark the midpoint on the dorsal (back) surface of the arm.
5. Ask the participant to relax their arm along the side of the body.
6. Draw the tape measure horizontally around the arm at the midpoint mark, do not indent the skin.
7. Use the measurement to determine the correct cuff size.
8. Record the measurement and cuff size on the form and use it as a reference for future measurements. Measurements should be obtained at each visit

Based on the participant's arm circumference measurement, choose the appropriate size blood pressure cuff."

If a supine blood pressure is being done, the participant should rest for 1 minute in the supine position with his/her legs uncrossed. If a sitting blood pressure is being done then the participant should rest for 5 minutes with his/her legs uncrossed.

1. Palpate the brachial artery at the medial antecubital space.

2. Place the appropriate sized cuff around the upper arm, one inch above where the brachial artery is palpated. Wrap the cuff snugly around the arm, with the inflatable bladder centered over the area of the brachial artery. You should be able to insert two fingers under the cuff.

3. Determine the Maximum Inflation Level (MIL). If the correct procedure (inflating to MIL) is not used, the participant's blood pressure measurement may be inaccurate. The only way to avoid this error is to obtain the MIL before BP measurement. The procedures for determining MIL are as follows:
    a. Palpate the radial pulse (if the radial is difficult to palpate, the brachial pulse may be used).
    b. Inflate the cuff to 70 mmHg. Then increase by 10 mmHg increments until the radial pulse is no longer felt (palpated systolic).
    c. Deflate the cuff quickly and completely.
    d. Inflate the cuff to 30 mmHg above the palpated systolic pressure for all subsequent readings.
    e. If the radial pulse is still felt at the level of 270 mmHg or higher (which means that the MIL is 30 mmHg higher) repeat the MIL. If the MIL is still 300 mmHg, terminate the blood pressure measurements and write in "300 MIL" on the form. Immediately refer the patient to their primary care physician via telephone before the patient leaves the clinic.

4. Use the bell of the stethoscope to obtain the blood pressure. The bell is designed to listen to low-pitched sounds (the early and late Korotkoff sounds are low-pitched). Place the bell just below, but not touching the cuff. Deflate the cuff at a rate of 2mmHg per second. The systolic phase is the pressure at which you hear the first of two or more knocking sounds in the appropriate rhythm. The diastolic is the pressure at which you hear the last muffled sound. Make the reading at the top of the meniscus, or rounded surface of the mercury column.

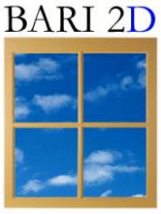
5. Record the systolic and diastolic in the spaces provided.

6. Take care to wait at least 30 seconds between consecutive blood pressure readings.

7. If you are measuring consecutive blood pressures in different positions (i.e., supine, sitting and then standing), you must wait 1 minute after the patient changes his/her position to measure the blood pressure.

Standard Blood Pressure Observation Form

	Trainee	Trainer	Difference
Initial arm circumference (cm)	_____	_____	_____
Cuff size selected	_____	_____	_____
Maximum inflation level (MIL)	_____	_____	_____
First SBP	_____	_____	_____
First DBP	_____	_____	_____
Second SBP	_____	_____	_____
Second DBP	_____	_____	_____
Third SBP	_____	_____	_____
Third DBP	_____	_____	_____



Certification for Blood Pressure Measurement

_____ has successfully completed the BARI 2D Standard Blood Pressure Training Program and is now certified to perform blood pressure measurements for the next two years. Recertification should be obtained after this time period.

_____

Trainee Signature and Date (mm/dd/yyyy)

_____

Certifying Signature and Date (mm/dd/yyyy)

CHAPTER TWELVE : SECTION FIVE STANDARD ANKLE/ARM BLOOD PRESSURE PROTOCOL

I. EQUIPMENT

1. Cuffs - 2 regular adult cuffs plus the appropriate size arm cuff
2. One Inflation bulb/Mercury sphygmomanometer
3. Doppler Probe, batteries in place
4. Doppler conducting gel
5. Stethoscope (if Doppler doesn't have speaker)
6. Black felt tip marker
7. Tissues to remove conducting gel
8. Data collection form

II. PROCEDURE

Blood pressures will be taken in each ankle and in the arm with the highest systolic blood pressure. To determine which arm to use, take the blood pressure in each arm (unless contraindicated as previously stated) and use the arm with the highest pressure. If the pressures are within 10 mmHg of each other then use the right arm. Record arm chosen as the reference arm.

All pressures are obtained using a standard pressure cuff and Doppler probe. One sphygmomanometer will be used for all blood pressures. One set of cuffs will be used for the duration of the study.

1. The participant is asked to remove shoes and socks/stockings. The participant will then lie down on the examining table with right side toward observer.

2. Three blood pressure cuffs are placed on the participant - one on the designated upper arm and one on each ankle. (Cuffs should be placed directly over the skin to insure an accurate measurement - they should never be placed over clothing).

Ankle cuffs are applied with the midpoint of the bladder over the posterior tibial artery, located just above the medial malleolus (ankle bone) on the inside portion of the ankle (great toe side).

For most subjects, the standard adult cuff fits best.

3. The blood pressure procedure begins after the participant has rested for 5 minutes.

4. The brachial artery is located in the right arm by palpation. The pulse can be located at the antecubital (the crease of the arm). After palpation of the artery, it may help to mark the pulse with a felt tip marker to help maintain position. Ultrasound gel is then applied to this area and the Doppler probe is positioned over the pulse so that the observer can hear the pulse clearly.

   The probe should be angled towards the shoulder. Generally, a probe angle of 45 to 60 degrees will obtain the best signal, however, adjustments may have to be made depending on the position of the artery.

   Because of the small size of the Doppler surface and the artery, it is critical to keep the Doppler absolutely still while inflating and deflating the cuff. The observer should have his/her hand resting comfortably so that the Doppler is not inadvertently moved during inflation of the cuff.

5. Using standard blood pressure measurement techniques, the systolic blood pressure is measured and recorded. The cuff should be inflated, listening constantly to the pulse beats. When a pulse is no longer heard the observer allows the mercury column to settle (by keeping the cuff inflated at that pressure for approximately 5 seconds). The pressure is then released , allowing the mercury column to drop at a rate of approximately 2 mmHg/sec. The point at which the pulse is heard is recorded as the systolic blood pressure. The observer then releases the cuff completely and moves to the end of the table where the procedure is repeated for each ankle.

6. The right ankle cuff is connected to the sphygmanometer. The posterior tibial artery (PT), located directly behind the medial malleolus (ankle bone), on the inside portion of the ankle, is palpated and/or auscultated with the Doppler probe. Again, systolic pressure is measured.

7. The sequence of pressures, from beginning of the test to the end is: reference arm, right PT, left PT, left PT, right PT, reference arm.

If the cuff is re-inflated for any reason (the second measurement on the left ankle or to take a repeat measurement), the cuff should be deflated entirely first. There should be a 15 second wait before re-inflating the cuff. This allows the artery to return to its normal state and helps to eliminate measurement error.

If unable to occlude vessel at or above 250 mmHg, please check box on form to indicate unable to occlude vessel. If incompressible at 100 mmHg and the patient can not tolerate, then check box on the form to indicate test could not be performed.

If there is an ulcerated area at the ankle where the blood pressure cuff is to be placed, place the cuff over the ulcerated area.

Measurements should be completed in 10 minutes or less.

III. COMMENTS

Several points will greatly improve the speed and accuracy of measurements.

1. Mark the brachial artery with a felt tip marker (before gel is applied) to improve the speed of localizing it the second time.

2. Hold the Doppler absolutely still and on an angle to the artery to avoid "crushing" the artery. Moving a few millimeters will lose the pulse.

Ankle/Arm Blood Pressure Observation Form

Trainee		**Trainee**		**Trainee**	
Subject #1		**Subject #2**		**Subject #3**	
Circle reference arm: **Right** **Left**		**Circle reference arm:** **Right** **Left**		**Circle reference arm:** **Right** **Left**	
Reference Arm	_____	Reference Arm	_____	Reference Arm	_____
Right PT	_____	Right PT	_____	Right PT	_____
Left PT	_____	Left PT	_____	Left PT	_____
Left PT	_____	Left PT	_____	Left PT	_____
Right PT	_____	Right PT	_____	Right PT	_____
Reference Arm	_____	Reference Arm	_____	Reference Arm	_____

Trainer

Subject #1

Circle reference arm:
Right
Left

Reference Arm	_____	Difference_____	Reference Arm	_____	Difference_____
Right PT	_____	Difference_____	Right PT	_____	Difference_____
Left PT	_____	Difference_____	Left PT	_____	Difference_____
Left PT	_____	Difference_____	Left PT	_____	Difference_____
Right PT	_____	Difference_____	Right PT	_____	Difference_____
Reference Arm	_____	Difference_____	Reference Arm	_____	Difference_____

Trainer

Subject #2

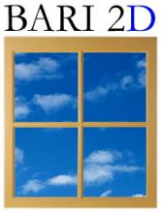
Circle reference arm:
Right
Left

Trainer

Subject #3

Circle reference arm:
Right
Left

Reference Arm	_____	Difference_____
Right PT	_____	Difference_____
Left PT	_____	Difference_____
Left PT	_____	Difference_____
Right PT	_____	Difference_____
Reference Arm	_____	Difference_____



Certification for Ankle/Arm Blood Pressure Measurement

_____ has successfully completed the BARI 2D Ankle/Arm Blood Pressure Training Program and is now certified to perform ankle/arm blood pressures for the next two years. Recertification should be obtained after this time period.

_____

Trainee Signature and Date (mm/dd/yyyy)

_____

Certifying Signature and Date (mm/dd/yyyy)

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CHAPTER TWELVE : SECTION SIX MICHIGAN NEUROPATHY SCREENING INSTRUMENT (MNSI)

I. PATIENT QUESTIONNAIRE

The self-administered portion of the questionnaire (BF-1 and FD-1) should be done prior to the physical exam (BF-4 and FD-2). Patients should fill out the form in a quiet, uninterrupted environment. Review the questionnaire both for errors (especially watch responses to items 7 and 13) and clues to presence of neuropathy.

II. PHYSICAL EXAMINATION

A. Equipment

10 gram filament, C128 tuning fork, reflex hammer

The examination should be performed when the foot is warm.

B. Appearance

Examine the foot for abnormalities (bony protrusions, fallen arches, or overlapping toes, swelling, redness, bunions, callous, fissures, abnormal toenails, etc). Grade callus and dry skin as present only if you feel the degree of callus/dry skin is beyond what you would normally expect. Record athletes foot as infection, but do not record onchomycosis (toenail fungus).

C. Ulceration

Examine the foot for neurophathic ulcers. Grade as present or absent. Wounds from known trauma are not ulceratons, and should not be recorded.

D. 10 Gram Filament

The bottom of the foot should be supported either with your hand or by the floor. This helps insure consistent pressure with each application. Pre-stress the filament a few times using your hand or the patient's hand. When the filament bends slightly (a "C" shape), then 10 gms of pressure has been delivered. Have the patient close their eyes. Apply the filament 10 times to each great toe, just distal to the DIP joint (just below the cuticle of the the toenail). Each application should last less than 1 second, and wait at least 1 second between applications. You may vary the rate of application. Instruct the patient to say "yes" each time he or she feels the filament.

Grade the response as present if the patient correctly responds to 8 or more filament application, reduced for 1 to 7 correct responses and absent if the patient does not correctly identify any of the10 stimulus applications.

E. Vibration

Vibration is tested by application of a C128 tuning fork to the great toe. Have the patient close his/her eyes. Apply the head of the tuning fork to the bony prominence of the DIP joint of the great toe. First without, and then with, it vibrating (i.e., striking it on a hard surface), ask the patient if they can feel the difference of the vibration. If not, you may need to strike the tuning fork more firmly. If they can't feel the vibration, place the vibrating tuning fork on the tibia near the knee or on the finger. If they can feel it vibrating there, but not on the toe record absent. If they feel vibration, ask the patient to say "STOP" when they can no longer feel any vibration. When that occurs, apply the still vibrating tuning fork to the DIP joint of your index finger and determine how much longer you can feel the vibration. If you can feel the vibration for greater than 10 seconds then record the vibration perception as reduced, if you feel the vibration for <10 seconds or cannot feel the vibration at all, then record as present.

Ideally, the foot should not be supported during the procedure, rather, the weight of the tuning fork should be used to keep the instrument in contact with the skin. If you are having trouble keeping the toe in contact with the tuning fork, lightly support the foot at the heel, or lightly grasp the sides of the toe with your thumb and index finger. You must avoid letting your hand or finger act as a conduit to abnormally distribute the vibration sensation away from the point of contact.

F. Achilles Stretch Reflex

Achilles Stretch Reflex (Ankle Reflex) is performed with the patient positioned so the ankle and foot are relaxed and freely mobile (i.e. at the edge of an examing table). Have the patient keep the foot/ankle as relaxed as possible. Slightly dorsiflex the foot to stretch the Achilles tendon. Sharply tap the Achilles tendon with a suitable reflex hammer and look and feel for the reflex responses.

If you do not get a response, try repositioning the foot and leg and encourage the patient to relax. If you are still unable to elicit a response, you may use a Jendrassic maneuver to help distract the patient.

Responses are graded as present for a response without using specific distracting maneuvers, present with reinforcement if the Jendrassic or other distracting maneuver is used or absent if no responses can be elicited.

MNSI Observation Form

	Trainee Initials	Trainer Initials
First Demonstration		
Able to demonstrate proper physical exam	_____	_____
Able to demonstrate proper data form completion	_____	_____
Second Demonstration		
Able to demonstrate proper physical exam	_____	_____
Able to demonstrate proper data form completion	_____	_____
Third Demonstration		
Able to demonstrate proper physical exam	_____	_____
Able to demonstrate proper data form completion	_____	_____

Certification for Michigan Neuropathy Screening Instrument

_____ has successfully completed the BARI 2D Michigan Neuropathy Screening Instrument (MNSI) Training Program and is now certified to administer the MNSI questionnaire and perform the physical exam for the next two years. Recertification should be obtained after this time period.

_____

Trainee Signature and Date (mm/dd/yyyy)

_____

Certifying Signature and Date (mm/dd/yyyy)

CHAPTER TWELVE : SECTION SEVEN STANDARD CLINICAL MEASUREMENT TRAINING/CERTIFICATION

One coordinator from each BARI 2D clinical site is required to be certified by the BARI 2D Coordinating Center to perform the standard clinical measurements. The Coordinating Center is permitting each certified coordinator to train/certify other BARI 2D personnel at their local clinical site. Any one performing BARI 2D clinical measurements must be certified. The certification procedure is as follows:

1. Review the BARI 2D Standard Height, Weight, Waist Circumference, Blood Pressure, Ankle/Arm Blood Pressure, and Michigan Neuropathy Screening Instrument (MNSI) Protocols with the trainee.

2. Demonstrate the proper technique to perform the standard waist circumference, blood pressure, ankle/arm blood pressure measurements, administration of the MNSI, along with review of proper data form completion for these measurements. It is important to stress the significance of recording each measurement on the data form immediately after it is done to reduce error.

3. Have the trainee perform the standard waist circumference, blood pressure, ankle/arm blood pressure measurements, and administration of the MNSI on someone using the following guidelines:

    a. The standard waist circumference must be performed three times by the trainee and trainer and recorded on the training observation form. The waist circumference measurements recorded by the trainee and trainer must be no more than 1 centimeter apart in order for the trainee to be certified. A certification form must be completed and signed by the trainer and trainee.

    b. The blood pressure must be performed three times using a training stethoscope (two ear piece sets). A training observation form must be completed to document the blood pressure measurements obtained by the trainee and trainer. The blood pressures recorded by the trainee and trainer must be no more than 4 mmHg apart in order for the trainee to be certified. A certification form must be completed and signed by the trainer and trainee. Each trainee must be certified to perform standard blood pressures before he/she can be certified to perform the ankle/arm blood pressures.

    c. The ankle/arm blood pressures must to be performed on five different subjects. For each subject the trainee should perform and record the measurements on the training observation form, as the trainer monitors the procedure, and then immediately the trainer should perform and record the measurements. The blood pressures recorded by the trainee and trainer must be no more than 4 mmHg apart in order for the trainee to be certified. A certification form must be completed and signed by the trainer and trainee.

    d. The MNSI must be administered three times and appropriately documented on the training observation form. A certification form must be completed and signed by the trainer and trainee.

4. Send the original completed observation forms and certification forms to:

BARI 2D Coordinating Center
University of Pittsburgh, GSPH
127 Parran Hall/130 Desoto St.
Pittsburgh, PA 15261
FAX: (412) 383-8690

CHAPTER THIRTEEN

STATISTICAL METHODS

I. INTRODUCTION

The two primary objectives of BARI 2D are to compare: (i) initial revascularization with aggressive medical therapy versus aggressive medical therapy alone; and (ii) management of hyperglycemia with a strategy of insulin sensitization versus insulin providing. The primary endpoint is 5-year all-cause mortality, and two-sided confidence intervals will be reported. Both primary treatment comparisons will be made according to treatment assigned (i.e., the intention-to-treat principle) rather than treatment received.

II. FACTORIAL DESIGN

In BARI 2D, a 2x2 factorial design will be used with a revascularization component and a glycemic control component. Data from all patients will be used in both of the primary treatment comparisons. For each patient, the glycemic treatment and the cardiology treatment will be administered simultaneously without modification since the two treatment protocols should not substantially interfere with each other.

A two-sided test with an α-level = 0.05 will be used to test each of the two primary treatment comparisons. In the literature[1] and in the recent past[2,3], there is precedent for choosing the α-level in a factorial design as if one were running a separate trial for each component rather than adjusting the α-level for multiple comparisons.

The factorial design is appropriate for BARI 2D where a substantial interaction between the cardiology component and the diabetes component is not expected yet the ability to detect an unexpected significant interaction is desirable[1,4]. It must be noted that the power to detect a significant interaction in this trial is quite low (this holds true for the interaction between main effects within a factorial design just as it does for the interaction between any factor and treatment in a standard two-arm trial).

III. POWER AND SAMPLE SIZE CONSIDERATIONS

The two primary comparisons in this 2x2 factorial study will be performed separately. Power calculations are provided for one of the treatment comparisons; identical power is available for the other comparison. Table 1 presents the power for detecting a 25% reduction and a 30% reduction in the primary endpoint all-cause mortality and in the principal secondary endpoint the combination of death, myocardial infarction or stroke.

The calculations are based on the following assumptions: α=0.05, an equal number of patients will be assigned to each treatment arm, the sample size will be N=2350, there will be 4 years of recruitment and an additional 2.17 years of follow-up (i.e. 3.84 years of follow-up on average), 5% of the patients will be lost to follow-up, the overall 5-year mortality rate will be 11.9%, and the overall 5-year death/MI/stroke rate will be 21%. For example, a 30% reduction with an overall 11.9% mortality rate corresponds to 14.0% and 9.8% 5-year event rates in the medical versus revascularization comparison or in the IS versus IP comparison; a 25% reduction in the death/MI/stroke rate with a 21% overall 5 year rate corresponds to a 24% versus 18% treatment comparison. Given that the 5-year mortality rate for the diabetic patients assigned to CABG in BARI was 19% and that the diabetic patients in BARI 2D will have CAD at an earlier stage of progression, we had hypothesized that the 5-year mortality rates for the overall group in

BARI 2D would be between 12% and 14%. The current estimate of a 5-year overall mortality rate at 11.9% includes an additional adjustment for the rigorous control of risk factors in BARI 2D.

Table 1
Power to Detect Significant Diffrerences in the Primary and Principal Secondary Endpoints

Sample Size	Power to Detect 25% Reduction in Mortality	Power to Detect 30% Reduction in Mortality	Power to Detect 25% Reduction in Dth/MI/Stroke	Power to Detect 30% Reduction in Dth/MI/Stroke
N=2350	55%	73%	84%	95%

If there were a 30% reduction in mortality with 2350 patients enrolled in the trial, the trial would have 73% power to detect a significant treatmen effect assuming 14.0% and 9.8% mortality rates for the two treatment groups (Table 1). Similarly, if there were a 25% reduction in the combined endpoint of death/MI/stroke with 2350 patients, the trial would have 84% power to detect a significant treatment effect given 24.0% versus 18.0% event rates. BARI 2D has 95.0% power to detect a 30% recudtion in the combined death/MI/stroke endpoint

Since the statistical variation of the interaction term is four times greater than the variation of the main effect in the factorial design, there is limited power to detect moderate interactions between the diabetes and the cardiology randomized treatments.

IV. RANDOMIZATION SCHEME

The BARI 2D randomization scheme is stratified by clinical center as well as the intended method of revascularization (i.e. "CABG is intended" or "PCI is intended" if randomized to the revascularization of choice treatment arm)[5]. Within each stratum, treatment assignments are made using randomized blocks where the lengths of the blocks are assigned at random.

V. SUBGROUP ANALYSES

For the primary hypotheses, subgroups will be examined based on limited number of *a priori* specified baseline factors (intended method of revascularization, history of prior CABG, receiving insulin at study entry, left ventricular function, creatinine level, and race). In order to correct for multiple treatment comparisons, a two-sided α-level=0.01 will be used for treatment comparisons within the *a priori* subgroups; these comparisons will clearly have less power than the full-scale comparison due to smaller sample sizes and stricter α-levels. Multivariable models that include treatment by subgroup interactions will be used to test whether the treatments have different effects on outcome depending on the subgroup variables.

VI. ENDPOINT ANALYSES

The primary endpoint of BARI 2D is all-cause mortality, and the principal secondary endpoint is the combination of death, myocardial infarction or stroke. Other secondary endpoints that will be compared across the randomized treatment groups are: cardiac mortality, myocardial infarction (Q-wave and non-Q-wave), angina, subsequent revascularization procedures (CABG and PCI), quality of life and employment status. Additional important endpoints based on core laboratory data are: total cost, cost-effectiveness, LV function, the extent of ischemia, lipids measured by NRM, t-PA antigen, and PAI-1 activity. The rates of diabetes complications, in particular retinopathy, neuropathy, nephropathy, peripheral vascular disease, and amputation, will be evaluated. Finally, other critical outcomes including HbA1c, hypoglycemia events, blood pressure and lipids (measured chimcally) are considered to be intermediate rather than truly study endpoints, and will be actively monitored by the BARI 2D management committees during the trial.

A. Survival Analyses

Time-to-event survival methods will be use to evaluate the BARI 2D primary endpoint, total mortality, the secondary endpoint death, MI or stroke, and a number of other important endpoints including cardiac mortality, myocardial infarction, and subsequent revascularization procedure. Kaplan-Meier curves along with log rank statistics or Wilcoxon statistics will be used to estimate and compare cumulative event rates over time. Tests for proportional hazards will be made. Assuming that the proportional hazards assumption is met, Cox proportional hazards models will also be used to model event-free survival adjusting for baseline covariates as well as treatment[6].

B. Cross-sectional and Longitudinal Analyses

A number of endpoints such as angina status, quality of life, employment status, and HbA_{1C} level, will be collected longitudinally at clinic visits during follow-up. These endpoints will be analyzed for treatment differences at each scheduled visit. Chi-square tests will be used for categorical data (e.g. presence of angina), while t-tests or Wilcoxon non-parametric tests will be used for continuous data. Data such as the HbA_{1C} level or albumin can be considered as a continuous variable or a categorical variable based on a clinically meaningful threshold (e.g. $HbA_{1C} < 7.0\%$).

Repeated measures techniques will also be used to study the longitudinal endpoints within a single model. Mixed or random effects models that analyze continuous repeated measures and incorporate time dependent covariates will be used[7,8]. For categorical variables, GEE models[9,10] or weighted least squares models[11] will be used. Importantly, these models offer the flexibility to account for multiple measurements per patient (correlated data) and missing measurements at some follow-up intervals."

C. Cost Analyses

The primary endpoint for the cost analyses is total cumulative cost. Total costs (e.g. total 5 year costs) will be estimated for each of the treatment groups using an adaptation of life-table methods for cost data[12]. This method sums quarterly costs while accounting for both censored patients and deceased patients. The variability for total cost data will be assessed with permutation tests.

Cost effectiveness is another important endpoint, particularly if significant treatment differences are found. The cost effectiveness for comparing treatment A to treatment B at time *t* is defined as:

$$(Cost_t \text{ A} - Cost_t \text{ B}) / (\text{Life-years}_t \text{ A} - \text{Life-years}_t \text{ B})$$

where "$Cost_t$" is total cumulative cost at time *t* and "Life-years_t" is the area under the survival curve between time 0 and time *t*. Bootstrap methods will be utilized to determine the precision of the estimated ratio[13,14].

VII. TRIAL MONITORING AND INTERIM ANALYSIS

A. Trial Monitoring Board

The Data and Safety Monitoring Board (DSMB) will meet every 6 months during the BARI 2D trial to review safety, efficacy, and adherence to protocol. The DSMB will examine recruitment data to determine whether enrollment goals are being achieved. Particular attention will be given to the enrollment figures for women and minority patients.

In order to protect the patients in the trial and to quickly report important medical information, the DSMB will also monitor outcome data. If one treatment is vastly superior to another, then termination of the trial or modification of the protocol will be seriously considered. The mortality treatment comparisons for the two main effects will be conducted annually. Mortality treatment comparisons in *a priori* subgroups will also be provided. Finally, mortality according to cause, with determinations provided by the Mortality and Morbidity Classification Committee, will be examined.

B. Spending Function

Accounting for the sequential monitoring of the outcome data is important so that the overall likelihood of observing a "significant difference" due to chance (the overall type I error) is maintained at the pre-specified level[15]. Therefore, boundaries for the hypothesis tests are calculated using an "alpha spending" function[16].

The total type I error allowed for each primary treatment comparison is $\alpha = 0.05$. The spending function defines the cumulative type I error allowed to be spent at each monitoring time; this is a function of the "information fraction" (the ratio of the number of events that have occurred to the final number of events expected). The O'Brien-Fleming spending function will be used in BARI 2D[17]. This standard spending function is extremely conservative at the first few monitoring times and spends most of the alpha over the second half of the trial. Thus, convincing evidence for a treatment effect will be needed to support early termination of the trial on the basis of the interim analysis results.

C. Test Statistics/Alternative Hypotheses

For the primary treatment comparisons, we assume that the proportional hazards assumption will be appropriate and that the exponential assumption for the survival curves will be reasonable. Thus, the log rank statistic will be used for these survival comparisons.

D. Permutation Test

A permutation test will be used to estimate the significance of the sequential monitoring test statistic[18]. If the significance of the permutation test is less than the α-level determined by the spending function for that monitoring time, then the test "crosses the boundary" and is considered statistically significant.

VIII. REFERENCES

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CHAPTER FOURTEEN

GENETICS PROTOCOL

I. INTRODUCTION

The purpose of the BARI 2D genetics research study is to collect and store genetic material for research related to diabetes and heart disease. Patients will be asked to participate in a genetics study where DNA will be obtained from blood samples already collected as part of the overall BARI 2D study. By studying the DNA from participating BARI 2D patients, researchers might identify the genes that carry the traits for predicting genetic risk factors for heart disease and diabetes and can evaluate the treatments genetically (pharmacogenetics). In the long term, this will lead to improved diagnosis and treatment for patients.

II. BLOOD SPECIMEN COLLECTION

By protocol, all BARI 2D patients provide blood samples to the Biochemistry Core Laboratory at baseline, 1 month, 3 months, 6 months and every 6 months thereafter. The genetics study requires that DNA be extracted from one of these blood samples. If consent for the genetics study is obtained at the time of randomization, the DNA comes from the baseline blood sample. If consent is obtained at a later time during the BARI 2D study, DNA will be extracted from a subsequent HbA1c patient blood sample. Participating in the genetics study, therefore, involves no additional blood draws for the patient. All aspects of the blood specimen collection for the genetics study follow the already approved BARI 2D HbA1c specimen collection protocol.

III. PATIENT CONFIDENTIALITY

When a BARI 2D patient is randomized, the clinical site assigns a unique BARI 2D identification number to that patient. The clinical site personnel will label each collected specimen with this BARI 2D identification number. At the Biochemistry Core Lab, the DNA blood samples will be identified by the clinical site number and by this unique patient number. The BARI 2D Coordinating Center at the University of Pittsburgh and the Biochemistry Core Lab will use only the BARI 2D identification number to identify the patients and to match up the specimen data with the other patient clinical trial data. Patient names and social security numbers will NOT leave the clinical site where the patient receives medical care. The blood specimen samples will not be destroyed unless the patient withdraws consent. Any genetic analyses involving these samples will use the anonymous code.

IV. DATA HYPOTHESIS

BARI 2D is a randomized clinical trial designed to determine the optimal treatment for patients with documented Type 2 diabetes and coronary artery disease. Throughout the study, each BARI 2D patient will receive comprehensive diabetes care (insulin providing strategy versus insulin sensitizing strategy) and cardiac care (aggressive medical care versus aggressive medical care plus revascularization). Detailed baseline phenotype data are collected: demographic characteristics, clinical history and symptoms, lab measures (e.g. HbA1c, lipids, serum creatinine, urine albumin and creatinine), and core lab analyzed angiographic data. Follow-up phenotyping including symptoms, lab measures, and subsequent collected regularly for an average of five years per patient. BARI 2D patients who agree to participate in the genetics study will provide DNA. Traits from this DNA will be analyzed to determine the influence of genomics, both pharmacogenetics and genes, on the effectiveness of treatments for diabetes, heart

disease and risk factor interventions. In particular, the primary hypotheses involve the impact of genes on the response to the BARI 2D interventions including efficacy of treatment for diabetes with metformin, rosiglitizone, and sulfonylurea and restenosis rates following revascularization.

V. ANCILLARY STUDY: INFLUENCE OF SINGLE NUCLEOTIDE POLYMORPHISM MTHFR 677T ON PERIPHERAL ARTERIAL DISEASE OUTCOMES

As described above, BARI 2D participants were asked to participate in a genetics study in which DNA was obtained from blood samples collected as part of the overall BARI 2D study. Depending on the time of consent for participation in the genetics study, DNA was extracted from either the baseline blood sample or a subsequent HbA1c blood sample. Confidentiality was maintained by the process described in Chapter Fourteen, Section III on page 293.

Beginning January 2013, BARI 2D investigators will analyze stored DNA samples for a single polymorphism in the gene coding for methylenetetrahydrofolate reductase (MTHFR) not yet analyzed in the BARI 2D samples. Previous research suggests that the MTHFR C677T polymorphism may be a risk factor for peripheral arterial disease; however, this has never been investigated in a large study with a sufficient number of events to draw meaningful conclusions about this association. The BARI 2D trial allows the opportunity to explore this association in detail with existing resources.

Hypothesis: BARI 2D participants with the T/T genotype or the C/T genotype for MTHFR 677 will have higher risk of developing PAD than those with the C/C genotype.

Patient confidentiality will be maintained using procedures outlined in Chapter Fourteen, Section IV on page 293 that have been used for prior genetics analyses.

CHAPTER FIFTEEN

POLICY GUIDELINES

I. INTRODUCTION

A. General Policy Issues

To achieve the objectives of BARI 2D, collaboration of many different people (patients, clinical site personnel, coordinating center personnel, consultants, core lab personnel, NHLBI staff, and industry sponsors) is required. This collaboration is necessary to maintain continuity of operation, to facilitate effective communication and cooperation among the various study units and to disseminate reports of progress and results of the trial to the scientific community and the public at large.

B. Statement of General Policy Guidelines

The policy and procedures adopted by the BARI 2D investigators for the use of BARI 2D data are intended to protect the interests of all study investigators and staff, to assure that data are accurately presented and interpreted , that communications which are to become part of the permanent public record are well-written, that all investigators are aware of ongoing projects, to avoid unnecessary duplication of analysis and to ensure that publication or presentation of the BARI 2D data does not occur without approval of the appropriate committees. The policies adopted by the BARI 2D investigators to guide analysis and publication of BARI 2D data are intended to:

1. protect the integrity of the study
2. protect the interests of all investigators and staff
3. clarify criteria for authorship
4. ensure clear, concise and accurate reporting of BARI 2D data
5. avoid unnecessary duplication of analyses
6. establish criteria and time lines for abstract presentation for meetings
7. provide a framework for establishing priorities for analysis of BARI 2D data.
8. ensure that all investigators and staff understand the process for committee, investigator, and NHLBI approval of proposed publications
9. establish clear policies regarding reporting of any BARI 2D baseline, outcome, and ancillary study data

C. Role of Data and Safety Monitoring Board

All BARI 2D policy recommendations will be reviewed by the Data and Safety Monitoring Board (DSMB). Release of BARI 2D results will require approval by the DSMB as well as approval by NIH after there is agreement among the BARI 2D investigators as to what to report.

II. PUBLICATION ISSUES

A. Publication Committee

The general purpose of the BARI 2D Publication Committee is to oversee and provide guidance relative to reporting of study data in order to assure expert input, a high standard of scientific quality, responsible conclusions, sound interpretations, clarity, and fulfillment of the overall BARI 2D study objectives. Committee responsibilities are expected to focus primarily on publication policy issues during the early part of the study and on actual publication issues during the latter part of the study. Specific responsibilities of the Committee are: 1) to make recommendations to the Steering Committee for specific policy in relation to data analysis and when baseline and outcome data can be released; 2) to review data analysis plans and release of results relative to various aspects of the study; 3) to facilitate the development of study reports, presentations, and publications by defining specific types of manuscripts, appointing writing groups, overseeing writing groups progress, conducting reviews and forwarding recommendations to writing groups; and 4) to recommend policy for reporting of ancillary studies that may be completed before the final five year outcome data are reported.

B. Editorial Policy

The scientific integrity of the trial requires that all protocol mandated data from all BARI 2D sites be combined for analysis and reported as such. Thus, an individual site is not permitted to report or publish data collected from its site related to the fundamental goals of the BARI 2D. Development of ancillary studies or data bank studies dealing with other specific hypotheses and analyses are strongly encouraged in order to optimally use the expertise available for the BARI 2D project. All presentation and publications of any type based upon data from such studies are expected to maintain the integrity of the objectives of the overall project.

Topics for consideration to be developed into publications will be generated from questions or hypotheses that are submitted to the Committee by investigators, study coordinators and other BARI 2D staff. The Committee will seek expert review and set priorities for requests. A writing group, with a designated Chair and appropriate representation from sites and the CC, will be recommended. The writing group will develop the request for data analysis as well as the abstract or manuscript reporting these data. These reports will be reviewed and require approval by the Committee.

Investigators at all BARI 2D sites, including the Core Laboratories, the Coordinating Center (CC) and the NHLBI Program Office may develop protocols, participate in such studies as approved by the Committee, and collaborate in the development and publication of research manuscripts based on BARI 2D material. With the approval of the Principal Investigator, study coordinators and other BARI 2D staff at the various sites are encouraged to participate in this process.

C. Authorship

The publications and presentations reporting the primary results (efficacy and safety outcome) of BARI 2D will have authorship "the BARI 2D Study Group." An appendix listing all Investigators in BARI 2D will be included and a footnote indicating the individuals who contributed to the manuscript preparation as the "writing group" will be given.

For manuscripts other than those reporting primary results, individual authors may be named. Each author must have contributed significantly to the submitted work as stated by the uniform requirements for manuscripts submitted to biomedical journals (1). Authorship is considered to include all of the following: 1) conception and design or analysis and interpretation of data, or both; 2) drafting of the manuscript or revising it critically for important intellectual content; and 3) final

approval of the manuscript submitted. Participation solely in the collection of data does not justify authorship, but may be appropriately given in the acknowledgement section.

It is expected that some manuscripts would have individual authors plus "for the BARI 2D Study Group" while some would just have individual authors (ancillary studies, for example). The Publication Committee would rule on whether a paper was authored by: 1) the BARI 2D Study Group; 2) individual named authors "and the BARI 2D Study Group"; or 3) individual authors.

D. Process for Manuscripts

1. Through the Coordinating Center, the Committee will receive publication proposals from Committees and individuals investigators.

2. Each proposal should include:
   Hypothesis, rationale, data and data analysis needed, nature of journal targeted for publication, writing group membership, time schedule, and, if applicable, dates for meeting abstract submission deadlines.

3. The Committee will coordinate proposals and set priorities for data analysis.

4. Review Process
   - Authors will submit the paper to the Coordinating Center.
   - The Chair of Policy and Publications will select two or more BARI 2D internal experts who will provide written review within two weeks
   - Authors revise, if appropriate, upon receiving reviews and resubmit paper.
   - Chair of Policy and Publications will determine whether further review is required.
   - Final version will be sent to all Steering Committee members for approval (two weeks turn around) before submission to the journal.

E. Acknowledgement of Funding

For all BARI 2D reports, the financial support of NHLBI and NIDDK as well as all non-federal sources will be acknowledged.

III. ANCILLARY STUDIES

A. General Considerations

Ancillary studies will refer to studies that propose questions and test hypotheses that are relevant to and congruent with the goals and purposes of BARI 2D. Such studies will require tests or data that are not routinely obtained for the main BARI 2D protocol. Ancillary studies may involve all BARI 2D patients and clinical sites, or subsets of either, depending on the eligibility criteria of the study, sample size needed, or interest of BARI 2D investigators in participating.

1. Ancillary studies must be independently funded by the investigator or by sources obtained by the investigator.

2. Investigators not a part of BARI 2D must have a BARI 2D investigator as a sponsor and collaborator.

3. All analyses of data must be confirmed at the BARI 2D Coordinating Center and resources provided to the Coordinating Center for these efforts.

4. The studies must first be approved by the Ancillary Studies Committee, followed by approval by the BARI 2D Steering Committee, Operations Committee, and Data and Safety Monitoring Board (DSMB). Protocols should follow the general guidelines outlined below.

5. Ancillary studies must have separate consent forms for patients. These consent forms as well as the ancillary protocol must first be approved by the University of Pittsburgh's IRB before submission to a participating clinical site's IRB.

6. Ancillary study data will be reviewed by the DSMB annually.

B. Format for Ancillary Study Protocols

Proposals should be brief (fewer than 10 pages in length), but contain sufficient detail to allow adequate scientific review and assessment of the relevance of the proposal to the BARI 2D study, as well as its impact on recruitment, follow-up and workload. Each proposal should include:

Criteria: Scientific

- list of current investigators (with principal investigator listed first)
- introduction and background with pertinent key references
- specific hypotheses and aims
- experimental design
- methods
- data analysis plan and sample size calculation

Criteria: Impact on BARI 2D

- list of sites that have expressed intent to participate
- resources required
- source of funding of project timeline
- relevance to BARI 2D hypothesis and interpretation of results
- impact on BARI 2D recruitment and conduct of study (details of the time and effort for patients and work requirements for clinic coordinator must be given)
- risks and safety concerns
- impact on Coordinating Center for data management and analysis.

C. Approval Process

Proposals should be sent to the BARI 2D Coordinating Center for consideration.

The Coordinating Center will forward the proposal to the Ancillary Studies Committee Chairs for review. If serious scientific, feasibility or safety concerns are raised by the Coordinating Center or Ancillary Studies Committee Chairs, the reviews will be forwarded to the principal investigator for his/her consideration

When the proposal does not have any serious scientific, feasibility or safety concerns rasied by the Coordianting Center or Ancillary Studies Committee Chairs, the proposal will then be sent to the Ancillary Studies Committee for a priority rating. The rating will be based upon the study's relevance to the BARI 2D hypothesis, scientific merit and impact on BARI 2D. The impact of the study on recruitment, follow-up and personnel time will have a major influence on priority. A priority score of 1 to 5 will be used, with one being the highest merit and five being the lowest merit.

An average will be calculated and the average priority score and the scientific reviews, along with the proposal itself, will be forwarded to Steering Committee members for comment and formal vote to approve or not.

The studies receiving a majority approval rating by the Steering Committee will be forwarded to the Operations Committee and DSMB for final decision.

Individual sites wishing to join in an ancillary study may do so at any point during its submission, by notification of the Coordinating Center and the principal investigator of the ancillary study.

D. Timing and Procedures for submission

A **letter of intent** sent to the address below is required **two weeks before the proposal**. The letter of intent should include the title of the study, a brief abstract and the names of the principal investigators.

A proposal must be submitted **no less than 6 weeks prior to a funding source submission date or starting date if funding is available.** This allows 2 weeks for ancillary study review, 2 weeks for Steering Committee review of the revised proposal and mail ballot and 2 weeks for Operations Committee and DSMB review.

IV. DATA STORAGE, SECURITY AND ACCESS

A. Access and Restrictions to BARI 2D Data

All data are stored at the Coordinating Center except the site specific data pertinent to each site. Access to the data is permissible only through approved protocols or as part of routine data collection, quality control, or analysis necessary for the conduct of the trial. Access to BARI 2D aggregate data is provided only to the BARI 2D Safety and Data Monitoring Board, the Coordinating Center Principal Investigator and staff, the Study Chair, and selected members of the NHLBI Program Office. These individuals have signed a statement agreeing to keep all BARI 2D data confidential.

All data will be stored at the Coordinating Center, Core Laboratories or Ancillary Study Coordinating Centers, with strict security systems in place. Access to the data will be permitted only through approved research protocols or as part of the daily conduct of the trial. BARI 2D data will be provided only to BARI 2D investigators. Others interested in access to BARI 2D data must collaborate with a BARI 2D investigator. Before publication of the final results of the trial, the core laboratories, ancillary study investigators data and clinical center investigators will not analyze aggregate data that could reveal outcomes in the two treatment groups.

B. Core Laboratory Data

1. There is an expectation of high quality Core Lab data, and these data are to be delivered to the BARI 2D Coordinating Center in a timely manner.

2. Any data collected on NIH study participants belongs to the BARI 2D study as a whole. Thus, ownership of all BARI 2D Core Lab data belongs to the Study, under the leadership of the BARI 2D Operations Committee, and not to the individual Core Labs. In particular, during the course of the BARI 2D study, the Core Lab data cannot be shared or presented to any individuals (including industry sponsors) outside of the BARI 2D Coordinating Center without the explicit permission of the BARI 2D Operations Committee.

3. The BARI 2D study, under the leadership of the BARI 2D Operations Committee, must approve all publications and presentations that contain any BARI 2D Core Lab data. This means that the BARI 2D study has the "veto" right regarding sections or entire publications based on BARI 2D Core Lab data. This is of course true for all BARI 2D data.

V. PARTICIPATION IN OTHER STUDIES

An exclusion criterion states that a patient cannot be enrolled in BARI 2D if he/she is enrolled in a "competing randomized trial or clinical study." Such a study is defined as having any one of the following characteristics:

1. The clinical study includes any experimental (i.e. not FDA approved) medications, devices or procedures.
2. The clinical study includes any long-term medical management of the patients.
3. The clinical study includes any medications, devices or procedures that are masked (blinded) to the clinician or patient.
4. The clinical study involves significant patient burden.

The Coordinating Center will review each competing randomized study or clinical study on an ad hoc basis to determine whether it is incompatible with BARI 2D.

The clinical sites for BARI 2D may participate in studies for which BARI 2D eligible patients are also eligible provided they continue to meet their individual commitments in recruitment for BARI 2D.

VI. FINANCIAL DISCLOSURE

Conflict of Interest Policy

BARI 2D investigators realize that concerns about real, potential conflicts of interest or the appearance of conflict of interest may arise at any time in the course of the project. In a trial evaluating treatments for cardiovascular disease and diabetes, it may be impossible to entirely eliminate any possible appearance of conflict of interest, as this would essentially require the investigators to give up many routine professional activities. Where potential conflicts exists, the BARI 2D investigators have endorsed the rational management of these potential conflicts according to pre-agreed guidelines and principles. The general guideline for conflict of interest has few specific restrictions, but a broad indication for disclosure of potential conflicts of interest. The BARI 2D investigators also endorse the spirit and content of the 21st Bethesda Conference: Ethics in Cardiovascular Medicine (2) dealing with these issues, and agree to make the BARI 2D policy consistent with the record of that conference.

The investigators agree to update their financial disclosures and related activities on an annual basis and submit these data to the CC. The CC will maintain the confidentiality of these records and present them to a review committee, to be constituted by the Study Chairperson. In the case of actual or perceived conflict of interest, the Study Chair will bring it to the attention of the NHLBI Program Office and the Data, Safety, Monitoring Board (DSMB). A copy of the financial disclosure statement is given in Appendix A.

Relationship to Institutional Policies on Conflict of Interest

Since existing policies on conflict of interest may vary between participating BARI 2D institutions, in addition to the above policy, it is expected that investigators will comply with conflict of interest policies which exist within their individual participating institutions (i.e. medical schools and hospitals). This is the responsibility of each individual investigator.

A. Purpose

The purpose of this disclosure statement is for the principal and co-principal investigators, directors of the core laboratories and central laboratories, and members of the Operations Committee of the (BARI 2D) trial to:

1. Clearly state the goal to obtain supplemental funding from industry in an impartial manner, fully consistent with NHLBI policy, and thus free of any present or foreseeable future personal financial advantage to any BARI 2D investigators or core lab directors;

2. Define and disclose financial interests that might be perceived to, or in reality, potentially influence:

    a. Selection of specific companies for:
       -- Preferential use of products; or
       -- Provision of additional funds in support of the trial.
    b. Analysis, interpretation and/or reporting of data.

3. Describe how the disclosure of financial interest will be used to achieve our goal of critically needed supplemental funding for the trial without compromising the integrity of the study and the public trust which is inherent in the commitment of resources from the National Heart, Lung, and Blood Institute.

B. Definitions

The following definitions of financial interests apply to commercial, for profit enterprises. Significant financial interests are defined as interests valued, over the course of a study year, at greater than $10,000 or interests representing more than 5% ownership of a specific entity, or an equity interest valued at $10,000 or greater for any one enterprise or entity when aggregated for the investigator and investigator's spouse and dependent children. These interests include:

1. Equity holdings (excluding mutual funds or blind trusts);
2. Research contracts or grants;
3. Intellectual property rights (e.g. patents, copyrights, royalties)
4. Salary or other payment for services (e.g. consulting fees, honoraria);
5. Travel or meeting expenses if received directly from industry;
6. Other forms of compensation such as equipment, property, paid trips, stock options or warrants or pensions.

Income from seminars, lectures, trips to desirable locations, service on advisory committees or review panels for non-profit entities **do not** constitute financial interests that must be reported.

C. Verbal Disclosure

As scientific issues that relate to use of specific drugs and or products are discussed and voted on, all voting members will be asked to consider if they have any important potential conflicts of interest on the subject to be discussed. If they or the oversight committee consider there to be a potential conflict of interest, they are expected to declare such and are expected to absent themselves from participation in any of these activities if they or the oversight committee judge that conflicting interest precludes them from making an impartial decision. Such disclosures will be recorded in the meeting minutes.

D. Publication of Conflict of Interest Policy

The BARI 2D trial will publish this conflict of interest policy. This policy will not be in effect until it is formally accepted by the BARI 2D Steering Committee. The BARI 2D Data and Safety Monitoring Board should be asked to review and provide comment on this policy. This full policy is to be made public on the BARI 2D web site and in publications when possible.

VIII. POLICY FOR THE PRESENTATION OF BARI 2D DATA DURING THE TRIAL

A. Background and Purpose

The Policy and Publication Committee recommended that the BARI 2D baseline data should not be published until the BARI 2D enrollment is complete (August 2004) and the baseline data have been cleaned. At that time, descriptions of the baseline characteristics of the BARI 2D study as well as cross-sectional baseline analyses can be completed and published. The Policy and Publication Committee also recommended that no post-randomization data should be published until the completion of the BARI 2D trial (2007). In addition, post-randomization data may not be presented at national or international meetings nor should they be published in any publicly available electronic or printed format.

This document describes the BARI 2D policy for releasing data to the BARI 2D investigators and to others who are not BARI 2D investigators before the completion of the clinical trial.

B. BARI 2D Data Available on the Web Site

Selected screening, baseline, and patient management data can be shared with local clinicians for the purpose of enhancing recruitment. The Coordinating Center will organize and make available current versions of data on the BARI 2D web site for PIs to use for this purpose. BARI 2D investigators can discuss these data with referring physicians, they can site these data in letters to referring physicians, and these slides can be presented at local meeting sites (e.g. grand rounds) at the BARI 2D clinical sites.

The screening, baseline, and management data contained in these slides are not to be presented at national or international meeting unless permission from the Operations Committee is obtained. If a BARI 2D investigator would like to present additional baseline or management data not included in these slides for a local presentation, he or she must obtain permission from the Operations Committee.

C. Follow-Up Patient Management Data

Post-randomization data that are directly related to BARI 2D treatment and risk factor protocol will be reviewed by the diabetes, lipids, hypertension management centers and the revascularization and non-pharmacologic working groups.

The Management Centers are responsible for continuously monitoring BARI 2D patient medical management regarding protocol adherence and patient safety issues. In particular, these centers are responsible for monitoring baseline and follow-up HbA1c levels, diabetes medications, and hypoglycemia episodes, lipid measurements and medications, and blood pressure measurements and medications.

The “working groups” are a group of BARI 2D investigators who assemble at the semi-annual working group meetings and advise the Steering Committee regarding selected issues. The BARI 2D

Non-pharmacologic Working Group monitors the BMI, exercise and dietary patterns, and smoking status during the study. The Revascularization

Working Group monitors the characteristics of the initial CABG or PCI procedures for those patients assigned to revascularization; this includes revascularization strategies (lesions intended, internal mammary artery graft used) but does not include procedure success.

The diabetes management center views the glycemic control data stratified by randomized treatment arm (IS versus IP)[1]. The other management data should not be viewed or presented by randomization assignment outside of the Coordinating Center and the DSMB[2]. The management data can be stratified by patient baseline characteristics such as number of diseased vessels, insulin use at baseline, or history of CHF when it is necessary for enhancing adherence to the protocol.

The management data may be presented to the clinical site investigators for the purposes of improving implementation of the protocol and enhancing patient safety. Dr. Genuth, chairman of the Diabetes Management Center, and Dr. Orchard, chairman of the Lipid Management Center, will use their judgment in determining what monitoring data should be shared with the BARI 2D investigators. The aggregate data for hypertension management, revascularization and non-pharmacologic management will be prepared by the Coordinating Center, in consultation with Dr. Nesto and Dr. August, for the working groups and for presentation to the BARI 2D investigators.

D. Follow-up Primary and Secondary Endpoint Data

BARI 2D endpoint data cannot be released to any of the BARI 2D clinical investigators or to anyone outside of the trial under any circumstances. Endpoint event rates for a single clinical site or for the entire study are considered strictly confidential trial data.

Specified BARI 2D endpoints include: mortality, cardiac mortality, myocardial infarction, stroke, angina, subsequent revascularization, quality of life, economic cumulative cost and cost-effectiveness, PAI-1, t-PA, LV function, and diabetes complications (retinopathy, neuropathy, nephropathy, peripheral vascular disease, and amputation). Intermediate outcome data in the BARI 2D trial such as success rates for the initial revascularization procedure should not be released to BARI 2D site investigators or anyone outside of the study.

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[1] The DMC needs to review its data by glycemic treatment arm for two reasons. One, the DMC is responsible for ensuring that patients are receiving diabetes drugs that are consistent with the glycemic arm they were randomized to (provided that they can safely do so). This is necessary to avoid contamination between the arms which would reduce the power to detect any treatment differences that might exist. Two, the DMC must also monitor that the intensity of glycemic control in each of the two study arms, as measured by the mean and median HbA1c in each arm, stay within close clinical and experimental proximity. This is necessary because the hypothesis being tested in BARI 2D involves the strategy by which good glycemic control is achieved (IS or IP), and not the intensity of the glycemic control. Significant differences in mean HbA1c between the two treatment groups could confound the comparisons between treatment strategies.

[2] In particular, the Lipid Management Center and the Hypertension Management Centers are responsible for ensuring that patients are being medicated as needed, and that persisting rates of dyslipidemia and hypertension are kept at a minimum. The DSMB will monitor differences in the rates of dyslipidemia or hypertension between either the IP and IS arm, or the medical and revascularization arm of BARI 2D. If any differences in the rates of either dyslipidemia or hypertension between treatment arms (whether IP vs IS or medical vs revascularization) exist, or gradually emerge, these will be regarded as part of the natural history under the respective treatment arms. If the DSMB finds that such a difference may negatively impact the interpretation of the BARI 2D study or put patients in a particular treatment arm at risk, the DSMB may alert the BARI 2D investigators and suggest a specific action.

These confidential outcome data are monitored by the BARI 2D Coordinating Center, the NIH project office, and the Data Safety Monitoring Board.

E. Individual Clinical Site Data

Data for patients at an individual clinical site are part of the BARI 2D study data. These site specific data are not to be presented or published on their own.

F. Core Laboratories and Ancillary Studies

BARI 2D Core Laboratory data belong to the BARI 2D study as a whole and should not be released by the Core Laboratory before the end of the study. In addition, Ancillary Study presentations should never include any data regarding BARI 2D endpoints or any data by randomization assignment before the end of the trial.

G. Other Follow-up Data

Other follow-up data not covered by the above sections (i.e. neither management data nor specified endpoint data) can be released only if permission from the Operations Committee is obtained. In general, the Operations Committee should deny release of post-randomization data unless, after a careful review of the data in question, a majority of the members are confident that the risk to the trial posed by such a release is minimal while the potential benefits are promising. Presentation of post-randomization data should not be stratified by randomized treatment group.

IX. REFERENCES

(1) International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *N Engl J Med* 1991;324:424-8.

(2) Frommer PL, Ross J, Benson JA, et al. Task Force IV : Scientific responsibility and integrity in medical research. *J Am Coll Cardiol* 1990;16:1-36.

APPENDIX A

BARI 2 DIABETES (BARI 2D) DISCLOSURE FORM: POTENTIAL CONFLICT OF INTEREST
For the Period: September 1, 2004 to September 1, 2005

Please indicate on the chart below if the level combined for yourself, your spouse and your dependent children is > $10,000 during the period September 1, 2004 to September 1, 2005

Company	Stock Ownership*	Intellectual Property Rights**	Personal Compensation***	Grants/Contract-Research	Grants/Contract-Unrestricted	Educational Travel ****
Abbott Laboratories						
Bayer Corp.						
Becton Dickinson						
Bristol-Myers Squibb Company						
Carlson Labs						
Centocor, Inc.						
DuPont Pharmaceuticals						
Eli Lilly & Co						
Fournier Pharma, Inc.						
Fujisawa Healthcare, Inc.						
GlaxoSmithKline						
Merck & Co						
Novartis Pharmaceuticals						
Pfizer, Inc						
Roche Laboratories						
Sanofi-Synthelabo						
Other: Specify						

Do you and/or your spouse and/or your dependents have financial holdings or other interests (whether financial or non-financial), activities, or gifts other than any mentioned above, that you consider to be potential conflict of interest? YES _____ NO _____

If YES, please specify:

_____

_____

_____

_____ _____ _____/_____/_____

Type or Print Investigator Name Signature Date Signed

_____

Type or Print Clinical Site Name/City/State

Return form to: Scott O'Neal, BARI 2D Coordinating Center
University of Pittsburgh
Graduate School of Public Health
127 Parran Hall
Pittsburgh PA 15261
FAX #: 412-383-8690

* includes stock options or other ownership interests
** patents, royalties, licensing fees
*** fees for presentations, honoraria, consulting fees; does not include expense reimbursement
**** industry-sponsored travel grants to educational symposia; does not include expenses reimbursed for consulting or speaking engagements

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CHAPTER SIXTEEN

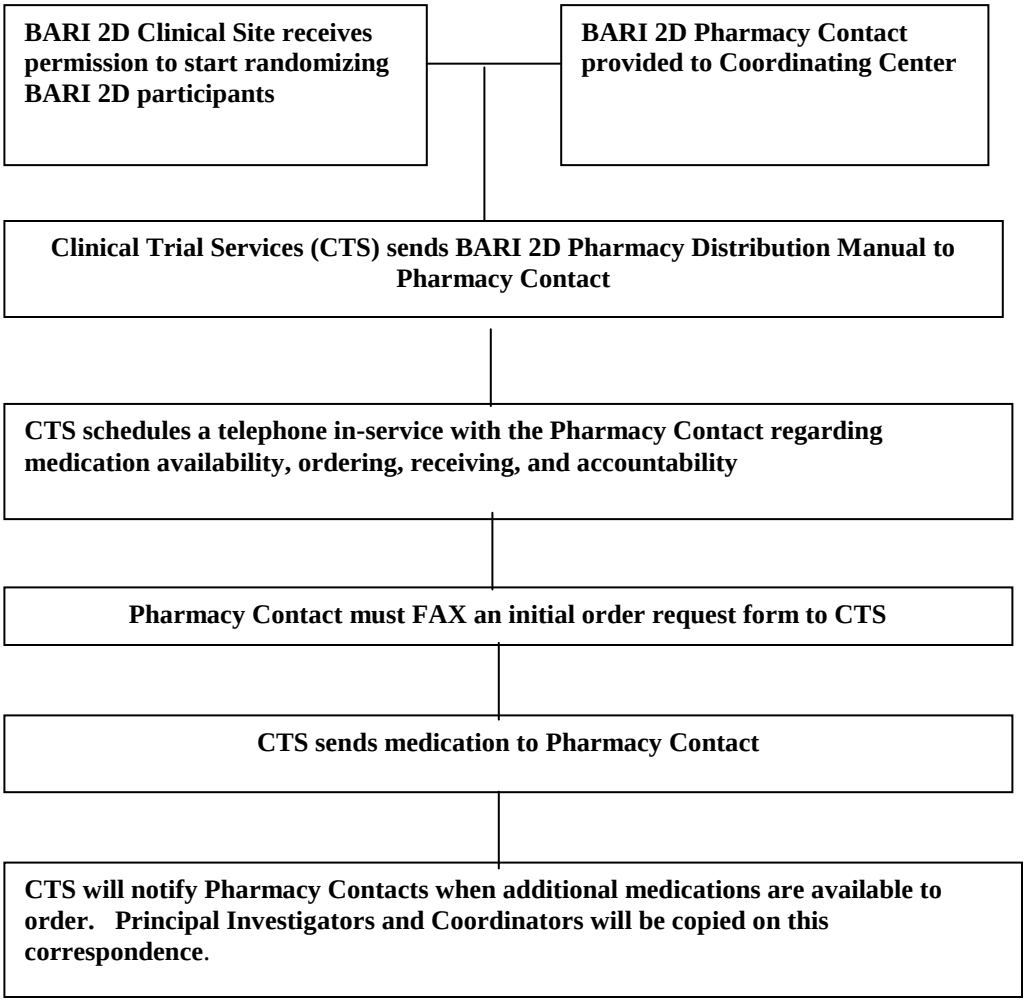
PHARMACY DISTRIBUTION

I. DISTRIBUTION CENTER

Many medications are available at no cost to BARI 2D participants or BARI 2D clinical sites. A list of available medications can be obtained on the BARI 2D web site. The BARI 2D Coordinating Center has purchased the metformin and the glucose monitoring strips. All other medications/supplies are donations from pharmaceutical companies.

Clinical Trial Services (CTS), Durham, NC, has been contracted by the BARI 2D Coordinating Center to distribute medications/supplies to the BARI 2D clinical sites. It is important for the Principal Investigator, Site Pharmacy Contact, Site Coordinator, and Clinical Trial Services (CTS) to work closely together to ensure that a continuous supply of medications is available to the sites for the BARI 2D study. In order to assist you with the process, we have outlined below a "pathway" to help you understand the roles of the coordinator, PI, pharmacy contact and CTS in meeting our objective of providing drug to the sites for BARI 2D.

PATHWAY TO RECEIVE BARI 2D FREE MEDICATIONS



II. MEDICATION/SUPPLY DISTRIBUTION

A. Notification of Availability of Study Medications

Clinical Trial Services (CTS) will notify all approved sites (Pharmacy Contact, Coordinator and PI) by e-mail when medications are newly available for distribution to the clinical sites. CTS will forward by US mail to the Site Pharmacy contact a revised drug order form which includes the new medications.

B. Study Drug Shipments

Do not dispense any drug until a patient has been properly randomized. Only <u>randomized</u> patients should receive BARI 2D drug.

The study drug will be provided to the sites in bulk (bottles of approximately 100 pills), packaged into storage boxes. Before requesting drug supplies for the site, the Site Pharmacy Contact, Site Coordinator and/or PI should discuss what needs to be ordered. The worksheet at the end of this section may help in determining your needs.

The Site Pharmacy Contact will complete and fax their request for drug supplies. These forms are located in the Pharmacy Manual. The pharmacy contact at site will need to track their inventory and fax an order to CTS when they need a resupply shipment. It is important that the site pharmacy contact and site coordinator discuss the study supply needs on a regular basis. Anticipated shipment periods are every 3 months.

If the resupply form is received by 2:00 pm it will be processed the same day. Shipment requests received after 2:00 pm will be processed the same day if time allows, otherwise, they will be shipped out the next business day. If study drug requires refrigeration, drug will be packaged in coolers via FedEx overnight priority for all North American sites. CTS will ship study drug to North American sites Monday through Thursday for receipt Tuesday through Friday. Study drug will not routinely be shipped on Friday. If this appears to be necessary, the site will be contacted by CTS and special arrangements will be made to ensure that there is personnel at the site to receive the shipment.

Site Pharmacy Contacts will be sent a fax notification the day the drug is shipped. The fax will contain the FedEx tracking number that can be used to track the drug if it does not arrive as expected. Sites should contact CTS if any shipment does not arrive within 24 hours of fax notification, as expected. Sites should verify receipt of shipments no later than 48 hours from the shipping date.

C. Drug Return and Destruction

Patients should return all unused and partially used study drug to the site. All returned drug received by the Site Coordinator should be sent to the Site Pharmacy Contact and entered into the **BARI 2D Drug Return and Destruction Log**. A blank log has been provided in the Pharmacy Manual.

Destruction of unused or returned drug will be recorded on the BARI 2D Bulk Drug Return and Destruction Log. All destruction must be witnessed and dated by two individuals. Logs will be reviewed during the CTS monitoring visits.

Each site should follow its guidelines for the destruction of investigational agents. If there are any questions in regard to the proper destruction of the study drug, please contact CTS at 919-479-8850.

It is the responsibility of the Site Pharmacy Contact to pull all expired drug and document the destruction on the CTS Drug Return and Destruction Log. This destruction must be performed in accordance with site destruction policy.

D. Monitoring

CTS will notify sites in advance of a monitoring visit. Monitoring visits will take place every six months to a year. The site monitoring visit encompasses monitoring the accountability logs and drug destruction logs. On occasion, CTS may call the site pharmacy contact and request a faxed copy or the drug accountability or destruction logs.

E. Contact Information

If you need assistance regarding medication/supply distribution, please contact one of the following individuals.

Pat DeLong, Senior Clinical Supplies Project Manager
Clinical Trial Services
4204 Technology Drive, Durham, NC 27704
919-479-8850 ext.832 (phone)
919-471-2633 (fax)

Trang Mendler, Project Coordinator
Clinical Trial Services
4204 Technology Drive, Durham, NC 27704
919-479-8850 ext 814(phone)
919-471-2633 (fax)

BARI 2D MEDICATION SHIPMENT WORKSHEET

TO BE COMPLETED BY COORDINATOR

Complete one worksheet per medication and strength

Medication_____ Strength_____

EXAMPLE

# of patients randomized_____15_____

# of those patients currently prescribed this medication and strength_____6_____(1)

Maximum number of tablets taken daily by a patient _____2_____(2)

_____6_____(1) X _____2_____(2) = _____12_____(3) Estimated Daily Need

_____12_____(3) X 90 days = _____1080_____(4) Estimated Quarterly Need

_____1080_____(4) / 100 = _____11_____Bottles

WORKSHEET

# of patients randomized_____

# of those patients currently prescribed this medication and strength_____(1)

Maximum number of tablets taken daily by a patient _____(2)

_____(1) X _____(2) = _____(3) Estimated Daily Need

_____(3) X 90 days = _____(4) Estimated Quarterly Need

_____(4) / 100 = _____Bottles

(Round the number of bottles up to nearest 25 and then place this amount on the Request for Initial Shipment /Resupply of Drug order form)

CHAPTER SEVENTEEN

POST-TREATMENT FOLLOW-UP PHASE

SECTION ONE: POST-TREATMENT FOLLOW-UP PHASE PROTOCOL

SECTION TWO: CONSENT FORM

SECTION THREE: CONTACT INFORMATION SHEET

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CHAPTER SEVENTEEN : SECTION ONE POST-TREATMENT FOLLOW-UP PHASE PROTOCOL

I. INTRODUCTION

The purpose of the Post-Treatment Follow-up Phase of BARI 2D is to continue to collect data on participants after the treatment and follow-up phase is complete. The primary aim of this phase is to collect event data on participants in BARI 2D in order to study the long-term outcomes of the treatment options to which participants were randomized.

II. RECRUITMENT

At the conclusion of the treatment and follow up phase of BARI 2D (i.e. the close out visit, an annual visit from November 2007 through November 2008 for most participants), participants will be asked to sign a new consent and, thereby, agree to an annual follow up to be conducted by a separate unit at the Department of Epidemiology, GSPH, University of Pittsburgh (Department of Epidemiology Follow Up Unit – DEFU).

In order to conduct this follow up, which is initially planned for 5 years (from December 2008 through December 2013), participants will supply personal identification data (name, address, phone number, fax, email, two contacts (relatives or friends) and Social Security Number) to the DEFU. The consent permits limiting the identifiers provided; however name and address [or phone?] will be required for participation. These identifiers will be kept separate from the BARI 2D Coordinating Center.

The clinical sites will obtain patient consent and the contact information. After that, follow-up will be carried out by the DEFU.

III. RESEARCH DESIGN AND METHODS

Each year during follow up, in the month preceding their randomization date, the DEFU will mail a covering letter and self-administered questionnaire to the participant, along with a prepaid reply envelope. If the questionnaire is not returned, as requested, in a month's time, the DEFU will attempt to call the participant or make contact in another manner (e.g. email), and request the participant return the questionnaire or if he/she prefers conduct the survey over the phone. If the address and phone number given initially by the participant no longer are no longer valid, the named secondary contacts will be called by the DEFU in order to obtain participants contact details. Finally if all else fails, where appropriate permission has been given, Social Security numbers will be used to trace participants to determine vital status.

IV. PATIENT CONFIDENTIALITY

The DEFU will code and enter the responses to the data questionnaire and identify the participant by the original BARI 2D ID number which will be provided to the DEFU by the clinical sites. A master list of names and BARI2D ID numbers will be kept separately in a locked cabinet and security coded data file. A data file with BARI 2D ID number will be periodically downloaded to the BARI 2D Coordinating Center stripped of all personal identifiers, thus ensuring the coordinating center receives only de-identified data and is independent of follow up data collection, similar to its role in the clinical phase of the BARI 2D.

CHAPTER SEVENTEEN : SECTION TWO CONSENT FORM

[draft of Consent Form for post-follow-up treatment phase]

CONSENT TO ACT AS A SUBJECT IN A RESEARCH STUDY

(Addendum for BARI 2D post-treatment follow-up phase)

Title: Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Study
(Post-treatment follow-up phase Addendum)

Principal Investigator: Sheryl F. Kelsey, Ph.D.
130 DeSoto St
127 Parran Hall
Pittsburgh PA, 15261
412-624-5157

Co-Investigators: [TBD}

Sponsor: [TBD]

Why is this research being done?

The purpose of this research study is to collect additional information on participants in the BARI 2D study, the treatment phase of which concludes on November 30, 2008. This information will be used to study the long-term effects of the treatment options to which participants in the treatment phase of BARI 2D were randomized.

Who is being asked to take part in this research study?

You are being asked to participate because you are currently participating in the BARI 2D study. This consent form is in addition to, and is not intended to replace or modify, the consent form for the research study (BARI 2D). Participation in this post-treatment follow-up phase of BARI 2D is entirely voluntary. Approximately 2400 subjects will be asked to participate in this post-treatment follow-up phase.

What procedures will be performed for research purposes?

If you agree to participate, study personnel at the University of Pittsburgh will contact you once a year for at least five years to ask a few questions about your current health status. Researchers may also search national public databases for information.

For Office Use Only

BARI 2D ID: __ __ __ __ __ __ __ __ __ __ __ __

What are the possible risks, side effects, and discomforts of this research study?

There are no risks of physical injury associated with your participation in this research study. Participation in this research study does involve the possible risk that information about your health might become known to individuals outside of the BARI 2D research team.

We will attempt to preserve your medical record confidentiality by using the same special research ID that was assigned to you when you joined the BARI 2D study. All computer data used for analysis of the study results includes only this research ID code for each patient without name or personal information.

What are possible benefits from taking part in this study?

It is unlikely that you will receive any direct benefit as a result of your participation. A possible indirect benefit is that your participation might contribute to the knowledge of the medical conditions you have and the best ways to treat them.

Will I or my insurance provider be charged for the costs of any procedures performed as part of this research study?

There will be no cost to you for participation in this research study.

Will I be paid if I take part in this research study?

You will not be paid for participation in this research study.

Who will know about my participation in this research study?

Any information about you obtained from this research will be kept as confidential (private) as possible. You will not be identified by name in any publication of research results unless you sign a separate form giving your permission (release). In unusual cases, your research records may be released in response to an order from a court of law. It is also possible that authorized representatives of the Food and Drug Administration, the National Institutes of Health, and/or the University of Pittsburgh may inspect your research records. The fact that you are participating in a research study may also be made known to individuals involved in administrative activities associated with the conduct of the study. Information resulting from the research will not be entered into your medical records.

Is my participation in this research study voluntary?

Your participation in this research study is completely voluntary. You do not have to take part in this research study and, should you change your mind, you can withdraw from the study at any time.

May I withdraw, at a future date, my consent for participation in this research study?

You may withdraw, at any time, your consent for participation in this research study. However, any medical information collected prior to the date that you formally withdraw your permission will not be destroyed.

For Office Use Only

BARI 2D ID: __ __ __ __ __ __ __ __ __ __ __

Participant's Initials_____

VOLUNTARY CONSENT:

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form.

Any questions I have about my rights as a research participant will be answered by [contact name and phone number].

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

☐ I agree to participate in the post-treatment follow-up phase of BARI 2D.

☐ I agree to provide my Social Security Number to the BARI 2D investigators for the purpose of searching national databases for publicly available information pertaining to my health.

☐ I agree to provide the BARI 2D investigators with alternate contact information in case they are unable to contact me. This information will be used to help the investigators contact me. My alternate contacts will not be asked for more than very basic information about my health.

_____ _____
Participant's Signature Date

_____ _____
Witness Signature Date

INVESTIGATOR'S CERTIFICATION:

I certify that the nature and purpose, the potential benefits and possible risks associated with participation in this research study have been explained to the above individual and that any questions about this information have been answered.

_____ _____
Investigator's Signature Date

For Office Use Only

BARI 2D ID: __ __ __ __ __ __ __ __ __ __ __

Participant's Initials_____

CHAPTER SEVENTEEN : SECTION THREE CONTACT INFORMATION

[DRAFT OF CONTACT INFORMATION SHEET]

BARI 2D POST-TREATMENT FOLLOW-UP PHASE

CONTACT INFORMATION

[Please Print]

Name: _____

Phone Numbers: Home**:**_____ Work**:**_____ Cell phone**:**_____

Address: _____

_____

_____

Email: _____

Social Security Number: __ __ __ - __ __ - __ __ __ __

Alternate Contact #1
(Someone who does not live with you)

Name: _____

Relationship to You: _____

Phone Numbers: Home**:**_____ Work**:**_____ Cell phone**:**_____

Address: _____

_____

_____

Email: _____

For Office Use Only

BARI 2D ID: __ __ __ __ __ __ __ __ __ __ __

Alternate Contact #2

Name: _____

Relationship to You: _____

Phone Numbers: Home**:**_____ Work**:**_____ Cell phone**:**_____

Address: _____

_____

_____

Email: _____

For Office Use Only

BARI 2D ID: __ __ __ __ __ __ __ __ __ __ __ __