Occluded Artery Trial (OAT)

Study Protocol

November 1, 2000

Pilot Phase Versions
November 28, 1997
February 2, 1998
June 1, 1998

Main Trial
June 1, 1999
Draft October 1, 1999
November 12, 1999
November 1, 2000

Table of Contents

Table of Contents *(cont.)*

Summary

Background The benefits of establishing early coronary perfusion in acute myocardial infarction (MI) have now been unequivocally established. However, current pharmacologic strategies fail to achieve effective reperfusion in 30% or more of patients, and many patients with occluded infarct arteries do not meet current criteria for use of these agents. Early angioplasty, an effective reperfusion method, is available to only a small proportion of potentially eligible acute MI patients. Hence, a substantial number of acute MI patients exceed the time beyond which acute reperfusion therapy provides any documented benefit. However, several lines of experimental and clinical evidence suggest that late coronary reperfusion may lead to clinically significant reductions in mortality and morbidity.

Hypothesis The central hypothesis of this Occluded Artery Trial (OAT) is that opening an occluded infarct artery 3-28 days after an acute MI (day 1= date of index MI) in asymptomatic patients who are at increased long-term risk (ejection fraction <50% or proximal occlusion of a large coronary artery) will reduce the composite endpoint of mortality, recurrent MI, and New York Heart Association (NYHA) Class IV congestive heart failure (CHF) over an average three-year follow-up.

Specific Aims The study is a prospective clinical trial with 3,200 patients to be allocated randomly in equal proportions to the two treatments over two years. One treatment will consist of conventional medical management (including aspirin, beta blockers, angiotensin converting enzyme (ACE) inhibitors and risk factor modification). The investigational treatment will consist of conventional medical therapy plus percutaneous coronary intervention and coronary stenting. Treatment will be compared using an intention-to-treat analysis in the Occluded Artery Trial (OAT). The one primary specific aim is to : 1) compare the composite outcome of all-cause mortality, non-fatal MI and Class IV CHF based on an average three-year follow-up among patients assigned to the two treatments. Three secondary specific aims are: 1) to compare the individual components of the study composite primary endpoint in the two treatment arms, 2) to compare the medical costs of the two treatments and assess the cost effectiveness of percutaneous revascularization in the study population and 3) to compare health-related quality of life in the two treatment groups.

Operations The study will be conducted at approximately 320 clinical sites. The Clinical Coordinating Center (CCC) is at St. Luke's-Roosevelt Hospital in New York City. The Data Coordinating Center (DCC) is at the Maryland Medical Research Institute. The Economics and Quality of Life Coordinating Center (EQOLCC) is at Duke University. The Angiography Core Laboratory is at the University of British Columbia.

1. Specific Aim

The primary aim of this multicenter trial is to test the hypothesis that opening an occluded infarct artery with percutaneous coronary intervention, including stents, 3-28 days after an acute MI (day 1 = date of index MI) in asymptomatic patients who are at increased long-term risk (ejection fraction <50% or proximal occlusion of a large coronary artery) will reduce a composite endpoint of mortality, recurrent nonfatal MI, and NYHA Class IV CHF over three years (average) of follow-up.

Secondary objectives of the trial are to compare (for the two treatment groups):

- the incremental cost effectiveness of percutaneous coronary intervention for patients with an occluded IRA.
- health related quality of life.
- the individual components of the primary endpoint.
- a composite of the first to occur of death, recurrent MI, Class IV CHF, sustained ventricular arrhythmia, automatic implantable cardiac defibrillator (AICD) placement or stroke.

2. Background

2.1 Significance

Cardiovascular disease remains the leading cause of death in the United States. Furthermore, the incidence of congestive heart failure has recently increased, due in part to late sequelae for patients who have survived an MI. The five-year health care expenditures for the average acute MI survivor were $50,000 in 1990, and is likely substantially greater in a cohort of asymptomatic patients at increased long-term risk.[1] Approximately one third of all hospitalized MI patients will have persistent total occlusion of the infarct-related artery. If intervention with PTCA and stent for these patients is demonstrated to reduce clinical events at three years, then a policy of routinely seeking occluded arteries after the acute phase of MI with the intent of percutaneous revascularization for totally occluded infarct arteries would be justified.

2.2 Overview

The sequence of early coronary reperfusion leading to myocardial salvage, with resultant preservation of global left ventricular function and improved patient survival, has been proven in experimental and clinical studies.[2] The clinical application of this concept has resulted in a dramatic advance in the treatment of myocardial infarction in the last 20 years. Three important parameters affecting the size of the ischemic damage are 1) the duration of complete coronary obstruction, 2) the area at risk and 3) the level of residual coronary flow in the infarct-related artery (antegrade or collaterals) during or after the occlusion.[3,4,5]

However, several lines of evidence have suggested that this paradigm should potentially be expanded.[2] Hochman and Choo[6] working in a rat model of myocardial infarction, demonstrated that re-establishing coronary flow at a point in time that was too late to limit the infarct size, nevertheless limited infarct expansion and left ventricular dilation, thus improving left ventricular size and geometry. This work was confirmed by Hale and Kloner[7] in the rat, and by Brown[8] et al in the dog. Observational clinical studies likewise have suggested that infarct artery patency is associated with improved survival, independent of post-infarction left ventricular function. However, there are no convincing prospective data at the present time that would support the

routine opening of occluded infarct arteries in asymptomatic patients who are at increased long-term risk for cardiac events. The purpose of this proposed study is to determine whether post-infarct patients with occluded infarct arteries who are at increased long-term risk should undergo percutaneous catheter revascularization to improve clinical outcome.

The concept that patency of the infarct artery might lead to improved survival independent of left ventricular (LV) function was first proposed based on observations from the early thrombolytic studies. In these trials, a disproportionate improvement in survival, considerably greater than might be expected from the improvement in ejection fraction alone, was observed. Subsequently, a wealth of observational data demonstrating a strong association between outcome after MI and the status of the infarct-related artery (IRA) has emerged[5, 9-15]. Patients with a patent IRA after pharmacologic or spontaneous reperfusion have a markedly lower mortality at one year than those with an occluded IRA. This observation has been made at many time intervals after MI, ranging from 90 minutes to several months. Pooled rates from 7 studies (n=2748) suggest a 40% reduction in mortality for those with an open artery post MI (mortality rate 7.4%) compared to those with an occluded artery (12.4%)[5,9-13,15]. Recent reports[10-12,16] have demonstrated that the association of occluded IRA and cardiac events is *independent* of other patient characteristics, including ejection fraction and coronary anatomy. White et al reported that for high-risk patients only this association is independent of left ventricular function, coronary anatomy and baseline characteristics. In this study, high risk was defined as an ejection fraction <50% or the infarct-related artery was large with a proximal occlusion.[10] The patency of the infarct-related artery in these trials was established either following thrombolytic administration, spontaneously or in a minority following angioplasty or coronary bypass surgery. Lamas et al reported similar findings in the Survival and Ventricular Enlargement (SAVE) study population with large, completed infarctions. The incidence of CHF and mortality was lower in those with an open IRA compared to a closed IRA after MI [11,17] Interestingly, a subgroup of 288 SAVE patients who had presented with an occluded infarct artery was reported. The occluded IRA was opened for clinical indications in 130 patients, and was not opened in 158. There were clinically insignificant differences in ejection fraction between groups (IRA occluded, then opened ejection fraction =32%; IRA occluded, not opened: ejection fraction =30%). Patients with opened IRAs had a mortality of 11% over 3.5 years. However, patients with persistently occluded IRAs had a much greater mortality (24%) over the same follow-up period.

A variety of mechanisms have been suggested to account for a beneficial effect of the late open artery.[2,18,19]

A. Prevention of infarct expansion, ventricular remodeling and aneurysm formation.
    1. Independent of myocardial salvage.
        a. Improved healing of infarct tissue.
        b. Salvage of a rim of subepicardial myocardium.
        c. Scaffolding effect of the blood filled vasculature.[2]
    2. Dependent on perfusion of hibernating myocardium.
B. Improvement in LV function by recovery of hibernating myocardium.
C. Increased electrical stability, lower incidence of signal averaged ECG late potentials and ventricular arrhythmias.
D. The capacity of a patent infarct-related artery to provide collaterals to another coronary artery territory should subsequent coronary occlusion occur.[2]

It should be noted, however, that extensive microvascular plugging which is associated with extensive infarction may result in persistent occlusion of the IRA due to poor distal run-off. The occluded IRA may be a marker for poor outcome, while the extensive infarction results in subsequent cardiac events.

2.3 Randomized Trials

Thrombolytic and mechanical reperfusion early after MI is a cornerstone of modern cardiovascular medicine, and has led to dramatic improvements in infarct survival. Early reperfusion with thrombolysis or early PTCA within 12 hours of MI, improves survival by preventing myocyte death and leading to a smaller infarct.[2,3] Despite the abundant retrospective clinical evidence that late opening of the IRA may be beneficial, there have been only three small randomized trials which assessed the role of PTCA for occluded IRAs beyond the 12 hour post-infarction time window. Two small trials of PTCA performed in the pre-stent era, TAMI 6 and TOMIIS, reported disappointing results. The Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) 6[20] trial randomized 197 patients with ST segment elevation MI and any infarct location primarily to receive t-PA versus placebo and secondarily to PTCA or no PTCA for those with an occluded IRA 12 to 48 hour after MI. The t-PA assigned patients had significantly less LV dilation at six months than the placebo group. Patency was established in 81% of the patients randomized to PTCA. However, only 60% had a patent IRA at six months. These low initial success and sustained patency rates were due in part to technical limitations in that era. Conversely, those with an initially occluded vessel and no attempted PTCA had a relatively high patency rate (38%) at six months. At six months, no difference was seen between the PTCA and no PTCA groups with respect to ventricular volumes and systolic function.

The Total Occlusion Post-Myocardial Infarction Intervention Study (TOMIIS)[21] pilot study, performed at the same time as TAMI 6, evaluated 44 patients with an occluded IRA who were randomized to no PTCA or PTCA performed at a mean of 21 days after Q-wave MI. The primary PTCA success rate (before the current guidewire era) was only 72% in the 25 patients randomized to that strategy. At four months, re-occlusion in the PTCA arm resulted in a particularly low rate of IRA patency (43%). There was no overall difference in LV size or function between those assigned to PTCA vs. no PTCA. The only positive randomized study of PTCA after MI was recently published.[22] Horie et al randomized 83 patients with total LAD occlusion to PTCA (no stent) vs. no PTCA 8.3 ± 9.7 days post MI. Ventricular volumes were smaller in the PTCA group and a composite endpoint of death, MI and CHF was reduced at 50±24 months. However, in this unblinded trial there were no criteria reported for recurrent MI or CHF, and no central adjudication of events.

In contrast, many large randomized trials of revascularization vs. medical therapy for coronary artery disease with long-term follow-up have demonstrated no survival benefit for those with one or two vessel CAD[23]. Patients with prior MI were included. Although these trials involved Coronary Artery Bypass Grafting (CABG), subsequent studies have not shown PTCA to be superior to CABG for these patients.[24] In the GUSTO I database of 11,228 patients, a patent IRA was associated with improved 30-day survival. However, among 30-day survivors, a patent IRA was not independently associated with lower 1-year survival after adjustment. [25]

2.4 Angioplasty/Stent for Total Occlusions

The presence of a coronary occlusion was originally a relative contraindication for angioplasty due to low primary PTCA success rates and high reocclusion rates. The high reocclusion and restenosis rates in the intervention group, when contrasted with the high spontaneous recanalization rates in the control group, rendered the present proposed study impractical until the advent of present-day guidewire and stent technology. Advances in guidewire technology have facilitated crossing of total occlusions and improved primary PTCA success rates. The routine use of intracoronary stents has made reopening occluded coronaries a more reliable and durable procedure. Recently reported acute success rates of 90-100% [26-30] and restenosis rates of 6-25% with stents [27,31,32] appear clearly superior to the results obtained during early pilot trials of late patency using balloon angioplasty alone. Non-randomized series suggest the reocclusion rate for selected recent occlusions treated with stents is approximately 3-10%.[26,27,30-33] Hence, the present study to test the benefit of opening the occluded IRA late after MI is both clinically relevant and now technically feasible.

2.5 Need for Randomized Trial

The strong experimental evidence and observational data in patients regarding a beneficial effect of an open artery make it appealing to recommend routine opening of occluded arteries in asymptomatic patients. However, it is possible that the persistently occluded IRA is a marker for subsequent events i.e., failure of sustained patency and poor outcome are both due to the presence of extensive infarction with microvascular plugging and poor distal runoff. Selection of the healthiest patients with the least co-morbidity for intervention confounds these data. Furthermore, extensive randomized trial data of revascularization vs. medical therapy for patients with one and two vessel CAD have failed to demonstrate reduced mortality with revascularization. Hence, there is a widespread strong consensus that a randomized clinical trial with clinically meaningful endpoints is needed before changes are made in recommended routine clinical care with routine angiography and PTCA.[18, 34-36]

3. Study Design

3.1 Overview

Eligible patients at least three days and up to 28 days after MI will be randomized to opening the infarct-related artery with PTCA or any approved device followed by stent implantation if technically feasible (any approved non-investigational stent) vs. medical therapy only. The primary specific aim is to compare the composite outcome of all-cause mortality, non-fatal MI and Class IV CHF based on an average 3-year follow-up among patients assigned to the two treatments. Three secondary specific aims are to compare; 1) the individual components of the study composite primary endpoint in the two treatments; 2) the medical costs of the two treatments and 3) health related quality of life in the two treatments.

3.2 Screening

All acute myocardial infarction patients at participating centers will be screened prospectively for eligibility for the trial (Fig. 1). Patients may or may not have been treated with early reperfusion therapy. For centers that perform post-MI coronary angiography routinely on a clinical basis for risk stratification as part of a cost effective approach to shorten the length of hospital stay,[37] patients will be assessed for clinical inclusion and exclusion criteria prior to the catheterization. Patients who meet the clinical inclusion criteria with no clinical exclusion criteria will be

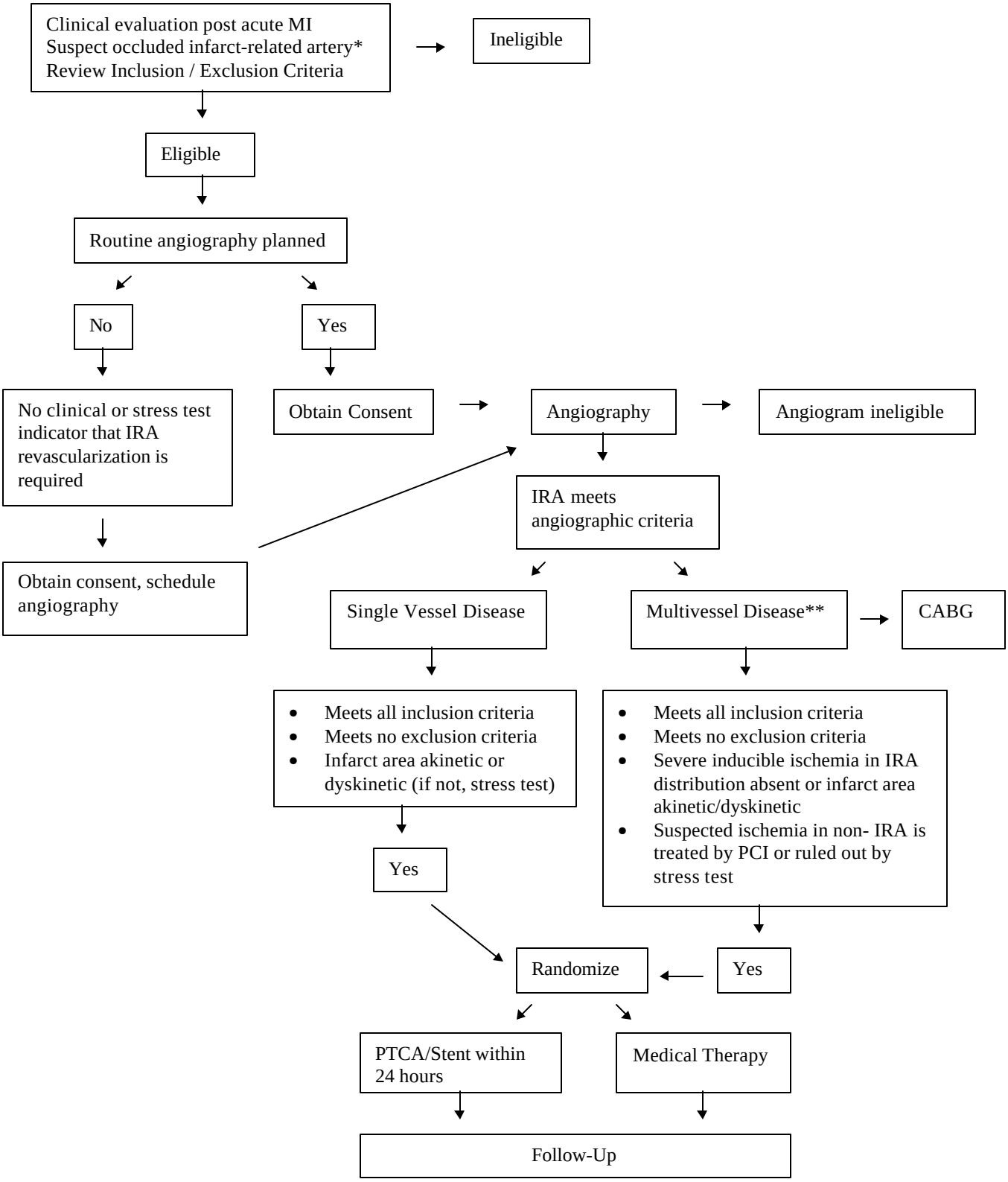
approached for consent for the trial. If all angiographic criteria are met the patient may be randomized for possible PTCA at that time. Alternately, consent may be obtained after the qualifying angiogram for a possible PTCA. The qualifying angiogram must have been performed on or after day 3 and before day 29 post index MI .

For all other patients, for whom risk stratification after myocardial infarction is done by noninvasive assessment, the echocardiographic criteria wall motion score index (WMSI) of ≥1.5 will be used as evidence for an increased likelihood of a persistent total occlusion of the infarct-related artery and moderate to high risk for subsequent events. Although a large wall motion abnormality does not always indicate persistent total occlusion, this evidence for a large infarct increases the likelihood that reperfusion has not occurred.

In the unlikely event that a coronary angiogram is not performed and a wall motion score index from an echocardiogram is not available, the ECG QRS score will be used to screen for patients with large infarcts and therefore an increased likelihood of persistent total occlusion.

Patients who meet these criteria and the clinical inclusion criteria with no clinical exclusion criteria will be approached for consent for the trial, including consent to undergo cardiac catheterization and coronary angiography to assess their eligibility for the trial.

Figure 1 - Screening and Enrollment



* Suspect occluded IRA if (a) large MI, (b) WMSI > 1.5 on echo, (c) no or late thrombolysis, (d) clinical evidence for thrombolysis failure

** Patients with significant three-vessel disease and LVEF < 50% may be referred for CABG and should not be considered for enrollment even when multivessel angioplasty of non- IRA is planned.

3.3 Stress Testing/ Interventions for Non-Infarct Related Arteries

This trial is not designed to test the hypothesis that PTCA for severe inducible ischemia reduces events. Therefore, severe ischemia will be tested for and excluded whenever suspected. Exercise testing or pharmacologic (dobutamine, dipyridamole, or adenosine) stress radionuclide perfusion or echocardiographic studies are recommended prior to randomization except as noted below. PTCA of the non-IRA is permitted, including as treatment for severe inducible ischemia, as long as the treatment of the IRA (PTCA or medical therapy only) is by study allocated assignment. For example, a patient has an anterior MI as the index event and an occluded LAD as the IRA. In addition, there is a 90% circumflex stenosis. Stress perfusion imaging has demonstrated a fixed anterior defect and ischemia in the circumflex distribution. If a successful PTCA of the circumflex is performed, the patient is eligible for randomization of the LAD to PTCA or medical therapy only.

***Exceptions to stress testing*:** For patients whose coronary anatomy is defined at routine coronary angiography after MI and who have single vessel total occlusion with akinesis or dyskinesis in the infarct zone, stress testing is not indicated. Although viable myocardium may be present, *severe inducible* ischemia is unlikely in this situation. Revascularization is optional[37] and therefore enrollment is ethical and appropriate. For patients with 2-vessel CAD (see above), a successful PTCA of the non-IRA results in a single vessel (IRA) with a significant stenosis. If this IRA supplies akinetic/dyskinetic myocardium, stress testing is not indicated.

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

- Recent MI (3-28 days) (Day 1 is the day of the MI onset).

- MI is defined based on at least 2 of 3 MI criteria confirmed by: 1) ischemic symptoms ≥30 minutes, 2) cardiac serum marker elevation (CPK 2x upper limit of normal and CPK-MB elevated above the upper limit of the laboratory normal) or troponin T, or troponin I elevated ≥ 2x above the upper limit of the laboratory normal and/or 3) EKG: New Q-waves of ≥0.03 sec and/or 1/3 of QRS complex in ≥2 related EKG leads. If cardiac serum markers are elevated (2), any one of the following EKG findings satisfy inclusion criteria; new ST-T changes (ST elevation or depression), new LBBB, loss of R-wave voltage ≥50% in ≥2 related leads or deep T wave inversions ≥3mm in ≥2 leads.[38-41]

- Total Occlusion (100%) of the infarct related artery with TIMI flow 0-1, defined as no flow beyond the site of occlusion (TIMI 0), or penetration of dye beyond the site of occlusion without the dye reaching the distal vessel (TIMI 1). This angiogram must have been performed on day 3 or later post index MI and before day 29.

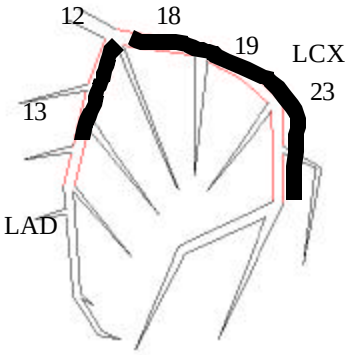
- Meets criteria for high risk: [10]

    1. EF <50%. The occlusion can be in any coronary artery or major branch, at any location if the EF is <50%
       OR
    2. If EF ≥50%, the site of occlusion should be ***proximal***[42] in a ***large***[43] vessel such that the myocardium supplied by the IRA is at least 25% of the LV (see Figure 2A-2C):

a. Left anterior descending (LAD) proximal third. (Figure 2A)
b. Circumflex if supplying large obtuse marginal, and part of the inferior wall (i.e., a large dominant or co-dominant vessel) (dependent on individual anatomy and circumflex dominance). (Figure 2A,2B)
c. Large right coronary artery (RCA) if supplying posterior descending artery (PDA), part of inferior myocardium, part of the posterolateral wall, and/or apex. (Figure 2C)

Figure 2: Qualifying Coronary Segments for patients with EF ³ 50%

2A: Dominant Left Coronary Artery



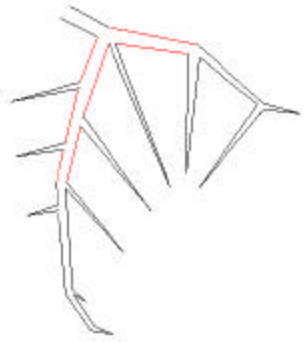
To qualify, the occluded segment must be:

1. in segments 12 or 13 of the left anterior descending coronary artery (i.e., proximal to the 2nd major diagonal branch)

or

2. in segment 18, 19, or 23 of the dominant left circumflex coronary artery supplying *at least* one significant posterior or posterolateral branch and the posterior descending artery (PDA) (each approximately 2.0 mm diameter or greater by visual estimate).

2B: Non-dominant Left Coronary Artery



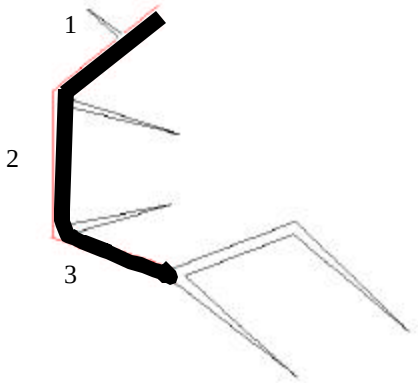
To qualify, the occluded segment must be:

1. in segments 12 or 13 of the anterior descending coronary artery (i.e., proximal to the 2nd major diagonal branch)

or

2. in segment 18 of the non-dominant left circumflex coronary artery supplying at least two significant marginal branches one significant posterior or posterolateral branch (each approximately 2.0 mm diameter or greater by visual estimate).

2C: Dominant Right Coronary Artery



To qualify, the occluded segment must be in segments 1, 2, or 3 of a dominant right coronary artery supplying *at least* the posterior descending artery (PDA) and 1 posterior/posterolateral (PL) wall branch. Both PDA and PL should be approximately 2.0 mm diameter or greater by visual estimate.

----------**The occluded segment should appear to be suitable for stenting.** ----------

MI location
As long as the defined criteria for site of occlusion and vessel size or EF are met, patients with any location of MI are eligible for the trial. Although, anterior MIs are at greatest risk for LV remodeling and death, multiple studies have demonstrated the strong association of survival with an open IRA for all MI locations. [10-13]

3.4.2 Exclusion Criteria (no exclusion criterion should be present)

- Age ≤18 years.
- Clinical indication for revascularization defined as follows: rest or low-threshold angina post MI, severe inducible ischemia on low level exercise or pharmacologic stress testing (ST depression ≥2 mm, inability to complete stage one or achieve 3-4 mets without angina, hypotension or reversible perfusion defects in multiple territories or decreased wall motion thickening in ≥two segments on echo), left main coronary disease (≥50% stenosis) or triple vessel disease (three major epicardial coronaries with ≥70% stenoses) or angina refractory to or intolerant of medical therapy.
- Other serious illness that limits 3-year survival such as cancer or severe pulmonary disease.
- Severe renal disease defined as serum creatinine > 2.5 mg/dl that would markedly increase the risk of radiographic contrast.
- Qualifying infarct-related artery that has been grafted previously, i.e., the recent total occlusion is in either the graft or in a native vessel that receives a graft. Patients who have had prior CABG may be enrolled if the IRA was not previously grafted.
- Severe valvular disease.
- History of anaphylaxis to radiographic contrast unless patient has been treated with a standard dose of corticosteroids.
- Infarct artery too small (reference segment diameter <2.5mm), target segment within or beyond extreme tortuosity (>90 degrees angulation), or otherwise technically a poor candidate for PTCA or stent implantation based on angiographic criteria.
- Chronic occlusion of the IRA defined as having been seen on a prior angiogram before the index MI, or by the presence of bridging collaterals.
- NYHA Class III-IV CHF at the time of screening.
- Cardiogenic shock or sustained hypotension: systolic blood pressure <90 mmHg or cardiac index (if obtained) <2.2 l/min/m^2 at the time of screening.
- Left ventricular aneurysm in the same location as the index infarction and known to be present before the index MI.
- Inability to cooperate with the protocol, including long-term follow-up.
- Patient refusal or inability to give informed consent.
- Refusal of the patient's physician to allow the patient to participate in the trial.
- Pregnancy (all pre-menopausal females should have a negative serum pregnancy test).
- Contraindication to anticoagulation during PTCA/stent or to administration of routine antiplatelet therapy following stent implantation.
- Dilated or hypertrophic cardiomyopathy.

3.4.3 Timing of enrollment

The timing of enrollment balances several competing considerations. For the greatest potential benefit on LV remodeling that is not dependent on the recovery of function of hibernating myocardium, the earlier the occluded vessel is opened, the greater the effect. However, the disadvantages of enrollment within the first few days include: 1) spontaneous opening of occluded vessels after randomization, 2) insufficient observation period to determine that the patient is asymptomatic with an uncomplicated MI and 3) insufficient time to exclude severe inducible

ischemia. Spontaneous opening of the IRA in the medical therapy group would dilute the difference between the two groups. Data from thrombolytic and pre-thrombolysis studies indicate that most spontaneous openings occur in the first few days after MI. Spontaneous reocclusions also occur in the same time frame. There is evidence that the beneficial effects of an open artery that are less time dependent, (recovery of hibernating myocardium and electrical stability) are observed when the artery is opened as late as 42 days after MI. Thus, inclusion of patients 3 to 28 days (day 1 is the calendar day of the MI) after MI allows for time to obtain necessary tests and for transfer of patients. The definition of the day of index MI was changed from day 0 to day 1 in protocol version 11/01/00. This change allows enrollment of patients who had baseline angiograms obtained one calendar day earlier than the prior 11/12/99 protocol version. The rationale for this change is presented in Appendix 5.

3.5 Consent

All participating centers will have approval of an IRB or Ethics Committee with certification from the NIH Office of Human Research Protection (OHRP). The IRB/Ethics Committee will be informed of all protocol changes by the site investigator in accordance with the IRB/Ethics Committee's established procedure. Written informed consent will be obtained after clinical eligibility is established. The Consent Form will be reviewed with the prospective study patient, and the investigator will be available to answer questions regarding procedures, risks and alternatives. Specific consent will be obtained before any protocol procedure, which requires consent (e.g., PTCA), is performed. For patients undergoing angiography to assess eligibility for the trial, consent for the trial will be obtained before consent for angiography with the specific stipulation that the angiogram is for assessment for the trial.

3.6 Randomization

Patients meeting all inclusion criteria with no exclusion criteria who give informed consent will be randomly assigned by a central computer to PTCA/stent or routine medical management with no PTCA/stent. Randomization will be automated and will be balanced within centers.

3.7 Enrollment of Patients at Sites Without PTCA

Eligible patients may be randomized at sites with IRB and OHRP approval and angiography facilities but without PTCA capability. **The qualifying angiogram must be reviewed by an OAT certified interventionalist before randomization.** In the case of an in-patient, randomization to intervention necessitates prompt transfer to an OAT PTCA site and performance of PTCA by an OAT certified operator within 24 hours. If patients randomized to the medical arm are discharged, they may be followed as an outpatient by an OAT study investigator and coordinator.

Patients identified as clinically and angiographically eligible following hospital discharge who are interested in study participation should be referred to OAT staff for an office appointment. Informed consent can be obtained and randomization performed in the out-patient setting. **Assignment to the interventional arm will necessitate performance of PTCA within 24 hours**. Those assigned to medical treatment only will return home and be followed by an OAT study investigator and coordinator.

If the patient is randomized as an outpatient and assigned to medical treatment alone, it is impractical to obtain the CPK-MB every 8 hours (see section 3.15). In this scenario, obtain the values just after randomization and again at 40-48 hours after the baseline value.

3.8 Trial Participants

It is recommended that all patients in the trial receive optimal routine care including aspirin, anticoagulation if indicated, ACE inhibitors and beta blockers, unless contraindicated, and risk factor modification. Agency for Health Care Policy Research (AHCPR) guidelines for CHF are recommended if CHF develops (Appendix 1). In the event of emergencies, all patients will be offered alternative medical procedures.

3.9 Patient Registry

A registry of all patients meeting inclusion criteria with no medical exclusion criteria will be compiled to insure that all potentially eligible patients are considered for the study and to minimize the potential exclusion of patient subgroups. Demographic, baseline, MI and management characteristics of non-enrolled patients will be recorded in this registry.

For two one-month periods, all MI patients at clinical sites will be logged. Age, sex, MI characteristics and performance of cardiac catheterization will be recorded.

3.10 Protection of Patients

Confidentiality: in this study, only the research staff at the local site will know the subjects' names. Facts about patients that are stored in the study computer will include initials, age, and gender. Reports from this study will not identify patients. The medical records, and answers to questions will be kept private. Data will be identified only by code numbers that cannot be traced back to study subjects by anyone outside of the study. Study staff will not give private information to anyone outside the study except to comply with legal demands (such as a court subpoena). In all cases, extreme caution will be exercised to assure patient confidentiality. Confidential study report forms will be kept in a secure and locked office.

A Data and Safety Monitoring Board (DSMB) will monitor unblinded data to confirm the safe treatment of all study patients.

All procedures performed in this study are commonly performed for clinical indications, with well-defined low risks. The risk of coronary angiography and PTCA will be minimized by the selection of experienced operators who meet study certification criteria, and with ongoing review by the DSMB to monitor patient safety. These low risks are justified by the potential long-term reduction in events as discussed in the background section. Furthermore, coronary angiography is frequently performed to risk stratify patients who are post MI while reducing length of hospital stay.

3.11 Clinical Aspects of Group Assignment: Percutaneous Revascularization

The major intervention to be tested in this trial is late percutaneous revascularization of the infarct-related artery 3 to 28 days after myocardial infarction using any approved device with stent implantation. Patients randomized to the revascularization arm will undergo the procedure within 24 hours of randomization. A 24-hour window is allowed to permit randomization at affiliated hospitals that do not perform PTCA, with transfer of patients who have been randomized to the revascularization group. In this selected population of uncomplicated patients 3 days post MI there is a low likelihood that death will occur in the 24-hour period between treatment assignment and revascularization. If it does, primary analysis includes all patients on intent to treat

basis. In the unlikely event another endpoint occurs in this 24 hour period, i.e., recurrent MI or Class IV CHF, the planned PTCA will be performed as soon as possible unless medically contraindicated. Revascularization for patients assigned to revascularization should be performed as soon as possible and within 24 hours of randomization.

Recommended routine medical care is described in Appendix 1. Clopidogrel or ticlopidine is recommended beginning at 48 hours prior to the stent placement (if possible) or immediately before and continued for two to four weeks. Routine use of calcium blockers post angioplasty is not recommended.

Angiography will be performed according to the following guidelines:

- Using the TIMI technique.
- Multiple views of the left and right coronaries. It is of primary importance to document the site of qualifying occlusion carefully and without overlap using projections in both RAO and LAO hemispheres with sufficient acquisition times to allow assessment of any residual antegrade flow and ipsilateral collateral filling. Similarly, when recording injections of the contralateral vessel, care should be taken to record collateral filling of the segments distal to the qualifying occlusion with appropriate panning when necessary.
- Ionic low osmolality radiographic contrast is preferred.
- Selective administration of intracoronary NTG 100-200 mcg with appropriate angiographic labeling should precede angiography of both left and right coronaries regardless of the location of the qualifying occlusion.
- Left ventriculography should be performed unless there is a contraindication and when possible, be recorded prior to coronary angiography and administration of NTG (and always prior to any intervention).
- Recommendations for patients with creatinine between 1.5-2.5 mg/dL: Hydrate prior to and following angiography/PTCA. (See Appendix 3). Minimize the volume of radiographic contrast (e.g., <200ml).

Balloon angioplasty, atherectomy, rotablator, or any other approved devices will be used to open the IRA, followed by stent placement (any approved, not investigational, stent). The choice of the catheter based technique will be individualized based on the patient's coronary anatomy and the institution's preferred approach. A PTCA/stent will be attempted on all patients, including those who may have spontaneously opened between the angiogram and PTCA procedures, as long as the stenosis is 50%.

Patients receiving heparin will receive standard weight-adjusted heparin to achieve an activated clotting time (ACT) of ≥250 seconds prior to the beginning of the procedure; additional weight-adjusted heparin will be administered every 30 minutes, as needed, for the duration of the procedure to maintain an ACT ≥250 seconds or a 10 U/Kg/hr continuous infusion of heparin will be initiated. Low molecular weight heparin may be used instead of unfractionated heparin when utilized according to standard clinical guidelines. Use of GP IIb/IIIa inhibitors are encouraged and the heparin dose will be decreased for these patients (see Appendix 3).

The lesion will be dilated and a stent will be deployed according to standard clinical practice when the target ACT is achieved. The stent should be dilated with standard clinical practice to ensure

full strut expansion. Intracoronary ultrasound may be employed at the discretion of the investigator, but it is not mandatory.

CABG surgery is not required for failed PTCA/stent due to the asymptomatic nature of the patient population selected. However, it is permissible and grafting of the qualifying infarct-related vessel is required if surgery is performed. CABG surgery may be required for a clinical indication that may develop during or after the procedure (i.e., dissection involving a non-infarct–related artery).

Immediate discontinuation of heparin upon completion of the procedure, with removal of the arterial sheath within six hours, is strongly recommended.

3.12 Clinical Aspects of Group Assignment: Medical Management Without Target Vessel (IRA) Revascularization

In patients who have been identified for the study before going for a scheduled routine post-MI coronary angiogram, the coronary angiogram will be performed with the same study technique as for the PTCA-assigned group. All patients must be enrolled between 3 and 28 days following MI. Angiograms performed before screening for the study are acceptable if angiography is performed within 3 to 28 days of the qualifying MI (day 1 = date of index MI).

3.13 Revascularization for Clinical Indications

This trial will compare a strategy of routine PTCA/stent versus an initial strategy of medical therapy only for the totally occluded IRA in these asymptomatic patients. Over the 27-51 months of follow-up, revascularization of newly symptomatic lesions in *other* vessels is based on clinical decision making. PTCA or CABG of the target vessel IRA in the absence of a primary endpoint event constitutes a crossover. Revascularization of the IRA during follow-up will be strongly discouraged unless the following clinical indications are present:

A. Occurrence of a primary endpoint event (MI, NYHA Class IV CHF).
B. Canadian Cardiovascular Society Class III or IV angina on maximal medical therapy.
C. Development of a significant left main coronary artery stenosis or three-vessel stenosis with impaired LV function determined by an angiogram performed for clinical indications, e.g., new, severe ischemic response on stress test.
D. Sustained ventricular tachycardia/fibrillation or NYHA Class III CHF due to ischemia.

Revascularization of the IRA after a primary endpoint (A above) is not a crossover. Revascularization of the IRA for a clinical event (B-D above) constitutes a secondary endpoint, but is a crossover for the primary endpoint. This rate is expected to be <17% because enrolled patients are asymptomatic and have no severe inducible ischemia. A total occlusion of the IRA after 6 weeks post MI becomes chronic and is not optimally suited for PTCA, setting a high threshold for performance of percutaneous intervention. PTCA of lesions (new or old) in vessels other than the IRA does not constitute a crossover.

3.14 Study Endpoints

3.14.1 Primary Endpoint

The primary endpoint of the trial will be the first occurrence of:

A. Death from any cause.
B. Recurrent MI after randomization confirmed by using at least 2 of 3 criteria for MI: 1) ischemic symptoms ≥30 minutes, 2) cardiac serum marker elevation (CPK >2x upper limit and CPK-MB elevated above the upper limit of laboratory normal; or T or Troponin I elevated ≥ 2x above the upper limit of laboratory normal if obtained ≥10 days after the

index MI. If the CK-MB level prior to suspected reinfarction was above the upper limit of normal i.e., due to the index MI, the CKMB must be elevated ≥ 50% above the prior level) and/or 3) EKG: New Q-waves of ≥0.03 msec and/or 1/3 of QRS complex in ≥2 related EKG leads. If cardiac serum markers are elevated (2), any one of the following EKG findings satisfy diagnostic criteria; new ST-T changes (ST elevation or depression), new LBBB, loss of R-wave voltage ≥50% in ≥2 related leads or deep T wave inversions ≥3mm in ≥2 leads.

The following level of enzyme elevation is required to confirm MI within 24 hours after a procedure; these must be associated with either symptoms or new ST elevation or Q waves, or both (as defined above) to meet the primary endpoint MI criteria:

1. Post-PTCA/Stent: Elevation of CPK-MB (or total CPK in the absence of CPK-MB values) to ≥3x upper limits of normal and at least 3% of total CPK if both CPK and CPK-MB are available, and ≥50% increased over the value preceding the procedure.
2. Post-CABG: Elevation of CPK-MB ≥5 times normal (or CPK in the absence of CPK-MB), and at least 3% of total CPK if both CPK and CPK-MB are available.

   For the interventions performed during the initial hospitalization when the patient is enrolled in OAT, CPK's will be obtained peri-procedure as specified (section 3.15 below). However, these CPK measurements may not be systematically obtained peri-intervention during recurrent hospitalizations over an average three-year follow-up, unless OAT study staff are involved. The Mortality and Morbidity Classification Committee (MMCC) will review all recurrent hospitalizations and assess whether a post PTCA or CABG MI has occurred utilizing the available data, including CPK-MB's obtained on a clinically routine basis.

C. NYHA Class IV CHF hospitalization or admission to a short stay unit; to qualify as a primary CHF endpoint the event must meet strict criteria which may include symptoms at rest, the administration of intravenous loop diuretics and documentation by chest radiography of pulmonary congestion (see Forms Instructions Criteria). Although Class III CHF is a meaningful clinical endpoint, it is more difficult to define and verify. The clinical diagnosis of heart failure could be subject to bias by unblinded investigators leading to less diagnosis in PTCA patients. Consequently, the endpoint for OAT must be objective and verifiable and consist only of hospitalization or admission to short stay unit for which the principal diagnosis at the time of discharge is Class IV heart failure. Furthermore, the objectivity of the hospitalization component will be improved by requiring strict documentation of criteria as detailed in the manual of operations. This and other primary endpoint events will be adjudicated by a blinded Mortality and Morbidity Committee.

The average follow-up is three years (27-51 months) and the primary analysis compares all patients in the two groups on an intention to treat basis. (See statistical design – section 3.18 and Appendix 2)

3.14.2 Notification and Collection of Primary Endpoint Data

Final, complete clinical data will be entered on the appropriate data collection form. The DCC packet will include copies of medical and laboratory records including ECGs for review by the blinded MMCC. In all cases the patient's name will be masked and replaced with the OAT patient's ID number and initials prior to transmission to the DCC.

3.14.3 Secondary Endpoints

- The economic endpoints are: 1) measurement and comparison of cumulative total medical costs for the two treatment arms in OAT by intention-to-treat, 2) estimation of the incremental cost effectiveness of the investigational percutaneous revascularization arm relative to the control medical therapy arm assessed as cost per life year added and cost per quality adjusted life year added and 3) identification of factors in addition to treatment assignment that are associated with variations in medical cost and cost effectiveness.
- Quality of Life endpoints are: 1) comparison of health-related quality of life for the two treatment arms by intention to treat and 2) identification of factors in addition to treatment assignment that are associated with variation in quality of life outcomes.

3.14.4 Other Endpoints

The individual components of the composite primary endpoint as well as other events are secondary endpoints:

- Death.
- Cardiovascular death - In this population >80% of deaths will be cardiovascular.[44]
- Recurrent MI.
- Death and non-fatal MI.
- NYHA Class IV CHF.
- Hospitalization for CHF
- Sustained ventricular tachycardia/ventricular fibrillation (VT/VF) requiring electrical cardioversion or defibrillation. Data supporting the diagnosis of sustained VT/VF requiring cardioversion including rhythm strips, EKG's, emergency medical service records and hospital records will be reviewed by the MMCC.
- Automatic Implantable Cardiac Defibrillator (AICD) implantation will be compared during follow-up. The reason for AICD implantation will be recorded as therapy for cardiac arrest, sustained VT/VF or prophylactic based on inducibility at electrophysiologic testing or other criteria. Documentation of AICD implantation and the indication will be reviewed by the MMCC.
- Revascularization of target vessel (index IRA). Target vessel revascularization (TVR) is defined as repeat percutaneous coronary intervention or coronary artery surgery involving the initially targeted totally occluded IRA. To qualify as a second procedure for those assigned to PTCA, the revascularization must be performed after final guidewire removal following the initial index PTCA.
- Revascularization of other coronary arteries. Revascularization of vessels other than the IRA will be assessed and compared in the two groups. These do not constitute crossovers for medical therapy assigned patients.
- Stroke. A stroke will be defined as a neurologic deficit of sudden onset, consistent with a vascular distribution, that is not reversible within 24 hours and which is not due to a readily identifiable non-vascular cause (i.e., brain tumor, trauma).[45] An event form will be completed and supporting data, including computed tomography, magnetic resonance imaging, cerebral angiography, and neurologist reports will be collected for transmittal to the DCC and review by the MMCC.
- A secondary composite endpoint of the first to occur of death, recurrent MI, hospitalization for heart failure, sustained arrhythmia, automatic implantable defibrillator (AICD) placement or stroke will also be evaluated.
- Post PTCA CPK and CPK-MB release will be routinely monitored on all PTCA assigned patients, and comparable measurements monitored on medical therapy patients (see section 3.15). CPK and CPK MB release to at least five-fold elevation after PTCA will be analyzed separately. CPK and CPK-MB will also be obtained routinely post CABG.

3.14.5 Safety Events

Complications related to angiography and PTCA/stent will be carefully monitored. Complications which occur within 48 hours of randomization, will be reported to the DCC for all of the following: major hemorrhage (Hct >15% or Hgb >3 gm/dl decrease), (TIMI criteria),[39] emergency CABG, acute limb ischemic complication, stroke, coronary perforation, aortic dissection and reocclusion with recurrent MI.

3.15 Measurement and Data Collection

The Study Report Forms (SRFs) will be used to collect all patient data and assessments that will be used for evaluation of the patient's response to treatment. The following measurements will be included in the initial case report:

- Baseline characteristics
- MI characteristics and location
- Baseline coronary angiography
- Ejection fraction (required)
- Stress testing, unless exemption criteria met
- Echo results, if applicable, including regional wall motion analysis.

Confirmation of the qualifying myocardial infarction will be recorded: positive troponin T, I, CPK-MB, symptoms and EKGs. EKGs will be performed during the index MI, at baseline (prerandomization), at 24-48 hours post-randomization (after PTCA, if applicable) and with events that constitute a primary or other ischemic event (i.e., reinfarction, Class II-IV angina).

All serious complications within 48 hours of randomization, including catheterization lab death and emergency surgery will be recorded on a separate form and faxed to the DCC within 72 hours of randomization. These events are described in safety events, section 3.14.5.

CPK-MB measurement after enrollment constitutes a special case. In order to capture potentially important CPK-MB rise after PTCA/stent (see section 3.14.1),[46] CPK-MB will be obtained pre and at 8, 16 and 24 hours post-PTCA. To avoid bias in endpoint ascertainment between the two groups, the medical therapy group will have CPK-MB obtained within 24 hours after randomization and 8, 16 and 24 hours thereafter or at randomization and 48 hours for outpatients. As PTCA must occur within 24 hours of randomization for the intervention group, these cardiac enzyme measurements will be within the same time frame for the two groups.

3.16 Data Collection for the Follow-Up Period Endpoints

Following enrollment, patients will be contacted by phone every four months for an average of three years (27-51 months) to ascertain:

A. Vital status.
B. Canadian Cardiovascular Society angina Class.
C. NYHA CHF Class.
D. Hospitalization for MI, CHF, revascularization, arrhythmia, AICD implantation and any recurrent hospitalization.

Hospitalization records will be obtained, extracted and reviewed for completion of subsequent hospitalization report form.

A visit to the study office at the scheduled time intervals may replace the phone contacts if agreeable to the patient and study staff.

All randomized patients will be included in the primary analysis of the primary and secondary endpoints. Thus, it is imperative to obtain complete follow-up data for all patients whether or not they receive their assigned treatment. Attempts to collect follow-up data will be made for all

except those who specifically withdraw consent for release of such information. Complete and accurate follow-up over 27-51 months of follow-up is extremely important.

3.16.1 Quality of Life and Health Status Data Collection

QOL questionnaire data will be collected at baseline, four months, years one and two; a sample of 100 patients in years one and two will have their QOL interviews repeated within a two-week interval by OAT EQOL Coordinating Center personnel at Duke University to assess test–retest reliability and standardization of the interviews.

Content of Health-Related Quality of Life Questionnaire

The QOL questionnaire will include a battery of validated instruments that build on a generic core supplemented by more detailed and/or disease-specific measures where necessary to provide a comprehensive assessment of health-related quality of life. The major quality of life effects of the percutaneous revascularization in this trial are likely to manifest themselves as a change in what the patient can do (or feels capable of doing) physically, the level of somatic symptoms and level of psychological well-being. These domains will be assessed in detail. Other quality of life effects such as altered role functioning and social functioning would be expected to occur as a consequence of changes in the physical or psychological status. These domains will be assessed briefly.

The generic core instrument is the Medical Outcomes Study Short Form (SF36). The SF-36 is composed of nine scales which can be used separately or as a set; they include physical function, role function-physical, role function-emotional, general health, bodily pain, social function, psychological well-being/mental health, vitality and health transitions. Each scale is scored separately and is transposed to a 0 to 100 scale.

Recent work has suggested that the SF-36 physical function scale is not as sensitive to clinically important changes over time in coronary disease patients as is a disease-specific measure. Thus, in lieu of this scale, we will use the Duke Activity Status Index CDAS will be used. Three brief supplemental measures of functional status, the Bed Days and Disability Days questions from the National Health Interview Survey and a four-level ordinal global assessment of the effect of the patient's health on his or her ability to do activities will also be obtained. Cardiac symptoms will be assessed with the Rose Angina and Rose Dyspnea Scales. These have been used extensively in prior epidemiologic and quality of life studies. They will be supplemented with the New York Heart Association (NYHA) congestive heart failure Class and the Canadian Cardiovascular Society Class for angina, which will be recorded on the clinical Study Report Form and collected during each follow-up telephone contact.

General psychological well being/mental health will be assessed using a five-item mental health scale from the SF-36. This measure has been shown to correlate well with clinically diagnosed anxiety and depression. General health perceptions will be assessed using the five-item scale from the SF-36 that includes a five-level ordinal ranking of the patient's overall health (excellent to poor). Scales from the SF-36 will be used to assess role functioning (both physical and emotional related limitations), bodily pain, social functioning and vitality. Employment details will be obtained using an abbreviated series of questions adapted from the NHLBI Bypass, Angioplasty Revascularization Investigation (BARI) Substudy in Economics and Quality of Life (SEQOL).

Measurement of Utilities

Patient-specific utilities will be measured by patient interview using the time trade-off technique. Patients will be asked, in a series of questions, how much of their life expectancy in their current health state they would be willing to give up to live the remaining years in excellent health. The life expectancy used in this assessment will be 10 years.

As a second global measure, patients will also be asked to rate their health on a 0-100 scale where 100 equals excellent health and 0 indicates a state of health equivalent to being dead. Although not strictly a utility measure, this rating scale assessment has been used to impute a time trade off value using a mathematical transformation developed by Torrance[47]. This calculation can be useful when patients are unable to follow the time trade-off questions but can provide a ratings scale assessment.

3.17 Economic Data/Hospital Billing Data (U.S. sites only)

Hospital bills (detailed, summary ledger and UB 92) will be collected, a photocopy retained and the original sent to EQOL Coordinating Center by the study site coordinators within 45 days of discharge from the hospital (baseline or follow-up) or as soon as possible after that, since some hospitalizations may not be identified by the study coordinator for up to four months. This will be done through an arrangement with an identified person in the billing office who will determine the most convenient means to collect the data for each individual site. That person can also help identify any site-specific information necessary to facilitate collection of the data (e.g., reference account code number to obtain detailed patient ledger for a hospitalization), and to work through problems as they arise. The patient's name will be masked and replaced with the OAT patient's study number and patient's initials before sending bills to the EQOL Coordinating Center in order to maintain confidentiality.

Follow-up hospital bills from institutions not participating in OAT will be collected from each hospital by the appropriate site coordinator who will call the head or the representative of the outside hospital's patient accounting department and request the bill following this request with a written letter including a copy of the signed consent form if requested or will contact the Chief of Medical Records and send a signed authorization for release of information, including bills.

In addition, cost to charge ratios (RCCs), specifically the Medicare Cost Report Worksheets C and D1 Part 2, will be obtained from each hospital where an OAT baseline or follow-up hospitalization is reported. These reports can be obtained from the hospital in question, the Medicare Intermediary for that Region, or the Health Care Financing Administration. Since these documents are in the public domain, we anticipate that 100% will be obtained.

3.18 Statistical Design

The number of patients required for the Occluded Artery Trial has been calculated based on the following conservative assumptions: three-year incidence of the primary endpoint, defined as the time to the first to occur of death, MI, or Class IV CHF, is 25% in the medical therapy group; with an alternative hypothesis of a 25% reduction in the primary endpoint with PTCA/stents. The reported event rates for the same composite endpoint are as high as 40% with 38% reduction in events.[16] These event rates were observed even though there was dilution of revascularization effect by spontaneous opening of IRA's in the medical therapy only group and reocclusion of the IRA in the PTCA group (Stents were not in use in this study). There will be a 24-month

recruitment period and a 27-month follow-up only period. Under the assumption that all patients receive their assigned treatments and are followed to the end of the study, enrollment of 1,704 patients would be required for the Occluded Artery Trial for 90% power.

It is expected that some patients will not receive the assigned treatment, but instead will receive the treatment expected for the other group; these patients are referred to as "crossovers." We estimate that $\leq$8% of the patients assigned to PTCA/stent will not have PTCA performed for technical or other reasons or the PTCA stent procedure will not be successful and that $\leq$17% of patients assigned medical therapy will undergo PTCA or CABG of the index occluded IRA during the 27-51 month period of follow-up. Adjustment for the expected crossover rate increases the number of patients from 1,704 to 3,029 to have 90% power to detect a 25% reduction in the primary endpoint. An additional adjustment for 5% loss to follow-up increases the required number of patients to 3,200 patients. The proposed study size of 3,200 patients will also have sufficient power to detect substantial reductions for outcomes that occur with lower frequency (such as death or MI). If the three-year incidence of a secondary outcome is 15% for patients assigned to medical therapy, there will still be at least 80% power to detect a 35% reduction in the outcome frequency in patients assigned to revascularization.

Three hundred-twenty clinical sites (320) will enroll patients. We have made a conservative assumption, that the primary endpoint event rate will be lower than 40% observed due to: 1) selection for a clinical trial and 2) consistent use of ACE inhibitors, cholesterol lowering agents and optimal medical management in OAT. Similarly, the magnitude of the treatment effect (i.e., PTCA/stent) may be less than that previously reported in the non-randomized studies.[48] Therefore, OAT is powered for a 25% treatment effect, not the 38% reduction in events observed in the non-randomized studies.

Intention to treat analyses of the primary study endpoint will be performed using the methods outlined below. The primary study endpoint will be the time to the first to occur of death, recurrent MI, or Class IV CHF. Follow-up for events will vary from 27 months to 51 months depending on when the patient is enrolled in the study. Patients will be counted according to the treatment strategy to which they were randomly assigned at the time of study enrollment, regardless of whether they do or do not receive revascularization. The comparison of the distributions for the primary outcome (time to the first to occur of death, MI or hospitalization for Class IV CHF) between the two treatments will be evaluated using the log-rank statistic.[49] The cumulative distributions of this outcome will be estimated using the methods of Kaplan and Meier.[50] Multivariate adjustments to this comparison will be made using Cox proportional hazards models.[51] The variables to be used in the latter analyses are the variables designated for subgroup analyses (see Appendix 2).

Patients who are lost to follow-up before the end of the follow-up interval will be censored at the time of their last visit. The primary outcome will be analyzed according to the patient's assigned treatment group (intention to treat analysis).

During the course of the Occluded Artery Trial, DCC staff will carry out interim data analysis and present data reports to the Data and Safety Monitoring Board (DSMB) to monitor the study for evidence of beneficial and adverse treatment effects. During the first year and subsequent years the DSMB will review reports on study performance including recruitment, protocol violations, complications of treatment observed during the first 48 hours of study entry, and the occurrence of crossovers.

Secondary endpoint analyses will also be performed for the individual events in the composite endpoint, that is, death, recurrent MI (fatal and nonfatal), and Class IV CHF (fatal and nonfatal) requiring hospitalization or short stay unit admission; and for the following events: cardiovascular death; quality of life; and direct medical costs. Other events to be analyzed include clinically significant ventricular arrhythmia (VF or VT) requiring cardioversion; AICD placement in response to VF or VT or prophylactic placement based on electrophysiologic testing or other indication; stroke, hospitalization for a cardiac event; and nonprotocol revascularization (PTCA or CABG). Quality of life and cost data will be analyzed by the OAT EQOL Coordinating Center. Treatments will also be compared on frequency of occurrence of adverse outcomes.

The Type I error rate for the comparison of the primary endpoint will be set at 0.05 for two-sided tests, using the methods described below to maintain that error rate while conducting interim monitoring of the primary outcome. For secondary analyses, p-values less than 0.01 will be considered to show some evidence of differences and p-values less than 0.001 to show strong evidence of differences.

We propose that a limited number of pre-specified subgroup analyses of the primary outcome be performed. These tests include: 1) a test for interaction between gender and study treatment, 2) interaction between minority status and study treatment, 3) interaction between age ($\leq$70versus >70 years) and study treatment, 4) interaction between time from index MI to recruitment and study treatment, 5) interaction between MI location, [anterior (LAD occlusion) versus non-anterior] and study treatment and 6) interaction between baseline ejection fraction and coronary anatomy (or severity of CAD) with study treatment. (see Appendix 2, section A2.3.)

A variety of other analyses will be performed to meet the objectives of the Occluded Artery Trial. These will include analyses of the association of various baseline factors including angiographic characteristics with mortality and other outcomes. Such secondary analyses are exploratory in nature and will involve hypothesis generation more than hypothesis testing. Since strict control of the Type I error rate is not possible in such analyses, we proposed that a p-value <0.01 be considered as showing some evidence of differences and a p-value <0.001 be considered as strong evidence of differences. (see Appendix A2, section 2.4)

4. Study Organization

The trial has a Clinical Coordinating Center (CCC) (Study Chair and Co-Chair's offices - Drs. Judith Hochman - St. Luke's-Roosevelt Hospital, New York, NY and Gervasio Lamas - Mount Sinai Medical Center, Miami, FL), Data Coordinating Center (DCC) (Maryland Medical Research Institute, P.I. Dr. Genell Knatterud), Economics and Quality of Life Coordinating Center (EQOL) (Duke Clinical Research Institute, P.I. Dr. Daniel Mark) and Angiography Core Laboratory (University of British Columbia, P.I's. Drs. G.B. John Mancini and Christopher Buller).

4.1 Clinical Coordinating Center

The Clinical Coordinating Center (CCC) and Study Chair's office is located at St. Luke's-Roosevelt Hospital Center. The Study Co-Chair's office is at Mt. Sinai Medical Center, Miami, FL. Dr. Judith Hochman Chair, and Co-Chair Dr. Gervasio Lamas will be responsible for scientific and administrative oversight of the trial. The CCC functions as a clinical trial center and is responsible for all aspects of conducting this trial, including protocol development and amendments, site recruitment and retention, regulatory documentation, protocol adherence, site

reimbursement and leadership in data analysis, study presentations and publications. Dr. Venu Menon (Co-Investigator) and a Project Manager will assist them.

4.2 Data Coordinating Center

The Data Coordinating Center (DCC) is responsible for the treatment allocations of eligible patients, receipt and processing of all data collected by the Clinical Sites and Central Units except economic data, quality control programs, and analysis of all study data except economic and quality of life data. DCC staff will prepare data reports at specified intervals for review by independent DSMB and will collaborate with other study investigators in the preparation of study presentations and publications.

4.3 Economic and Quality of Life Coordinating Center

In collaboration with the Clinical Coordinating Center and the Data Coordinating Center, the Economics and Quality of Life Coordinating Center will perform the following major functions: 1) obtain baseline economic status and quality of life data from all patients enrolled at each participating study site at the time of randomization; 2) collect detailed health resource consumption data from the index hospitalization; 3) assess detailed Economics and Quality of Life data at 4 months, 1 year and 2 years after enrollment; 4) assess angina and heart failure-related functional status by telephone contacts every 4 months during study follow-up; 5) identify all major medical encounters that occur during follow-up and collect detailed health care resource consumption data and cost data for each; 6) compare cost and quality of life outcomes for the two treatment arms according to intention-to-treat; 7) estimate the incremental cost effectiveness ratio for the experimental arm and perform extensive sensitivity analyses.

4.4 The Angiography Core Laboratory

The Angiography Core Laboratory (ACL) personnel are responsible for: 1) development of training material and certification of enrolling clinical sites and 2) quality control for screening angiograms and PTCA/stent procedures. The latter will be accomplished by review of all angiograms/PTCA from all sites. All coronary angiograms and ventriculograms obtained from the revascularization and the medical management groups will be sent to the ACL within 30 days of discharge. The Angiography Core Lab will review the films for extent of CAD (number of diseased vessels and severity of stenosis), TIMI flow, frame counting, collateral grades, thrombus grades, and LVEF when a LV gram is included. Evaluation of angioplasty success will be made using TIMI criteria. Change in stenosis severity will be measured. As all infarct-related arteries are occluded, quantitative coronary angiography is not necessary. The ACL will read and return the films to the site within 30 days.

4.5 The Executive Committee

This is the primary decision-making body for the study. Members include the Study Chair and Co-Chair, Principal Investigator (PI) and Co-PI from the DCC, and a *National Heart, Lung and Blood Institutes* (NHLBI) project officer, Angiography Core Lab Co-director, EQOL CC Director, Canadian consortium leader and selected other country leaders.

4.6 The Steering Committee

The Steering Committee will include the Executive Committee members, and investigator leaders of consortia of participating hospitals and a representation of Investigators who provide unique expertise. The role of the Steering Committee is to address protocol issues, facilitate communication between local investigators and keep local investigators involved and aware of the progress of the study. On issues requiring a vote, only one vote will be allowed per center. The Steering Committee will meet 2-3 times a year, i.e., during the national meetings of the American Heart Association, American College of Cardiology and possibly the European Society of Cardiology to review the progress of the trial. They will report to the Executive Committee and will include members from the Executive Committee.

4.7 Mortality and Morbidity Classification Committee

The members of this committee will be independent of the OAT study, e.g., not participating OAT investigators and will be blinded to treatment assignment. This committee will review abstracted clinical data to determine when primary endpoints and major events have occurred. All criteria and definitions will be pre- specified in detail in the manual of operations

4.8 Operations Committee

The Operations Committee will include an NHLBI project officer, Study Chair and Co-Chair, DCC Principal Investigator, DCC Project Manager, CCC Project Coordinator and EQOL CC Principal Investigator and Coordinator. This committee will have regular conference calls to review trial enrollment, conduct of the protocol, feasibility (patient burden, site burden, cost), scientific merit and issues raised by the site and core laboratories. The Angiography Core Laboratory Co-Director will join the conference call every other month. Such calls will ensure smooth day-to-day operations of the trial and help to identify issues that need to be brought before the Steering Committee. For the first two years of the trial there will be weekly conference calls, then biweekly.

4.9 Data and Safety Monitoring Board

The Data Safety and Monitoring Board (DSMB) will be appointed by and report to the NHLBI director. The DSMB will monitor accruing data in order to confirm that the patients in the trial are being cared for safely. The DSMB will be responsible for:

A. The adequate implementation of the treatment arms.
B. Ensuring data quality.
C. Amendments to the trial protocol if warranted.
D. Reviewing interim analyses and recommending early stopping or continuation of the trial.

The DCC and the Executive Committee provide input to this committee as requested. The DSMB will meet at least once a year and review trial data by conference call every six months.

4.10 Publications, Presentations and Ancillary Studies (PPAS) Committee

This is a 6-10 member committee, which reviews all proposals for, and final versions of research abstracts, presentations and manuscripts to be submitted to journals and national meetings. The committee will also review proposals for ancillary studies.

References

1. Wittels EH, Hay JW, Gotto AM. Medical costs of coronary artery disease in the United States. *AJC* 1990;65:432-40.

2. Kim CB, Braunwald E. Potential benefits of late reperfusion of infarcted myocardium, The open artery hypothesis. *Circ* 1993;88:2426-36.

3. Ross J. Left ventricular function after coronary artery reperfusion. *AJC* 1993;72:91G-97G.

4. Sabia PJ, Powers ER, Ragosta M, et al. An association between collateral blood flow and myocardial viability in patients with recent myocardial infarction. *NEJM* 1992;327(26):1825-31.

5. Galvani M, Ottani F, Ferrini D, et al. Patency of the infarct-related artery and left ventricular function as the major determinants of survival after Q-wave acute myocardial infarction. *AJC 1993*;71(1):1-7.

6. Hochman JS, Choo H. Limitation of myocardial infarct expansion by reperfusion independent of myocardial salvage. *Circ* 1987;75(1):299-306.

7. Hale SL, Kloner RA. Left ventricular topographic alterations in the completely healed rat infarct caused by early and late coronary artery reperfusion. *AHJ* 1998; 116: 1508-13.

8. Brown EJ Jr, Swinford RD, Gadde P, et al. Acute effects of delayed reperfusion on infarct shape and left ventricular volume: a potential mechanism of additional benefits from thrombolytic therapy. *JACC* 1991;17(7):1641-50.

9. Cigarroa RG, Lange RG, Hillis RD. Prognosis after acute MI in patients with and without residual anteriograde coronary blood flow. *AJC* 1989;64:155-60.

10. White HD, Cross DB, Elliot JM, et al. Long term prognostic importance of patency of the infarct-related coronary artery after thrombolytic therapy for acute myocardial infarction. *Circ* 1994;89(1):61-67.

11. Lamas GA, Flaker GC, Mitchell G, et al. Effect of infarct artery patency on prognosis after acute myocardial infarction. The Survival and Ventricular Enlargement Investigators. *Circ* 1995;92(5):1101-9.

12. Welty FK, Mittleman MA, Lewis SM, et al. A patent infarct-related artery is associated with reduced long-term mortality after angioplasty for postinfarction ischemia and an ejection fraction <50%. *Circ* 1996;93(8):1496-501.

13. Gohlke H, Heim E, Roskamim H. Prognostic importance of collateral flow and residual coronary stenosis of myocardial infarct artery after anterior wall Q wave acute myocardial infarction. *Am J Cardiol* 1991;67:1165-1169.

14. Topol EJ, Califf RM, George BS, et al, for the TAMI Study Group. Insights derived from the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trials. *JACC* 1988;12 (Suppl A):24A-31A.

15. Brodie BR, Stuckey TD, Kissling G, et al. Importance of IRA patency for recovery of LV function and late survival after primary PTCA for acute MI. *JACC*, 1996; 28(2): 319-25.

16. Lundergan CF, Reiner JS, Ross AM. Determinants of 30 day and 1 year mortality in acute myocardial infarction: benefit of early angiography. *JACC* 1996;27:153A.

17. Survival and Ventricular Enlargement (SAVE), personal communication, Gervasio Lamas

18. White HD. Mechanism of late benefit in ISIS-2. *Lancet* 1988;2(8616):914.

19. Hochman JS. Has the time come to seek and open all occluded infarct related arteries after myocardial infarction? *JACC* 1996;28:846-848.

20. Topol EJ, Califf RM, Grines CL, and the Thrombolysis and Angioplasty in Myocardial Infarction - TAMI 6 Study Group. A randomized trial of late reperfusion therapy for acute myocardial infarction. *Circ* 1992;85:2090-2099.

21. Dzavik V, Beanlands DS, Davies RF, et. al. Effects of late percutaneous transiuminal coronary angioplasty of an occluded infarct-related coronary artery on left ventricular function in patients with a recent (<6 weeks) Q-wave acute myocardial infarction (Total Occlusion Post-Myocardial Infarction Intervention-Study [TOMIIS-A pilot study). *AJC* 1994;73(12):856-61.

22. Horie H, Takahashi M, Minai K, et. al. Long-term beneficial effect of late reperfusion for acute anterior myocardial infarction with percutaneous transluminal coronary angioplasty. *Circ*.1998;2377-82.

23. Yusuf S, Zucker D, Peduzzi P, et. al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994;344:563-570.

24. Pocock S, Henderson R, Rickards A, et. al. Meta-analysis of randomized trials comparing coronary angioplasty with bypass surgery. *Lancet* 1995;346:1184-1189.

25. Puma JA, Sketch MH Jr, Thompson TD et al. Support for the open artery hypothesis in survivors of acute myocardial infarction: analyses of 11,228 patients with thrombolytic therapy. *AJC* 1999;83:482-7.

26. Antoniucci D, Santoro GM, Bolognese R, et al. Elective stenting inacute myocardial infarction: preliminary results of the Florence Randomized Elective Stenting in Acute Coronary Occlusion (FRESCO) study. *JACC* 1997;29:456 A.

27. Elezi S, Kastarati A, Herzzentiurm D, et al. Stent placement in chronic versus acute coronary occlusion: 6 month angiographic follow-up. *Circ* 1997;96(8); I-269.

28. Puma JA, Sketch MH, Tcheng JE, et al. Percutaneous revascularization of chronic coronary occlusions-an overview. *JACC* 1995;26(1):1-11.

29. Stone GW, Rutherford BD, McConahay DR, et al. Procedural outcome of angioplasty for total coronary occlusion: An Analysis of 971 lesions in 905 patients. *JACC* 1990;15(4):849-56.

30. Buller CE, Dzavik V, Carere RG, et al. Primary stenting versus balloon angioplasty in occluded coronary arteries: The Total Occlusion Study of Canada (TOSCA). *Circ* 1999;100:236-42.

31. Park SW, Park SJ, Hong, S, et al. Intracoronary stenting in patients with acute myocardial infarction. *JACC* 1997;29:456A

32. Serruys PW, deJaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent study group. *NEJM* 1994;331(8):489-95

33. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *NEJM* 1994;331(8):489-501.

34. Califf RM, Topol EJ, Gersh BJ. From myocardial salvage to patient salvage in acute myocardial infarction: the role of reperfusion therapy. *JACC* 1989;14(5):1382-8.

35. Hillis LD, Lange RA. Time for a randomized trial of the " open artery hypothesis" in survivors of acute myocardial infarction. *AJC* 1992;69:1359-60

36. White HD. Should all occluded infarct-related arteries be opened? *Eur Heart J* 1997;18:1207-1209

37. Guetta V, Topol EJ. Pacifying the infarct vessel. *Circ* 1997;96:713-715.

38. Ryan T, et al. ACC/AHA Guidelines for the management of patients with acute MI. *JACC 1996*; 28(5)1328-428.

39. The TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. *Circ* 1994;89:1545-1556.

40. ACC National Cardiovascular Data Registry. Core Data Element Documentation, Maryland 1998.

41. Myocardial infarcation and coronary deaths in the World Health Organization. MONICA Project. *Circ* 1994;90:583-612.

42. Alderman E, Stadius M. The angiographic definitions of the Bypass Angioplasty Revascularization Investigation. (BARI) *CAD* 1992;3:1189-1207.

43. CASS Investigators, Killip T, Fisher LD, Mock MB. National Heart, Lung, and Blood Institute Coronary Artery Surgery Study (CASS): a multicenter comparison of the effects of randomized medical and surgical treatment of mildly sympotmatic patients with coronary artery disease, and a registry of consecutive patients undergoing coronary angiography. *Circ* 1981;63(Suppl I, part II):1-81.

44. Rutherford JD, Pfeffer MA, Moye LA, et al. Effects of captopril on ischemic events after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. *Circ* 1994;90:1731-1738.

45. Stroke Prevention in Atrial Fibrillation Study Group Investigators. Special Report. Preliminary report of the Stroke Prevention in Atrial Fibrillation Study. *NEJM* 1990;322(12) 863-863.

46. Califf RM, Abdelmeguid AK, Kuntz RE, et al. Myonecrosis after revascularization procedures. *JACC* 1998;31:241-251.

47. Torrance GW. Utility approach to measuring health-related quality of life. *J Chron Dis 1987;40:595-600.*

48. Terrin ML. Individual subject random assignment is the preferred means of evaluating behavioral lifestyle modification. *Controlled Clinical Trials* 1997;18:500-505.

49. Peto R, Pike MC, Armitage N, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part 2. Analysis and examples. *Br J Cancer* 1977; 35:1-39.

50. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53:457-81.

51. Cox DR. Regression models and life tables. *J R Stat Soc B* 1972; 34:187-220.

Occluded Artery Trial

Appendix 1

Routine Medical Care

ACC/ AHA Guidelines for the Management of Patients with Acute Myocardial Infarction AHCPR Heart Failure Guidelines: Management of Patients with Left Ventricular Systolic Dysfunction

Appendix 1

Routine Medical Care

Recommended medical treatment for all patients enrolled in the OAT trial is based on current AHA/ACC guidelines. Uniformity of medical treatment in both groups is important in this trial designed to test percutaneous intervention in addition to medical therapy. A summary of recommended therapies is presented below and is dealt with in greater detail on subsequent pages.

Risk Factor Modification

1. **Cholesterol Lowering Therapy:** All patients in the OAT trial have documented coronary artery disease and an index myocardial infarction. A target LDL of <100 mg/dL is hence the recommended goal. Therapy with an AHA step II diet should be initiated in all patients. For those with LDL >125mg/dL on a step II diet, a HMG Co-A reductase inhibitor should also be initiated. For the group with HDL <35 mg/dL, therapy with gemfibrizol or niacin is recommended.

2. **Smoking:** Cessation should be recommended for all active smokers during their index medical admission.

3. **Diabetes:** Strict diabetic management to achieve euglycemia should be practiced.

4. **Hypertension:** Blood pressure management to achieve JNC VI targets is strongly advocated.

5. **Lifestyle Modification:** Appropriate physical exercise regimens in sedentary patients and behavioral modification should be addressed for all patients during index hospital stay and follow-up. Cardiac rehabilitation programs are strongly encouraged but not mandated.

Medical Therapy

Prevention of future events:
The use of aspirin and beta-blockers are of proven benefit for secondary prevention of death and MI. Long-term ACE inhibitors, especially in the setting of left ventricular dysfunction (LV) or symptomatic heart failure also improve long-term prognosis. Furthermore, because OAT selects for patients at increased risk of progressive LV dilatation, it is recommended for all OAT patients without contraindications.

Relief of Angina:
The use of beta-blockade, short or long-term nitrate therapy is recommended for the relief of symptomatic chronic stable angina. Calcium channel antagonists may be added as needed if LV function is preserved.

.

ACC/ AHA Guidelines for the Management of Patients with Acute Myocardial Infarction
Ryan TJ, Antman EM, Brook NH, Califf RM, Hillis LD, Hiratzka LF, Rapaport E, Riegel B, Russell RO, Smith EE, Weaver D. 1999 Updated Guidelines-*JACC* Sept. 1999.

Secondary Prevention

Management of Lipids

Recommendations

Class 1

1. The AHA Step II diet, which is low in saturated fat and cholesterol (less than 7% of total calories as saturated fat and less than 200 mg/d cholesterol), should be instituted in all patients after recovery from an acute MI.
2. Patients with LDL cholesterol levels greater than 125 mg/dL despite the AHA Step II diet should be placed on drug therapy with the goal of reducing LDL to less than 100 mg/dL.
3. Patients with normal plasma cholesterol levels who have a high-density lipoprotein (HDL) cholesterol level less than 35 mg/dL should receive nonpharmachological therapy (e.g., exercise) designed to raise it.

Class IIa

1. Drug therapy may be added to diet in patients with LDL cholesterol levels less than 130 mg/dL but greater than 100 mg/dL after an appropriate trial of the AHA Step II diet alone.
2. Patients with normal total cholesterol levels but HDL cholesterol less than 35 mg/dL despite dietary and other nonpharmachological therapy may be started on drugs such as niacin to raise HDL levels.

Class IIb

1. Drug therapy using either niacin or gemfibrozil may be added to diet regardless of LDL and HDL levels when triglyceride levels are greater then 200 mg/dL.

Smoking Cessation
Smoking cessation is essential in patients following acute MI. Smoking triggers coronary spasm, reduces the anti-ischemic effects of β-adrenoceptor blockers, and doubles mortality after acute MI. Smoking cessation reduces rates of reinfarction and death within one year of quitting, but one third to one half of patients who had an MI relapse within 6 to 12 months.

Houston-Miller and Taylor advocate a stepped approach to smoking cessation:

- Provide a firm, unequivocal message to quit smoking
- Determine if the patient is willing to quit
- Determine the best quitting method
- Plan for problems associated with withdrawal
- Set a quit date
- Help the patient cope with urges to smoke
- Provide additional help as needed
- Follow up by telephone call or visit

Nicotine gum and patches have been shown to mitigate symptoms of nicotine withdrawal in recovering patients. These agents are not recommended during hospitalization due to sympathomimetic effects of the active ingredient nicotine. However, the dose of nicotine in gums and patches is significantly lower than that found in cigarettes and may be preferable to cigarette smoking if the patient is experiencing acute withdrawal. Clonidine has been shown to be effective in women but not men, the reason for this finding is unclear. Lobeline has not been shown to have any advantage over placebo but is again under investigation.

Long-Term Use of Aspirin

The long-term use of aspirin in the post-infarct patient also results in a significant reduction in subsequent mortality. In six randomized, placebo-controlled trials in which patients were randomly selected between 1 week and 7 years after the initial infarct, meta-analysis reveals a reduction in vascular mortality of 13% among those randomly assigned to aspirin with a reduction in nonfatal reinfarction of 31% and nonfatal stroke of 42%. Although all of these trials involved the use of aspirin in doses ranging from 300 to 1500 mg/d, a recent trial of patients with chronic stable angina pectoris in which aspirin 75 mg/d was used demonstrated a significant reduction of 34% in the primary endpoint of nonfatal MI and sudden death. This suggests long-term use of aspirin in the postinfarction patient in a dose as low as 75 mg/d can be effective, with the likelihood that side effects can be reduced. Clopidigrel may be used as an alternative in aspirin allergic patients. Ticlopidine, an antiplatelet agent that has been effectively used in unstable angina and cerebrovascular disease, has not been studied in major clinical trials involving patients with acute MI. Other antiplatelet agents such as sulfinpyrazone and dipyridamole have been used in the post-infarct patient, but there is no evidence from these clinical trials that they were any more efficacious than aspirin alone

Angiotensin Converting Enzyme Inhibitors

ACE inhibitors are also of value in selected patients who have recovered from an acute infarction through their ability to interfere with ventricular remodeling and thus attenuating ventricular dilation over time. The clinical result is a lessened likelihood for development for CHF and death. In addition, the likelihood of a recurrent MI may also be reduced.

The expression of tissue ACE within the heart probably arises from vascular endothelium. In the setting of myocardial necrosis and fibrosis, relatively high concentrations of ACE can be found in the myocardium compared with normal ventricular myocardium. These observations, coupled with experience in both rat model of MI and large randomized clinical trials, have established that use of ACE inhibitors begun after a patient has recovered from acute MI improves long-term survival, provided the infarct was large and anterior in location and results in significant impairment of LV contractility. Specifically, in the Survival and Ventricular Enlargement (SAVE) trial, patients received captopril at a mean 11 days after onset of infarction, resulting in approximately 20% reduction in mortality. The Acute Infarction Ramipril Efficacy (AIRE) trial, in which patients who had been in clinical heart failure during the first day of their infarct and were then randomly assigned an average of 5 days after onset of infarction to either ramipril or placebo, resulted in an approximate risk reduction of 27% in all-cause mortality. Similarly, the Trandolapril Cardiac Evaluation (TRACE) trial, in which patients with LV dysfunction on

echocardiogram were randomly assigned to receive either trandolapril or placebo a median of 4 days after onset of infarction, demonstrated a 22% reduction in mortality.

The Studies of Left Ventricular Dysfunction (SOLVD) trial evaluated the ACE inhibitor enalapril in 4228 asymptomatic patients with LV ejection fraction less than 0.35, 80% of whom had experienced a prior MI. However, randomization was carried out considerably later on the average than in the SAVE and AIRE trials. The prevention arm of the SOLVD trial revealed a trend toward improved mortality but not a statistically significant difference. On the other hand, SOLVD did demonstrate a significant risk reduction of 20% for the combined endpoints of death or development of CHF requiring hospitalization.

In secondary analyses of the ACE inhibitor trials, the benefit of treatment appears to be primarily in patients with anterior infarctions of LV ejection fraction below 40%. Some rationale exists for the use of these drugs in all patients after MI, based on the observation in the SAVE trial that the likelihood of recurrent MI was reduced by approximately 25% in treated patients. However, this finding is based on post hoc analysis and is currently being studied in prospective trials. There is also preliminary evidence that patients who express a homozygous deletional form of the ACE gene (dd) have an increased circulating ACE level and are more likely to develop MI than those with the II allele gene. This reasoning is also supported by recent observations that myocardial levels of ACE are also higher in patients expressing the dd gene.

Beta-Adrenoreceptor Blockers
Recommendations for Long-Term Therapy in Survivors of Myocardial Infarction

Class I

1. All but low-risk patients without a clear contraindication to Beta-adrenoreceptor blocker therapy. Treatment should begin within a few days of the event (if not initiated acutely) and continue indefinitely.

Class IIa

1. Low-risk patients without a clear contraindication to Beta-adrenoreceptor blocker therapy.
2. Survivors of non-ST elevation MI.

Class IIb

1. Patients with moderate or severe LV failure or other relative contraindications to Beta-adrenonceptor blocker therapy provided they are monitored closely.

Class III

None.

Anticoagulants
Recommendations for Long-Term Anticoagulation After Acute Myocardial Infarction (AMI)

Class I

For secondary prevention of MI in post-MI patients unable to take daily aspirin.

Post-MI patients in persistent AF.
Patients with LV thrombus.

Class IIa

1. Post-MI patients with extensive wall motion abnormalities.
2. Patients with paroxysmal AF.

Class IIb

1. Post-MI patients with severe LV systolic dysfunction with or without CHF.

The indications for long-term anticoagulation after acute MI remain controversial. A series of studies comparing warfarin with conventional therapy has demonstrated a reduction in risk of death of 13% and reduction in relative risk of both stroke and reinfarction of 41%. The lack of aspirin use in the control groups in these trials has made it difficult to assess the relative merits of aspirin alone versus warfarin alone. Although cost-effectiveness analysis demonstrates that warfarin compared with standard therapy without aspirin meets the general criteria for cost-effective therapy, the more impressive cost-effectiveness of aspirin makes aspirin alone the current standard antithrombotic regimen for secondary prevention Although an ample theoretical rationale can be developed for using aspirin and warfarin in combination as a secondary preventive strategy, inadequate empirical information currently exists to recommend it at this time. In a recent report evaluating 160 mg aspirin versus 80 mg aspirin plus 3 mg warfarin versus 80 mg aspirin plus 1 mg warfarin, there was no evidence that combined low-dose aspirin and warfarin reduced subsequent events in 8800 patients after MI. Thromboembolic stroke rates tended to be higher in low-dose warfarin-treated patients as well.

The previous ACC/AHA guidelines strongly recommended the use of oral anticoagulants with an International Normalized Ratio (INR) ratio of 2.0 to 3.0 in patients with a ventricular mural thrombus or a large akinetic region of the left ventricle for at least 3 months. Despite a number of small observational studies demonstrating a higher risk of embolic stroke in patients with large anterior infarction and a better outcome in patients with warfarin after demonstration of LV mural thrombus by echocardiography, randomized controlled trials are not available to support this recommendation. Concern exists that patients at lower risk were treated in the observational studies, so that a firm recommendation based on empirical information cannot be made. Warfarin is indicated in patients with persistent AF after MI, based on results of multiple trials in other patients with AF.

Calcium Channel Blockers

Calcium channel blockers are not presently recommended for routine treatment or secondary prevention after acute MI. In general, calcium channel blockers should be reserved to treat the subset of patients with angina or hypertension inadequately controlled by other agents. If Beta-adrenoreceptor blockers are contraindicated or poorly tolerated, calcium antagonists that slow heart rate (such as verapamil or diltiazem) may be appropriate as an alternative for secondary prevention in those patients with preserved LV function.

.

Estrogen Replacement Therapy and MI

1. Hormone replacement therapy (HRT) with estrogen plus progestin for secondary prevention of coronary events should not be given de novo to post menopausal women after AMI.
2. Post menopausal women who are already taking HRT with estrogen plus progestin at the time of an AMI can continue this therapy.

Recommended Medical Practice

Heart Failure: Management of Patients with Left Ventricular Systolic Dysfunction
(U.S. Department of Health and Human Services. AHCPR Guidelines Publication No. 94-0613 June 1994)

Hospital Management
The presence or suspicion of heart failure and any of the following findings usually indicate a need for hospitalization:

- Clinical or electrocardiographic evidence of acute myocardial ischemia.
- Pulmonary edema or severe respiratory distress.
- Oxygen saturation below 90 percent (not due to pulmonary disease).
- Severe complicating medical illness (e.g., pneumonia).
- Anasarca.
- Symptomatic hypotension or syncope.
- Heart failure refractory to outpatient therapy.
- Inadequate social support for safe outpatient management.

Occasionally, patients with one of the above findings may be managed at home or in an assisted living or nursing home setting if the clinician believes it is safe to do so and adequate follow-up can be arranged. Heart failure is one of the most common causes for recurrent admission to hospitals, and many of these admissions may be avoidable. Readmission rates as high as 57 percent within 90 days have been reported in patients over the age of 70 years. Proper discharge planning is essential to prevent those unnecessary readmissions.

Patients with heart failure should be discharged from the hospital only when:

- Symptoms of heart failure have been adequately controlled.
- All reversible causes of morbidity have been treated or stabilized.
- Patients and caregivers have been educated about medications, diet, activity, and exercise recommendations, and symptoms of worsening heart failure.
- Adequate outpatient support and follow-up care have been arranged.

Patients who have been hospitalized for heart failure should be seen or contacted within 1 week of discharge to make sure that they are stable in the outpatient setting and to check their understanding of and compliance with the treatment plan. This guideline does not address

management strategies specific to the hospital setting (e.g., invasive hemodynamic monitoring, intravenous dobutamine).

Clinical Volume Overload

During initial evaluation, the clinician should determine if the patient manifests symptoms or signs of volume overload including orthopnea, paroxysmal nocturnal dyspnea, dyspnea on exertion, pulmonary rales, a third heart sound, jugular venous distention, hepatic engorgement, ascites, peripheral edema, and pulmonary vascular congestion or pulmonary edema on chest x-ray.

Patients suspected of heart failure with signs of significant volume overload should be started immediately on a diuretic. Patients with mild volume overload can be managed adequately on thiazide diuretics, while those with more severe volume overload should be started on a loop diuretic. Patients with severe volume overload may require intravenous loop diuretics and/or hospitalization.

Left-Ventricular Function

Measurement of left-ventricular performance is a critical step in the evaluation and management of almost all patients with suspected or clinically apparent heart failure. The combined use of history, physical examination, chest radiography, and electrocardiography does not appear to be reliable in determining whether a patient's symptoms and physical findings are due to dilated cardiomyopathy, left-ventricular diastolic dysfunction, valvular heart disease, or a noncardiac etiology. Therefore, echocardiography or radionuclide ventriculography can substantially improve diagnostic accuracy.

Patients with suspected heart failure should undergo echocardiography or radionuclide ventriculography to measure left-ventricular ejection fraction (if information about ventricular function is not available from previous tests).

Most patients with signs and symptoms of heart failure are found to have EF's less than 40 percent. Patients with an EF of 40 percent or greater may still have heart failure on the basis of valvular disease or stiffness of the ventricular wall (diastolic dysfunction). The recommendations contained in this *Quick Reference Guide for Clinicians* are designed for patients with heart failure due to left-ventricular systolic dysfunction, i.e., EF's less than 35-40 percent.

General Counseling

Patients with heart failure should be informed about their diagnoses including the prognosis, symptoms of worsening heart failure, and what to do if these symptoms occur. Information should also be provided concerning the benefits of regular activity, dietary restrictions, necessary medications, and the importance of compliance with recommendations. It is vital that patients understand their disease and be involved in developing the plan for their care. In addition, family members and other responsible caregivers should be included in counseling and decision making sessions.

Activity. Regular exercise such as walking or cycling should be encouraged for all patients with stable heart failure. Even short periods of bedrest result in reduced exercise tolerance and aerobic capacity, muscular atrophy, and weakness. Recent studies show that patients with heart failure can exercise safely, and regular exercise may improve functional status and decrease symptoms.

An explanation of the importance of exercise can help prevent patients from becoming afraid to perform daily activities that might provoke some shortness of breath. Patients should be advised to stay as active as possible.

There is insufficient evidence at this time to recommend the routine use of formal rehabilitation programs for patients with heart failure, although patients who are anxious about exercising on their own or are dyspneic at a low work level may benefit from such programs.

Diet. Dietary sodium should be restricted to as close to 2 grams per day as possible. In no case should sodium intake exceed 3 grams daily. Alcohol use should be discouraged. Patients who drink alcohol should be advised to consume no more than one drink per day. One drink equals a glass of beer or wine, or a mixed drink or cocktail containing no more than 1 ounce of alcohol. Patients with heart failure should be advised to avoid excessive fluid intake. However, fluid restriction is not advisable unless patients develop hyponatremia. Patients should be advised to keep a diary of their daily weights and to advise the clinicians if a weight gain of 3-5 pounds or more occurs within 1 week or since the previous visit with the clinician.

Medications. Medications are prescribed for patients with heart failure for two basic reasons: (1) to reduce mortality (angiotensin-converting enzyme [ACE] inhibitors, isosorbide dinitrate/hydralazine) and (2) to reduce symptoms and improve functional status (ACE inhibitors, diuretics, digoxin). Patients should be provided with complete and accurate information concerning the medications they are being asked to take, including the reasons the medications are being prescribed, dosing requirements, and possible side effects.

Compliance. Because noncompliance is a major cause of morbidity and unnecessary hospital admissions for heart failure, educational programs or support groups can be very helpful in the care of patients with heart failure. Noncompliance may reduce life expectancy (e.g., if patients are not taking beneficial medications) and is also a major cause of hospitalizations. Practitioners should be aware of the problem of noncompliance and its causes and should discuss the importance of compliance at follow-up visits and assist patients in removing barriers to compliance (e.g., cost, side effects, or complexity of the medical regimen).

Initial Pharmacological Management

Diuretics. Diuretics are extremely useful for reducing symptoms of volume overload, including orthopnea and paroxysmal nocturnal dyspnea. As noted above under "Clinical Volume Overload" diuretics should be started immediately when patients present with symptoms or signs of volume overload.

Although initiation of diuretics is important in these patients, it is also important to avoid overdiuresis before starting ACE inhibitors. Volume depletion may lead to hypotension or renal insufficiency when ACE inhibitors are started or when the doses of these agents are increased to full therapeutic levels. After the ACE inhibitor is increased to full therapeutic levels, additional diuretic therapy may be necessary to optimize the patient's status.

ACE Inhibitors. Because of their beneficial effects on mortality risk and functional status, ACE inhibitors should be prescribed for all patients with left-ventricular systolic dysfunction unless specific contraindications exist (i.e., history of intolerance or adverse reactions to these agents, serum potassium >5.5 mmol/L, or symptomatic hypotension). Patients with contraindications to ACE inhibitors or who cannot tolerate them should be placed on isosorbide dinitrate/hydralazine**, or direct angiotensin receptor blockers.**

ACE inhibitors may be considered as sole therapy in patients who present with fatigue or mild dyspnea on exertion and who do not have any signs or symptoms of volume overload. Diuretics should be added if symptoms persist in these patients despite ACE inhibitors or if volume overload develops at a later time.

Digoxin. Digoxin increases the force of ventricular contraction in patients with left-ventricular systolic dysfunction. Although physical functioning and symptoms may be improved with digoxin, its effect on mortality is not known. Digoxin should be initiated along with ACE inhibitors and diuretics in patients with severe heart failure. Patients with mild-to-moderate heart failure will often become asymptomatic on optimal doses of ACE inhibitors and diuretics; these patients do not require digoxin. Digoxin should be added to the therapeutic regimen of those patients whose symptoms persist despite optimal doses of ACE inhibitors and diuretics.

Anticoagulation. Routine anticoagulation is not recommended. Patients with a history of systemic or pulmonary embolism or recent atrial fibrillation should be anticoagulated to a prothrombin time ratio of 1.2—1.8 times each individual control time (International Normalization Ratio of 2.0—3.0). Although there has never been a controlled trial of anticoagulation for patients with heart failure, the risks of routine treatment, including intracranial or gastrointestinal hemorrhage, do not appear warranted given the relatively low incidence of significant thromboembolic events in this population.

Additional Pharmacological Management

Patients with persistent dyspnea after optimal doses of diuretics, ACE inhibitors, and digoxin should be given a trial of hydralazine and/or nitrates. The addition of a vasodilator to an ACE inhibitor may also relieve symptoms. Direct vasodilators may be particularly helpful in patients with hypertension or evidence of severe mitral regurgitation. Even patients with blood pressure in the usual normal range may benefit by reducing their blood pressure with direct vasodilators. Alternatively, if a patient primarily has symptoms of pulmonary congestion or has a low systolic blood pressure, nitrates are preferred over arterial vasodilators.

There is evidence that gradually incremental therapy with low dose beta blockers may produce long-term improvements in symptoms and in natural history in patients with heart failure. However, because beta blockers may also cause acute deterioration in patients with heart failure, this form of treatment **is not currently indicated for decompensated Class IV CHF**.

Heart Transplantation

Consideration should be given to cardiac transplantation in patients with severe limitation and/or repeated hospitalization because of heart failure, despite aggressive medical therapy, and in whom revascularization is not likely to convey benefit. Patients with severe symptoms should be referred

to a cardiologist to ensure that medical therapy is optimized prior to referral for possible transplantation. Practitioners should refer to existing documents concerning heart transplantation for further information on patient selection criteria.

Patients with poor systolic function whose symptoms are controlled on optimal medical management need not be referred for transplantation. Where appropriate, patients with severe symptoms uncontrolled by optimal medical management who are unable to obtain a heart transplant should be informed of the availability of experimental treatment protocols for which they may be eligible (e.g., new drugs, mechanical assist devices).

NOTE: Bold items are modifications of the AHCPR document.

Occluded Artery Trial

Appendix 2

Statistical Considerations

Appendix 2

Statistical Considerations

A2.1 Study Size

The number of patients required for the Occluded Artery Trial was calculated based on the assumptions stated in the first paragraph of Section 3.18 of the OAT Protocol and based on the analysis plan to compare the occurrence of the primary endpoint in the two treatment groups using the log-rank test.[1] The total number of events (D) required for the study was estimated using the following formula:[2]

$$D = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2}{(\ln(rr))^2 \cdot P_r(\text{Event}) \cdot (1-P_r(\text{Event}))}$$

In the denominator, ln(rr) is the natural logarithm of the hazard rate ratio. Table 1 shows the values of D for alpha =0.0484 and for power 0.8 and 0.9. Alpha is set at 0.0484 for the final analysis to take account of interim analyses (see Section A2.2 below).

TABLE 1
Number of Events Required to Detect
Specified Hazard Rate Ratios
(Alpha =0.0484)

	Hazard Rate Ratio					
Power	0.60	0.65	0.70	0.72	0.75	0.80
0.8	121	170	248	293	382	636
0.9	162	228	332	392	511	850

Once the values of D were determined, the number of patients required was calculated by dividing D by P_r(Event), that is, the probability that a patient selected at random will have one of the events (death, MI or Class IV CHF). Schoenfeld and Richter[3] show the conditional probability of a patient having one of the events given treatment i to be:

$$P_r(\text{Event /trt i}) = 1 - \{(1- \exp(-\lambda_i \bullet A)) \bullet \exp(-\lambda_i F)/(\lambda_i \bullet A)\},$$

where A=24 months and F=27 months and under the assumption that accrual is uniformly distributed and the event time has an exponential distribution. The unconditional probability is obtained by averaging the two conditional probabilities (under the assumption of 1:1 randomization). Relative risks (ratio of the probabilities of having the primary endpoint at three years) are converted to hazard rate ratios. A 25% reduction of a three-year incidence of 25% (relative risk =0.75) corresponds to a hazard rate ratio of 0.72. According to Schoenfeld's formula,[2] a hazard rate ratio of 0.72 requires 392 events (α=0.0484, 1-β=0.9). Calculating the unconditional probability of an event in the trial from the above formula indicated that 1,704 patients would be required for OAT under

the assumptions that all patients received their assigned treatment and were followed to the end of the study.

Study size was adjusted for the expected "crossover" rates in each treatment group. The proportion of patients who cross over (that is, do not receive the assigned treatment but instead receive the treatment expected for the comparison group) was estimated for each of the two treatment groups, and the number of patients is increased by the reciprocal of the square of one minus the sum of proportions of patients who cross over in each treatment group.[4] The participation of only highly committed investigators in OAT should minimize the number of crossovers in both treatment groups.

"Crossovers" in the revascularization group include: 1) those in whom PTCA/stent could not be performed for technical reasons; 2) those with failed PTCA/stent and 3) those who do not undergo PTCA/stent attempt due to death or withdrawal of consent, etc. The total of these crossovers is expected to be $\leq$8%. Selection of patients for the trial after angiography assures that only patients with angiographic characteristics associated with successful PTCA for IRA occlusions are enrolled. In the TOSCA Registry <8% of the attempts to cross the total occlusion with a guidewire failed.[5] Once the lesion was crossed, only 0.5% of PTCAs failed. TOSCA enrolled patients with chronic and recent occlusions with the former typically most difficult to cross with a guidewire. In OAT only patients with recent occlusions are eligible and primary failures should be less likely than for chronic occlusions. Also, in OAT patients are randomized only after they know that they have a coronary occlusion and that options for treatment include PTCA, therefore, we expect <3% will refuse to have PTCA after entry. The rate of death of this stable 3-28 day post-MI cohort in the $\leq$24-hour period between randomization and PTCA will be very low.

Crossovers in the medical therapy group include those who undergo PTCA or CABG of the index occluded IRA (not other coronaries). After six weeks this lesion becomes a chronic occlusion which is not optimally suited for PTCA. Revascularization subsequent to the occurrence of a primary endpoint event, MI Class IV CHF, is not a crossover. But revascularization for some other clinical event is considered a crossover for purposes of calculating study size for the primary endpoint. The crossover rate in the medical therapy group is expected to be $\leq$17% because enrolled patients are asymptomatic and have no severe inducible ischemia. Furthermore, the coronary anatomy is known prior to randomization, in contrast to many trials of direct invasive versus conservative strategy[6] where anatomy is unknown. Therefore, the patient and physician will consider all options for therapy based on knowledge of the angiographic findings prior to enrollment. Also, as the time interval between myocardial infarction and the contemplated PTCA lengthens, the patient becomes progressively less well suited for percutaneous coronary intervention of the now "chronic" total occlusion. A recent trial (DANAMI) of post-MI patients with significant inducible ischemia randomized to revascularization or medical therapy had a one-year medical group revascularization rate of 15%.[7] Although the medical practice in Denmark may be more conservative than that in the United States, patients with inducible ischemia would be expected to have a higher rate of crossover for revascularization than the patients enrolled in OAT, since patients with significant

inducible ischemia are not eligible for OAT. An upper bound on the crossover rate of 17% in the medical therapy group during the 27-51 month follow-up in our trial of asymptomatic patients with predominantly single vessel CAD and without significant inducible ischemia is reasonable.

In prior cardiology trials coordinated by MMRI, 95 to 100% of patients have had complete follow-up for vital status and occurrence of reinfarction. Thus, we have adjusted the required study size to account for 5% of patients lost to follow-up.

Assuming a 25% "crossover rate" for the two treatment groups combined and a 5% loss to follow-up rate, 3,189 [1,704/(0.75^2 x 0.95)] patients must be recruited to detect a 25% reduction in the event rate associated with revascularization and maintain 0.9 power. These considerations have resulted in specifying a goal of 3,200 patients for OAT.

The total number of patients for the trial is presented in Table 2 as a function of the three-year incidence of the primary endpoint in the medical therapy group and the risk reduction of this endpoint in the PTCA/stent group. A total of 3,189 patients will allow the detection of a 25% reduction in the three-year incidence of the primary outcome in the PTCA/stent group with 0.9 power if the three-year incidence of the primary outcome in the medical therapy group is at least 25% (Table 2. Part B). A total of 2,966 patients would be required to detect a 30% reduction with PTCA/stent therapy of the primary outcome with 0.8 power if the three-year incidence of the primary endpoint in the medical therapy group is only 15% (Table 2. Part A).

TABLE 2
Study Size by Three-Year Event Rate with Medical Therapy
and Risk Reduction with PTCA/Stent
(Alpha = 0.0484, 24 Months Recruitment and a
Minimum of 27 Months of Follow-up)

Three-year Event Rate		Risk Reduction				
Medical Therapy		40%	35%	30%	25%	20%
A.	Power = 0.8					
	0.10	2426	3298	4655	6930	11167
	0.15	1551	2105	2966	4403	7090
	0.20	1113	1507	2120	3145	5049
	0.25	850	1148	1611	2385	3821
B.	Power = 0.9					
	0.10	3244	4410	6224	9267	14932
	0.15	2074	2814	3966	5894	9481
	0.20	1488	2016	2835	4205	6751
	0.25	1136	1535	2155	3189	5110

The estimates of power in Table 3 show that the power with a total of 3,200 patients is $\geq$0.83 for 30% or greater reductions if the primary outcome event rate is only 15% in the medical therapy group. If the three-year incidence of the outcome measure in the

medical therapy group is 40% or higher, the proposed number of patients has power of $\geq$0.95 to detect reductions of 20%. Thus, if the frequency of the primary outcome measure is as high as 40% (a possibility given the preliminary data), the proposed size of the trial is large enough to rule out all but the smallest of benefits associated with revascularization.

TABLE 3
Power of the Trial by Three-Year Event Rate
With Medical Therapy and Risk Reduction with PTCA/Stent
N=3,200 with 24 Months Recruitment and 27-51 Months Follow-up
(Alpha=0.0484)

Three-year Event Rate	Risk Reduction								
	50%	45%	40%	35%	30%	25%	20%	15%	10%
0.10	0.99	0.96	0.90	0.79	0.64	0.48	0.32	0.19	0.11
0.15	1.00	1.00	0.98	0.93	0.83	0.66	0.47	0.28	0.15
0.20	1.00	1.00	1.00	0.98	0.93	0.81	0.60	0.38	0.19
0.25	1.00	1.00	1.00	1.00	0.98	0.90	0.73	0.47	0.24
0.30	1.00	1.00	1.00	1.00	0.99	0.96	0.82	0.57	0.29
0.35	1.00	1.00	1.00	1.00	1.00	0.98	0.90	0.67	0.35
0.40	1.00	1.00	1.00	1.00	1.00	0.99	0.95	0.76	0.42
0.45	1.00	1.00	1.00	1.00	1.00	1.00	0.98	0.83	0.49

After accounting for differing lengths of follow-up (27 months to 51 months), treatment crossovers and patients lost to follow-up, it has been determined that 3,200 patients will provide sufficient (power $\geq$0.81) to detect a 25% or greater reduction in the incidence of the primary outcome (first to occur of death, MI, or Class IV congestive heart failure) in the PTCA/stent group compared to medical therapy group if the incidence of the primary endpoint at three years is at least 20%.

Based on our registry and clinical experience, we believe we will be able to maintain an aggregate crossover rate (sum of the two crossover rates) that is less than 25%. Thus, we project excellent statistical power (more than 90%) to detect a 25% reduction in the primary endpoint in the intervention group compared with a 25% event rate in the medical therapy group. OAT will have acceptable power if the aggregate crossover rate is as high as 30%. However, should the aggregate crossover rate be above 30%, the intervention will have to produce larger reductions in risk for the study to have an adequate power. If the percent reduction is as high as 50% as observed in some prior studies, and the event rate is 25% in the medical therapy group, the study will have nearly 80% power even if the aggregate crossover rate is as high as 70% (e.g., 35% in each group). Moderate levels of crossover will not substantially affect the operating characteristics of OAT. If substantial crossover rates are encountered, the observed event rates and treatment effect sizes will have to be higher than the conservative event rates

and/or the conservative effect sizes we have hypothesized for the study to have adequate power. The crossover rates and event rates will be monitored by the Executive Committee and the Data and Safety Monitoring Board.

A2.2 Interim Monitoring

The first formal look or interim monitoring of the primary endpoint will be scheduled one year after the start of patient recruitment. Based on the assumptions given in Section A2.1, approximately 67 primary events would have been reported by 1 year after the start of patient recruitment. Interim monitoring reports will be prepared at approximately six-month intervals thereafter, so that differences in the primary outcome will be tested seven times (six interim analyses, and one final analysis) during the course of the study. Extreme evidence (α=0.001) of treatment differences will be required in the interim analyses to demonstrate the efficacy of the proposed intervention, while a p-value just under the conventional 0.05 will be required to reject the null hypothesis at the final analysis. The proposed nominal alpha levels of the monitoring plan for OAT were calculated using the program "NEWGLAN"[8] which is based on the methods of Lan and DeMets.[9]

TABLE 4
P-Values for Interim Analyses

Month of Study	Type of Report	p-value
15	Interim	0.001
21	Interim	0.001
27	Interim	0.001
33	Interim	0.001
39	Interim	0.001
45	Interim	0.001
56*	Final analysis	0.0484

*All follow-up is to be completed by month 54 of the study and two months are required to close the data files.

If appropriate, the Data and Safety Monitoring Board may decide to alter the above, either the number and/or the scheduled dates of the interim analysis; the method of Lan and DeMets[9] would then be used to determine the actual "spending" of the alpha over the course of the study.

A2.3 Subgroup Analyses of the Primary Outcome

A limited number of pre-specified subgroup analyses of the primary outcome will be carried out with Cox proportional hazards regression with each test performed at α-level =0.01. These tests include: 1) a test for interaction between gender and study treatment; 2) interaction between minority status and study treatment; 3) interaction between age ($\leq$70 versus >70 years) and study treatment; 4) interaction between time from index MI to recruitment and coronary anatomy (or severity of CAD) with study treatment; 5) interaction between MI location, [anterior (LAD occlusion) versus non-anterior] and study treatment; and 6) interaction between baseline ejection fraction and study

treatment. Other, 'a posterior' subgroup analyses that may be performed testing for interaction between treatment and baseline characteristics including angiographic characteristics should be regarded as exploratory or hypothesis-generating, since testing among multiple subgroups can easily lead to "finding" spurious differences that may be due to chance alone.

The formula for determining the required study size for detecting interactions between patient characteristics and treatment when the endpoint being considered is a time to event is similar to the formula used to determine the number of patients required to detect main effects for time to event endpoints.[10] The study size formula for interactions is:

$$D = \frac{2}{\rho(1-\rho)} \quad \frac{(Z_{\alpha/2} + Z_{1-\beta})^2}{(\ln (rr))^2}$$

where Z_α and $Z_{1-\beta}$ are the alpha and $(1-\beta)$ levels for the test under consideration, ρ indicates the proportion of patients with the characteristic, and D is the number of events expected in the study. In this formula, RR is the ratio formed by taking treatment risk ratio for patients with a certain characteristic and dividing that by the treatment risk ratio for patients without the characteristic (the interaction effect). Rewriting the above formula yields the following equation for evaluating power:

$$Z_{1-\beta} = \sqrt{\frac{D\,(\rho)\,(1-\rho)}{2}} \quad \left| \ln (RR) \right| - Z_\alpha$$

Using this formula, it can be shown that if Z_α is set to 1.645 (α=0.1), and D=400 events are observed in a clinical trial (the number of events expected in OAT), interactions of magnitudes similar to treatment main effects (e.g., 30% difference in the ratio of the relative risks), can be detected with 0.80 power to detect interaction when ρ=0.4, and 0.70 power when ρ=0.25. It is expected that at least 40% of the patients enrolled in OAT will be women (i.e., ρ=0.40) due to the extra effort the investigators will make to recruit women.

A2.4 Other Analyses

Non-proportionality of the hazards will be investigated by plotting log[-log(S(t))], in which S(t) is the survival function, for important stratifying variables such as age, race, gender and diabetes. Should the above function be non-parallel (and cross) for any of the specified variables, the primary analysis will be stratified by those variables. Cox proportional hazards models will be stratified for variables that demonstrate non-proportional hazards (crossing or non-crossing). As a global test for non-proportionality, we will compare marginal residuals for groups of patients by including a number of grouping variables to check the hypothesis that globally all residuals associated with

these variables are zero versus the alternative that they are different from zero. A graphical plotting technique for this analysis was developed by Schoenfeld[11] and a formal test was presented by Verweij et al.[12] Should this test prove to be significant, an extensive search for stratification variables will be undertaken to determine how the analysis should be stratified. Once determined, we will include these variables as stratification variables in the Cox regression. Analyses for the regressors will be summarized across the strata.

Differences between treatments in the occurrence of other clinical outcomes will be compared using chi-square tests for the occurrence of events in hospital (e.g., fatal or non-fatal stroke, recurrent ischemia in hospital, or hemorrhage), log-rank tests and survival plots for occurrence of events (e.g., non-protocol revascularizations) by year, and Mantel-Haenszel chi-square tests for trends of differences in ordinal outcomes (e.g., severity of angina ranked on the Canadian Cardiovascular Society Classification).

A variety of other analyses may be anticipated to meet the objectives of the Occluded Artery Trial and to take full scientific advantage of the data collected. These will include comparison of treatments on secondary outcome measures, and analyses of the association of various baseline factors with mortality and other outcomes. Such secondary analyses are exploratory in nature and will involve hypothesis generation more than hypothesis testing. Since strict control of the Type I error rate is not possible in such analyses, we propose that a p-value <0.01 be considered as showing some evidence of differences and a p-value <0.001 be considered as strong evidence of differences.

Intention to treat analysis of other events that are secondary outcomes and other outcomes will be performed using standard methods of analysis.

For outcomes that can be analyzed as time to events, the log-rank tests, will be used to test treatment differences. Adjusted analyses will be carried out with the Cox proportional hazards model. Survival curves will be estimated with Kaplan-Meier estimates and confidence intervals for the survival curves will be estimated using Greenwood's formula.[13]

For outcomes that can be analyzed as dichotomous categories, chi-square analyses will be used to compare the two treatment groups. Logistic regression[14] will be used to perform adjusted analyses of treatment differences for these outcomes.

For outcomes that can be analyzed as continuous variables, Student's t-test will be used to compare the treatments. The Wilcoxon rank sum test will be used for data with highly skewed distributions. Adjusted analyses will be performed using analysis of variance techniques.

Outcome variables such as CHF Class that can be collected repeatedly over time, will be analyzed using the Generalized Estimating Equations approach of Liang and Zeger.[15] This analysis procedure will allow for the analysis of binary or continuous outcome variables.

References

1. Peto R, Pike MC, Armitage N, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part 2. Analysis and examples. Br J Cancer 1977; 35:1-39.

2. Schoenfeld DA. Sample size formula for the proportional hazards regression model. Biometrics 1983; 39:499-503.

3. Schoenfeld DA, Richter JR. Nonograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. Biometrics 1982; 38:163-70.

4. Lachin JM, Foulkes MA. Evaluation of sample size and power for analyses of survival with allowance for nonuniform patient entry, losses to follow-up, noncompliance, and stratification. Biometrics 1986; 42:507-19.

5. Dzavik V, Marquis JF, Knudtson Met al. Total Occlusion Study of Canada (TOSCA). Presented at the American College of Cardiology Meetings, Atlanta, Georgia, 1998.

6. The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction. N Engl J Med 1989; 320:618-27.

7. Madsen JK, Grande P, Saunamaki k, et al. Danish Multicenter Randomized Study of invasive versus conservative treatment in patients with inducible ischemia after thrombolysis in acute myocardial infarction (DANAMI). Circulation 1994; 90(4):1706-14.

8. Reboussin DM, DeMets DL, Kim K, Lan KKG. Programs for computing group sequential bounds using the Lan-DeMets method. Technical Report #60 University of Wisconsin Department of Biostatistics, Madison, 1992.

9. Lan KK, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983; 70:659.

10. Peterson B, George SL. Sample size requirements and length of study for testing interaction in a 2 X 2 factorial design when time-to-failure is the outcome. Controlled Clin Trials 1993; 14:511-22.

11. Schoenfeld D. Partial residuals for the proportional hazards regression model. Biometrika 1982;69:239-241.

12. Verweij PJM, van Houwelingen HC, Stijnen T. A goodness-of-fit test for Cox's proportional hazards model based on martingale residuals. Biometrics 1998;54:1517-26. 12.

13. Greenwood M. The natural duration of cancer. Reports on Public Health and Medical Subjects, 1926, 33, London, Her Majesty's Stationery Office, 1-26.

14. Walker SH, Duncan DB: Estimation of the probability of an event as a function of several independent variables. Biometrika 1967; 54:1:167.

15. Liang KY, Zeger SL. Longitudinal data analysis using generalized models. Biometrika 1982; 73:13-22.

.

Occluded Artery Trial

Appendix 3

Guidelines for Angiography, Percutaneous Coronary Intervention, and Angiography Core Laboratory Analysis

Appendix 3

Guidelines for Angiography, Percutaneous Coronary Intervention, And Angiography Core Laboratory Analysis

Table of Contents

Appendix 3

Guidelines for Angiography, Percutaneous Coronary Intervention, And Angiography Core Laboratory Analysis

Table of Contents (Continued)

Appendix 3

Guidelines for Angiography, Percutaneous Coronary Intervention, And Angiography Core Laboratory Analysis

A3.1 Introduction and Purpose of Core Laboratory Analysis

Although the Occluded Artery Trial (OAT) is designed to test clinical rather than angiographic outcomes, the qualifying angiographic characteristics of enrolled patients constitute both a key measure of protocol adherence, and contain important baseline information central to the analysis of the trial. Furthermore, because the randomized intervention consists solely of infarct artery revascularization by percutaneous coronary intervention, independent analysis of qualitative and quantitative measures of procedural success are deemed essential to the credibility and acceptance of the results of the trial. Thus, an Angiography Core Laboratory (ACL) at the University of British Columbia (Vancouver General Hospital, Jack Bell Research Center) has been specified. The purpose of the Angiography Core Laboratory is to:

A. Perform pre-trial certification of participating Clinical Sites and investigators with respect to angiographic volume, quality, and core laboratory compatibility, and angioplasty volume and competence;
B. Provide independent confirmation of angiographic eligibility of patients enrolled in the trial;
C. Provide a database of core laboratory determined baseline angiographic patient characteristics of each enrolled patient (see Section A.3.7.1. on angiographic variables);
D. Independently validate and quantitate angiographic results of protocol-driven revascularization procedures; and
E. Provide ongoing quality assurance during progress of the trial with respect to protocol adherence and good clinical practice as determined by the angiographic record of coronary angiography and interventions.

A3.2 Qualifying Contrast Coronary Cineangiography and Ventricular Function

Investigators must confirm that patients considered for enrollment in the study have an infarct-related coronary artery occlusion with TIMI 0 or TIMI 1 flow and meet the definition of high risk status (see also Enrollment Criteria):

A. Ejection fraction (EF) <50%; or
B. Site of occlusion proximal in large vessel (Addendum A3-1, Figures A3-1 and A3-2):
    1. Left anterior descending (LAD) coronary artery proximal third -- Coronary Artery Surgery Study (CASS)* segments 12 or 13,
    2. Large right coronary artery (RCA) if supplying posterior descending artery (PDA) and part of posterolateral wall or apex -- CASS segments 1, 2, or 3, and
    3. Circumflex if supplying at least one large obtuse marginal plus a portion of the inferior wall -- CASS segments 18 through 22 dependent upon individual anatomy and circumflex dominance.

*CASS coronary segment codes are contained in Angiography Core Laboratory Addendum A3-1, Figure A3-1. Right, left, and co-dominant coronary diagram worksheets to assist enrollment screening are provided in Addendum A3-1, Figure A3-2.

A3.2.1 Optimum Methods for Angiography

A. Selective administration of intracoronary nitroglycerin (NTG) 100-200 mcg with appropriate angiographic labeling should precede angiography of both left and right coronaries regardless of the location of the qualifying occlusion;

B. Multiple views of the left and right coronaries conforming to the angulations suggested in Section A.3.2.3 below should be obtained. It is of primary importance to document the site of qualifying occlusion carefully and without overlap using projections in both right anterior oblique (RAO) and left anterior oblique (LAO) hemispheres with sufficient acquisition times to allow assessment of any residual antegrade flow and ipsilateral collateral filling. Similarly, when recording injections of the contralateral vessel, care should be taken to record collateral filling of the segments distal to the qualifying occlusion with appropriate panning when necessary; and

C. Left ventricular angiography should, when possible, be recorded prior to coronary angiography and administration of nitroglycerin (and always prior to any intervention).

D. Recommended protocol for patients with creatinine $\geq$1.5 mg/dl

1. Hydration begins 2 hours prior to the angiographic or PTCA procedure.
2. Hour 1 -- 0.45 N/S + 30 meq KCL/litre at 300 cc/hr.
3. Hour 2 -- 0.45 N/S + 30 meq KCL/litre at 20 cc/hr. + replace the urine output from the previous hour.
4. During the procedure and 4 hours post procedure -- 0.45 N/S + 30 meq KCL/litre at 20 cc/hr. + replace the urine output from the previous hr.
5. Minimize angiographic contrast dye volume (e.g., <200ml)

A3.2.2 Minimally Acceptable Qualifying Angiography

Some candidates for enrollment in the trial will not be identified before completion of coronary angiography. In order to avoid clinically unnecessary repeat angiography, and in order not to disqualify individuals identified in this way, the minimum acceptable standard for coronary angiography will require:

A. Clear identification of the qualifying occlusion, and
B. Assessment of residual antegrade flow.

Use of intracoronary nitroglycerin, conformance to suggested views, and inclusion of a left ventricular angiogram are not absolute requirements for entry into the trial.

A3.2.3 Recommended Angiographic Views

A. Left Ventricular Angiography
1. 9 or 10" mode, at least 15 frames/sec.
2. 30^0 RAO
3. Injection of not less than 48 cc contrast over 4 seconds
4. Recording of iso-centered calibration ball or grid

B. Coronary Angiography
   1. 5, 6, or 7" mode, at least 15 frames/sec.
      a) LCA:
         - RAO 20-30 / caudal 20-30
         - RAO 30-40 / cranial 30-40
         - RAO 30-40 / 0
         - LAO 25-40 / 20-40 cranial
         - LAO 80-100/ 0
         - LAO 40-60/ 20-30 caudal
         - AP ±_10 / 25-40 cranial
      b) RCA:
         - LAO 45-60/ 0
         - LAO 10-20/ 20-30 cranial
         - RAO 30-40/0
         - RAO 30-40/20-30 cranial

A3.2.4 Angiographic Media

Only 35 mm cineangiographic films (minimum 15 frames/sec) and Dicom Standard CD-ROM recordings are permitted. Other media such as VHS or S-VHS recordings are not sufficient for enrollment. Participating Clinical Sites must be capable of providing angiographic records in appropriate media formats.

A3.3 Certification of Cardiac Catheterization Laboratories

Angiography/angioplasty criteria must be documented for Clinical Site, lead interventionalist and individual operator certification as follows.

A. Each lead interventionalist in the Clinical Site must be documented to have the following qualifications (See Exhibit A3-1):
   1. Coronary angiography complication (death, MI, CVA) rate <0.5% during the past calendar year,
   2. Coronary interventional volume >75 per individual operator, per year
   3. Angioplasty success rate >95%,
   4. Angioplasty complication rate: death, Q wave MI or emergency CABG <2% in the past year,
   5. Implantation of >50 coronary stents, after training, per certified operator with the above success and complication rates, and
   6. Cumulative total of interventional cases must be ≥ 500.

B. Each individual angioplasty operator must meet the criteria 2, 3, 4, and 5 listed above in A and document this experience by submitting completed Exhibit A.3.2.

C. Each Clinical Site Principal Investigator must submit completed form in Exhibit A.3.3 and two diagnostic studies to the Angiography Core Laboratory prior to site certification, each study identifying at least one total occlusion of a major epicardial vessel. Samples should meet the following criteria for angiography provided in the protocol:

   1. 35mm Cine film or DICOM standard CD-ROM,
   2. clear, unobstructed demonstration in at least two nearly orthogonal views of an occlusion in a major epicardial segment,

3. clear inclusion of catheter tips in all views,
4. use of most or all of the recommended angulations modified as necessary for the individual patient anatomy,
5. demonstration of all ipsilateral and contralateral collateral flow, and
6. left ventricular angiography in RAO projection.

Each diagnostic study will be assessed with respect to its conformance to angiographic guidelines. Specifically, images will be assessed for media compatibility, image quality, angiographic labeling, variety and adequacy of views, visualization of collaterals, and adequacy of left ventriculography. Also, to be certified Clinical Sites must pass review of a coronary angiogram and angioplasty cine film demonstrating total coronary occlusion with successful PTCA and stent implantation. If present, deficiencies will be identified and angiography performance practices for OAT corrected prior to certification of the Clinical Site. Each Clinical Site must be documented to have the following qualifications:

A. Availability of at least 3 different guidewires incorporating variable tip stiffness characteristics and hydrophilic coatings,
B. Coronary interventional volume $\geq$ 150/center per year,
C. Coronary angiography volume $\geq$500 / year in the past year, and
D. Cardiac surgical back-up.

A3.4 Percutaneous Coronary Intervention Angiograms

Cineangiographic recordings obtained during performance of protocol assigned PTCA procedures should include documentation of each balloon inflation, including those performed for deployment of stents. When other interventional devices are utilized (such as atherectomy catheters, laser catheters, or thrombectomy devices), cineangiographic documentation of the catheter within the treated segment should be obtained. Final post-interventional cineangiographic recordings should be obtained using the guiding catheter after repeat administration of intracoronary nitroglycerin, nitroglycerin labeling, and withdrawal of the guidewire. At least two approximately orthogonal views should be recorded which demonstrate the treated target lesion clearly with minimum vessel overlap. The chosen views should, when possible, reproduce baseline views obtained prior to intervention. Importantly, the cineangiographic runs must be of sufficient duration and framed appropriately to demonstrate both the filling and clearing phases of the entire distal vessel. Post-intervention views meeting these standards must be obtained irrespective of the operator's clinical impression of success or failure of the procedure.

A3.5 Guidelines for Percutaneous Coronary Intervention (PCI)

Rather than establish rigid guidelines for technical aspects of protocol assigned percutaneous coronary intervention (PCI), it is the intent of the coronary intervention guidelines to provide broad based technical parameters which recognize legitimate site-to-site and inter-operator variability of practice. The overall purpose of such guidelines is two-fold:

(1) to ensure patient safety by encouraging good interventional clinical practice, and
(2) to maximize the likelihood of achieving and sustaining patency in subjects assigned to coronary intervention.

A3.5.1 Optimum Intervention Results

Operators are instructed to seek an optimum angiographic result characterized by:

A. re-establishment of TIMI grade 3 antegrade flow in the target vessel and its major branches,
B. <20% residual diameter stenosis by visual assessment,
C. complete coverage of target lesion and any adjacent dissection with stent(s), and
D. treatment (to< 20% visual stenosis) of all other significant lesions (>50% diameter stenosis) in major segments of the target vessel.

A3.5.2 General Technical and Pharmacologic Considerations

Coronary interventions may be performed via femoral, radial, or brachial artery access using 6, 7, or 8 French diameter guiding catheters, and may be performed at the time of diagnostic angiography (providing written consent for trial enrollment has been previously obtained) or during a separate procedure. Instructions specifically addressing angiography during coronary interventions are contained in Section A.3.4.

Aspirin (at least 160 mg po) must be administered within 12 hours prior to starting protocol determined interventions. Ticlopidine 250 - 500 mg or clopidogrel 300-375 mg po should also be administered whenever possible during the 24-hour period prior to intervention except when diagnostic angiography and intervention are combined in a single procedure, or in exceptional circumstances (for instance, when an a priori decision to avoid stent placement has been made).

Using the operators' and laboratories' usual heparin administration regimen, an activated clotting time (ACT) should be measured upon commencing procedures and at least hourly during procedures. An ACT of at least 250 seconds should be present prior to advancing guidewires or other interventional equipment sub-selectively into the target coronary artery, and should be sustained throughout the procedure. When a GpIIb/IIIa antagonist is administered primarily, weight-adjusted heparin (initial load 70 u/kg) to achieve and sustain an ACT of 200-250 seconds is recommended.

Following interventions, early sheath removal (within 6 hours of completion of the intervention) facilitated by immediate post-procedural cessation of heparin is recommended. Details regarding sheath removal, use of arterial hemostatic devices, post-procedural measurement of ACT, timing of ambulation, and timing of discharge should be determined by local practice. Use of investigational internally deployed hemostatic devices, however, is not permitted.

ASA 325 mg daily should be administered to all patients without an absolute contraindication. Ticlopidine 250 mg twice daily or clopidogrel 75 g daily for 2 to 4 weeks should be administered to all patients without a contraindication who have received a coronary stent. Neutrophil and platelet counts must be routinely determined 2 weeks following initiation of ticlopidine and again upon cessation of therapy (when therapy exceeds 2 weeks). The initial dose of ticlopidine or loading dose of clopidogrel should be administered immediately after completion of the intervention in patients not pre-treated.

Clopidogrel or ticlopidine must be administered as an alternative to ASA in all intervention patients when a contraindication prevents ASA administration. Clopidogrel and ticlopidine should not be administered concomitantly.

When a clinical indication for warfarin therapy exists, investigators must weigh the relative importance of full dose combination antiplatelet therapy (for at least 2 weeks) and delayed anticoagulation, versus single agent antiplatelet therapy (ASA 80 – 325 mg od for at least 4 weeks) and immediate oral anticoagulation. This decision should be individualized. A known need for immediate post-procedural anticoagulation may influence use of coronary stents (see Coronary Stents below).

A3.5.3 GpIIb/IIIa Antagonist Use

Notwithstanding the results of trials evaluating GpIIb/IIIa antagonist in balloon angioplasty and stent based coronary interventions, its routine primary administration for interventions involving coronary occlusions is untested. Compared to procedures in non-occluded coronaries, interventions for occluded coronaries are more likely to end in primary failure (due principally to inability to advance a guidewire across the occlusion) and also carry a higher risk of coronary perforation. For these reasons, the efficacy and safety of GpIIb/IIIa antagonist may differ substantially in the setting of coronary occlusion interventions. However, since total occlusions post MI are at risk for re-occlusion and use of GpIIb/IIIa antagonists are associated with less CPK MB rise post procedure their use is recommended. Operators are advised, to consider GpIIb/IIIa antagonist administration on an individual patient basis after appropriate attention to factors including but not limited to:

A. the presence or absence of lesion associated thrombus,
B. the degree of concern regarding risk of perforation (small vessel caliber, extended occlusion length, moderate or severe segment angulation, tortuosity, or calcification), and
C. unusual risk of hemorrhage (history of bleeding, ACT > 250 sec., low platelet count, advanced age, etc.).

A3.5.4 Guidewire Selection

Because the hypothesis of the Occluded Artery Trial is contingent upon establishing patency of the infarct-related artery, the magnitude of any potential treatment effect is presumed to be related to initial patency rates achieved in the intervention arm. Failure to advance a guidewire through the occluded segment constitutes the commonest mode of failure during coronary occlusion interventions. Thus, guidewire technique and selection constitute important technical aspects of protocol determined interventions.

Compared to procedures involving non-occluded target lesions, achieving a successful result during coronary occlusion angioplasty often requires greater operator persistence, prolonged fluoroscopy, and use of multiple guidewires of varying stiffness, shape, or construction. It is vital that patients randomized to intervention in the trial undergo procedures in which a concerted and thorough effort to establish patency is made.

Operator preferences and experience with specific proprietary guidewires for coronary occlusion interventions is acknowledged. In general, however, the use of soft or medium stiffness steerable wires should precede the use of stiff wires. Lubricious, hydrophilic-coated wires are now commonly

employed in coronary occlusions and anecdotally may be superior to conventional guidewires. Their use is recommended before use of stiff guidewires.

Overall and site-specific rates of procedural success will be monitored by the Steering Committee based on case report forms and analyses from the ACL. When site-specific procedure success falls below 80% (after 5 or more protocol assigned interventions) or when a procedural failure occurs during the first 4 protocol assigned interventions, a review process will be initiated addressing case specific factors, operator specific issues, and laboratory technical practices. Site visits by angioplasty experts from the ACL will be initiated as necessary.

A3.5.5 Coronary Stents

Primary use of stents in occlusions has now been demonstrated to improve patency. Therefore, eligibility criteria require all patients to be 'angiographically suitable for coronary stenting of the qualifying occlusion by a priori intention of the operator.' However, several factors exist which influence an operator's ability to safely deliver a coronary stent to an occlusion, and which cannot be assessed by qualifying angiography alone. These factors (such as vessel pliability, catheter fit, occult vessel angulations, downstream vessel size and anatomy) can only be assessed after initiating an intervention. As such, stent deployment cannot be mandated but is strongly recommended. Limited relative contra-indications to stent use in the current study consist of:

A. severe vessel tortuosity, angulation, or calcification preventing safe delivery,
B. vessel size unable to accommodate 2.5 mm diameter balloon,
C. suspected coronary perforation,
D. patient refusal to accept stent, and
E. contraindication to both ticlopidine and clopidogrel (e.g., need for immediate anticoagulation).

Lesion length, thrombus, side branches, moderate tortuosity or calcification, or achievement of an optimum "stent-like" balloon angioplasty result do not constitute reasons for withholding stents.

Approved stents must be used in OAT. However, stents approved for sale vary between regulatory jurisdictions, and moreover, are likely to change during the expected period of enrollment. Recommended stents include a variety of slotted tube variants for which clinical data exist demonstrating approximate equivalence (the Cordis Palmaz-Schatz Crown; ACS Multilink or Duet, Boston Scientific NIR, Medtronic BeStent, Biocompatibles BiodivYsio; AVE GFX). Coil type stents such as the Cook GR2 and Cordis CrossFlex and self-expanding stents such as the Boston Scientific Radius or Wallstent are recommended only if delivery of the available slotted tube stents is not feasible.

A3.5.6 Pro-active Quality Assurance of Interventional Procedures

There will be case reviews at all investigator meetings. The ACL staff will select 3-5 cases for review which illustrate issues related to good clinical practice, protocol adherence (particularly angiographic enrollment criteria), treatment of complex occlusion, or management of complications. Investigators will also be encouraged to bring angiographic records of illustrative cases to these meetings.

Progress in evidence-based interventional cardiology practices during the course of the trial will be incorporated into the PCI guidelines as necessary. Changes will be disseminated through both regular OAT memos, newsletters and at investigator meetings.

A3.6 Shipment of Cineangiograms

All qualifying and interventional procedure cineangiographic films or CD-ROM discs with the completed Angiography Transmittal Forms should be sent by registered or certified mail or any inexpensive traceable method to the Angiography Core Laboratory within 30 days of patient discharge. Films and discs should be clearly and securely labeled with the unique patient identifier number and site identifier number, and packaged in impact resistant cases to prevent damage during shipment.

The Address for shipment is: Jack Bell Research Centre
Cardiac Imaging Research Laboratory, Room 236
2660 Oak Street
Vancouver, B.C. Canada, V6H 3Z6
Attention: Eunice Yeoh – OAT Study

1. For participating centers outside Canada it is vital to label the package as follows to avoid delays in Canada Customs at the border. Significant delays may result if the films are not labeled as follows: **Patient X-Rays for Medical Research only, No Commercial Value.** The declared value should be less than $5.00 US.
2. Every effort will be made to return the films within two weeks. The Angiography Core Laboratory will maintain current information on the individual at the Clinical Site responsible for study films, correct mailing addresses, and current phone/fax numbers.
3. When clinical circumstances require early return of cineangiograms, the ACL can be notified by telephone or fax, and will return films by overnight courier within one working day.

Angiography Core Laboratory Phone Canada (01) 604 -875-5477
Angiography Core Laboratory Fax (01) 604-875-5471

A3.7 Angiography Core laboratory Procedures

A3.7.1 Angiographic Variables

Core Laboratory analysis will include quantitative or qualitative assessment of the following variables in all 3200 baseline angiograms and all 1600 protocol assigned interventions.

A. Study Artery:
   1. Identification and confirmation of site of qualifying occlusion (CASS coronary segment code, *Addendum A3-1*);
   2. Initial TIMI Flow grade *(Addendum A3-2)*;* and
   3. Suitability for percutaneous intervention (see Coronary Intervention below).

Some recently performed reperfusion studies have utilized the TIMI frame count system to improve accuracy and resolution of assessment of infarct-related artery antegrade flow (Gibson, CH. *Circ* 1996;93:879-888). This method is particularly valuable in refining analysis of TIMI grade 2 flow states. In contrast to acute reperfusion studies in which TIMI grade 2 flow is a common observation,

the non-acute population screened for the present study will have a very low incidence of TIMI grade 2 flow, and TIMI grade 2 flow states will be excluded from enrollment. Thus, the additional work and expense required to perform TIMI frame count analysis over and above core laboratory visual flow grade analysis using the standard TIMI grading is considered unwarranted.

B. Coronary Tree:

(1) Initial collateral flow (modified TIMI collateral grades, *Addendum A3-3*);
It is recognized that occluded and functionally occluded coronary arteries may receive flow from several sources including (1) antegrade residual flow through the functionally occluded lumen *[antegrade TIMI flow grade 1]* (2) ipsilateral collateral flow (3) contralateral collateral flow. Further, these three sources of flow may coexist.

In order to fully describe residual flow in randomized occluded coronary arteries in OAT, all three sources of residual flow will be assessed separately by the Core Angiographic Laboratory in all randomized patients. The sum of the flow scores will be calculated and termed "total TIMI flow". This variable will be examined in an exploratory manner to determine its association to baseline wall motion, wall motion recovery, and clinical outcome.

(2) Categorical semi-quantitative caliper assisted visual analysis of the most severe lesion in each non-target coronary artery (LAD, LCX, RCA, and LMCA) and its major branches (<30%, 30-50%, 51%-70%, 71%-99%, 100%).

C. Left Ventricle:

Ejection fraction and regional motion of infarct segment: The Sheehan-Bolson-Dodge quantitative package will be used to assess global ejection and centerline measurements of regional wall motion expressed in standard deviations per chord. This methodology is considered the gold-standard for ventriculographic analyses and is available within the quantitative analysis package used in the core laboratory.

D. Confirmation of High Risk Status:

1. EF <50%, or
2. Site of occlusion proximal in large vessel supplying at least 25% of left ventricle (Addendum A3-1, Figures A3-1 and A3-2):
   (a) LAD proximal third (CASS segments 12 or 13)*;
   (b) Large RCA if supplying PDA and part of posterolateral wall or apex (CASS segments 1, 2, or 3); or
   (c) Circumflex if supplying at least one large obtuse marginal plus a portion of the inferior wall (CASS segments 18 through 22 dependent upon individual anatomy and circumflex dominance).

*CASS Coronary segment codes are contained in Angiography Core Laboratory Addendum A3-1, Figure A3-1. Right, left, and co-dominant coronary diagram worksheets to assist enrollment screening are provided in Addendum A3-1, Figure A3-2.

E. Coronary Intervention:

1. Suitability of qualifying occlusion for intervention:
   (a) location of target segment meets inclusion criteria;
   (b) vessel able to accommodate 2.75 mm diameter balloon and stent, i.e reference segment diameter at least 2.5 mm;

(c) target segment not beyond or within extreme tortuosity (>90 degrees angulation).

1. Post intervention reference segment diameter, minimum luminal diameter, and percent diameter stenosis;
2. Post intervention TIMI flow grade;
3. Insertion of stent(s) at target occlusion (y/n); operators will be required to identify reason for not deploying a stent;
4. Angiographic failure (y/n); failure to reduce target vessel occlusion/stenoses to <50% residual diameter stenosis by QCA, or failure to restore TIMI flow grade ≥2; and
5. Suboptimum angiographic result (y/n); in the absence of angiographic failure, failure to reduce target vessel occlusion/stenosis to <30% residual diameter stenosis by QCA.

Angiographic complications including coronary perforation, proximal coronary dissection, etc. will be categorized and tracked. Where review of a diagnostic or interventional film raises substantial concerns regarding any aspect of good clinical practice or protocol adherence (with respect to case selection, technique, or the final angiographic intervention result) the film will be reviewed again within two working days in collaboration with a second University of British Columbia clinical faculty interventional cardiologist. If re-review confirms substantial cause for concern, the Study Chair will be notified within two additional working days with a written report outlining the nature of the concerns, identifying the Clinical Site and investigator, and where possible, suggestions for corrective action.

A3.7.2 Laboratory Accuracy and Precision

This laboratory has recently completed analysis of over 800 paired films for the Prospective Randomized Evaluation of the Vascular Effects of Norvasc (amlodipine) Trial ("PREVENT"). This analysis entailed complete segmental analysis of all stenoses and normal segments in the entire coronary tree. A unique aspect of this trial was the re-submission of films to the core laboratory in a completely blinded fashion for reanalysis. This was done to monitor and quantify the laboratory's reproducibility performance. This was a highly rigorous test because films may be read a second time by a completely different technician who was free to select optimal views, frames, digitizing parameters, and reference segments as if performing the study anew. In spite of these multiple sources of variability, the results showed sustained accuracy and precision throughout the trial as shown in the following table:

	Precision	Accuracy	Absolute Difference
Minimum Lumen Diameter (n=462)	0.32 mm	-0.007 mm *	0.24 mm
Diameter Stenosis (n=471)	12%	-0.363% *	8%

(* Not significantly different from 0)

A3.7.3 Assessment of Angiogram Quality

The ACL staff will assess the quality of all films according to the criteria given below. All assessments will be provided to the Clinical Site Principal Investigator and will be available to the Study Chair and Executive Committee for review.

(1) Scoring System
- Unacceptable
- Marginally Acceptable
- Acceptable
- Superior
- Absent

(2) Categories for Assessment
- Labeling and Documentation
- Image quality
  - framing
  - contrast
  - resolution
  - artifacts
- Coronary Views
  - variety of projections
  - identification of occluded segment
  - documentation of antegrade flow beyond occlusion
  - collateral visualization
- Left Ventriculography
  - sinus or paced rhythm during injection
  - LV filling

(3) Documentation of Format
- 35 mm Cine Film
- CD-ROM (DICOM standard compatible)
- Not compatible format

(4) Report Summary
- Acceptable
- Unacceptable

(5) Problem Resolution

(6) Misidentification of IRA

Using the above parameters, qualitative feedback on individual patient cineangiograms will be provided to each participating Clinical Site and investigator. When appropriate, specific written instructions for rectifying problems will accompany these reports.

The ACL staff have been able to achieve less than a 15% angiographic rejection rate after the first 3-6 months of previous studies among sites that are enrolling regularly. In our experience, sites with poor quality beyond this period tend to remain intransigent to change. Thus, a monthly site-specific report on angiographic quality and adherence to angiographic enrollment criteria will be provided to the Executive Committee.

A3.7.4 Data Collection, Management, and Coordination

The angiographic data to be collected will consist of those parameters previously outlined. The data will be archived on specially developed data sheets (*Addendum A3-4*) , in a database maintained on a microcomputer in the laboratory, in the image files that will be archived on optical disk, and on video printouts of the analyzed segments which also includes a printout of the data of interest. All data will be transferred either by modem or disc to the Data Coordinating Center at the Maryland Medical Research Institute on a regular weekly basis. These multiple archiving approaches will insure against data loss and allow for easy cross checking of data. All statistical analyses, other than descriptive analyses of blinded data accumulated during the course of the study, will be the responsibility of the Data Coordinating Center. The laboratory will produce descriptive data summaries to be used to update investigators as to the progress of the angiographic analyses.

An important aspect of coordination is to require that all films or CDs be sent to the ACL immediately after the patient is discharged. This is to ensure that the final, angiographic database will be available for statistical analysis within a short time period after completion of the final angiogram in the last patient enrolled in the study.

A second important aspect of coordination is to regularly generate a descriptive display of the data that are being accumulated to identify outliers. This process is useful as another measure of quality assurance. In some cases, outlying data points reveal previously undetected non-compliance to protocol, transcription errors, etc.

References

1. Mancini GBJ, Simon SB, McGillem MJ, et al. Automated quantitative coronary arteriography: In-vivo morphologic and physiologic validation of a rapid method utilizing digital angiography. Circulation 1987;75: 452-460.

2. Sanz ML, Mancini GBJ, LeFree MT, et al. Variability of quantitative digital subtraction coronary angiography before and after percutaneous transluminal coronary angioplasty. Am J Cardiol 1987; 60: 55-60.

3. LeFree MT, Simon SB, Mancini GBJ, et al. A comparison of 35mm cine film and digital radiographic imaging for quantitative coronary angiography. Invest Radiol 1988; 23: 176-183.

4. Mancini GBJ: Editorial: Quantitative coronary arteriography. American J Cardiac Imag 1989; 3: 169-171.

5. Kalbfleisch SJ, McGillem MJ, Simon SB, et al. Automated quantitation of indexes of coronary lesion complexity: Comparison between patients with stable and unstable angina. Circulation 1990; 82: 233-239.

6. Kavanaugh KM, Pinto IMF, McGillem MJ, et al. Effects of video frame averaging, smoothing and edge enhancement on the accuracy and precision of quantitative coronary arteriography. Int J Cardiac Imag 1990; 5 233-239.

7. Ellis SG, Pinto IMF, McGillem MJ, et al. Accuracy and reproducibility of quantitative coronary arteriography using 6 French catheters with cine angiographic and digital acquisition. Cathet CV Diag 1991; 22: 52-5.

8. Mancini GBJ: Quantitative coronary arteriographic methods in the interventional catheterization laboratory: An update and perspective. J Am Coll Cardiol 1991; 17: 23B-33B.

9. DeCesare NB, Williamson PR, Moore NB, et al. Establishing comprehensive, quantitative criteria for detection of restenosis and remodeling after percutaneous transluminal coronary angioplasty. Am J Cardiol 1992; 69: 77-83.

10. Mancini GBJ: Quantitative coronary arteriography: Development of methods, limitation and clinical applications. Amer J Cardiac Imag 1988; 2: 98-109.

11. Mancini GBJ: (editor) "Cardiac Applications of Digital Angiography" Raven Press, New York, 1988.

12. Mancini GBJ, Williamson PR, DeBoe SF: Effect of coronary stenosis severity on variability of quantitative arteriography and implications for interventional trials. Am J Cardiol 1992; 69: 806-7.

13. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circ 1996; 93: 879-888

14. Pomerantsev EV, Kobayashi Y, Fitzgerald PJ, et al. Coronary Stents: In vitro aspects of an angiographic and ultrasound quantification with in vivo correlation. Circulation 1998; 98: 1495-1503.

Exhibit A3.1

OAT- Angioplasty Operator Certification for Lead Interventionalist

- Oat Enrolling Center Name:_____
- PTCA Site Names if more than one or different from above

(1)_____(2) _____(3)_____

OAT PI: _____

Lead Interventionalist Name (if not PI):_____

Participating CENTER qualifying certification:

_____ Number of annual coronary interventional cases (not less than 150 cases per year)

_____ Number of annual diagnostic coronary cases (not less than 500 cases per year)

Availability of at least 3 different guidewires incorporating variable tip stiffness characteristics and hydrophilic coatings. Yes ____ No ____

Cardiac surgical back-up Yes ____ No ___

Criteria for certification of lead interventionalist - Answer all questions:

(A) Coronary Angiography in-hospital complication (death, MI, CVA) rate <0.5% during the past calendar year. Yes ____ No ____

(B) Non-emergent coronary interventional volume >75 per year. Yes ____ No ____

(C) Non-emergent angioplasty success rate >95%. Yes ____ No ____

(D) In-hospital angioplasty complication rate: death, Q wave MI or emergency CABG <2% in the past year for non-emergent procedures. Yes ____ No ____

(E) Implantation of >50 coronary stents, after training, per certified operator with the above success and complication rates. Yes ____ No ____

(F) Cumulative total of interventional cases must be ≥500. State volume or approximate Yes ____ No ____

_____ _____

PI / Lead Interventionalist (Sign) **Printed Name**

_____ _____

Department or Division Chief (Sign) **Printed Name**

_____ _____

Date **Date**

Upon Completion Fax to Randy Plant at (305) 674-2162

Accepted by OAT Clinical Coordinating Center:

Date _____ **Signature** _____

Exhibit A3.2

OAT - Angioplasty Operator Certification
Fill one form for each operator performing PCI on OAT Subjects other than Lead Interventionalist

Name of interventionalist: _____

OAT Enrolling Center:_____

PTCA Site Names if more than one or different from above

(1)_____(2) _____(3)_____

OAT PI (may be same as above): _____

Criteria (provide number or state "Yes" if criteria are met) for certification

_____ Number of personal annual non-emergent interventional cases (not less than 75 cases per year)

_____ Major in-hospital angioplasty complication rate (death, Q wave MI, emergency revascularization by re-intervention or surgery) not greater than 2% in the last calendar year for non-emergent procedures

_____ Angioplasty success rate (must be > 95%) for non-emergent procedures

_____ Cumulative total number of coronary stents implanted as principal operator (must be greater than 50)

_____ Cumulative total number of interventional cases as a principal operator

Signatures: _____ Date _____
Principal Investigator or Lead Interventionalist

_____ Date _____
PTCA Operator being certified

_____ Date _____
Division or Department Head

UPON COMPLETION FAX TO RANDY PLANT AT (305) 674-2162

Accepted by OAT Clinical Coordinating Center: Date _____

Signature _____

Exhibit A3.3

Cath/Interventional Profile

- **Name of OAT Enrolling Center:** _____
- **In table below, list hospital sites under above-named Enrolling Center where angiographic eligibility for OAT will be confirmed.**
- Are all hospitals listed below enrolling as one OAT Enrolling Center- Single Site # / randomization sequence- Yes_____ No _____
- If answer to above is no, describe how enrolling site is divided-fill additional forms if necessary or call CCC at (212) 523-3550.

PTCA sites

Hospital Name	Your Group's PTCA Operators at This Site

Cath Only Sites

Hospital Name	**Name of hospital within same group/affiliated institutions where PTCA is performed (must be listed above)**	**Name of PTCA site at Other Institutions/Group***

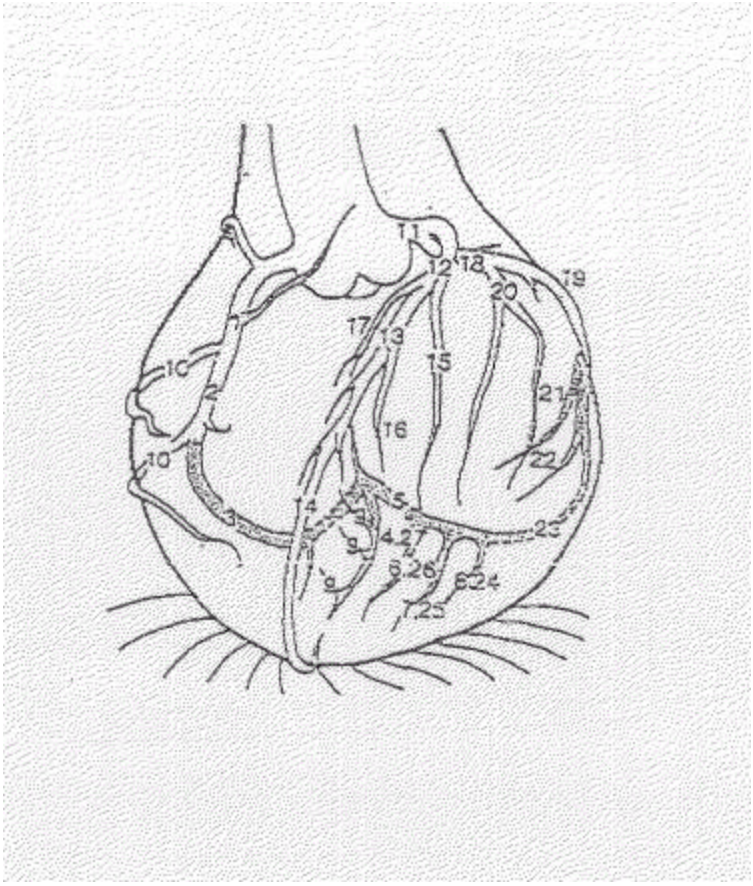
All operators for OAT patients must have OAT certification (call CCC if this needs to be arranged) Names of all operators (1)_____ (2)_____

(3)_____ (4)_____ (5) _____

Upon Completion Fax to Randy Plant at (305) 674-2162

Addendum A3-1

Figure A3-1
CASS Coronary Segment Code

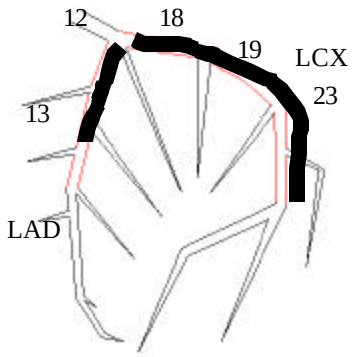


1. Proximal Right;
2. Mid-Right;
3. Distal Right;
4. R. Post Descending;
5. R Post Lateral;
6. 1st R Lateral;
7. 2nd R Post Lateral;
8. 3 rd R Post Lateral;
9. Inferior Septal
10. Acute Marginal;
11. Left Main;
12. Proximal LAD;
13. Mid-Lad;
14. Distal LAD;
15. 1st Diagonal;
16. 2nd Diagonal;
17. 1st Septal;
18. Proximal CX;
19. Distal CX;
20. 1st Obtuse Marginal;
21. 2nd OM;
22. 3rd OM;
23. L. Atrioventricular;
24. 1st L. Post Lateral;
25. 2nd L. Post Lateral;
26. 3rd L. Post Lateral;
27. L. Posterior Descending

Addendum A3-1 (Continued)

Figure A3-2
Qualifying Left Coronary Segments for Patients with EF ≥ 50%

2A: Dominant Left Coronary Artery

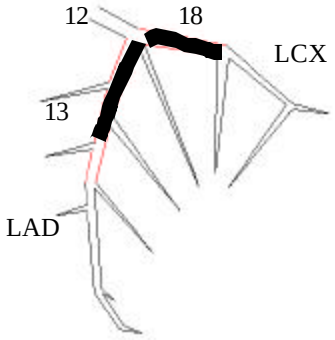


To qualify, the occluded segment must be:
1. in segments 12 or 13 of the left anterior descending coronary artery (i.e., proximal to the 2nd major diagonal branch)

or

2. in segment 18, 19, or 23 of the dominant left circumflex coronary artery supplying *at least* one significant posterior or posterolateral branch and the posterior descending artery (PDA) (each approximately 2.0 mm diameter or greater by visual estimate).

2B: Non-dominant Left Coronary Artery

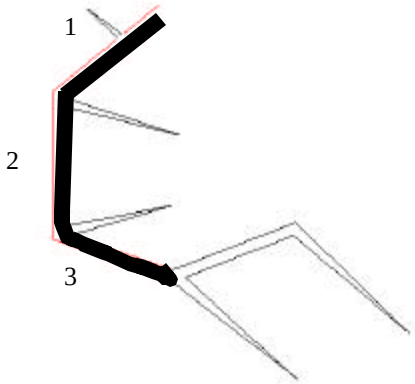


To qualify, the occluded segment must be
1. in segments 12 or 13 of the anterior descending coronary artery (i.e., proximal to the 2nd major diagonal branch)

or

2. in segment 18 of the non-dominant left circumflex coronary artery supplying at least two significant marginal branches and one significant posterior or posterolateral branch (each approximately 2.0 mm diameter or greater by visual estimate).

2C: Dominant Right Coronary Artery



To qualify, the occluded segment must be in segments 1, 2, or 3 of a dominant right coronary artery supplying *at least* the posterior descending artery (PDA) and 1 posterior/posterolateral (PL) wall branch. Both PDA and PL should be approximately 2.0 mm diameter or greater by visual estimate.
----------**The occluded segment should appear to be suitable for stenting.**----------

Addendum A3-2

TIMI Flow Grades

Grade 0: (No perfusion)	No contrast flow through the stenosis.
Grade 1: (Penetration with minimal perfusion)	A small amount of contrast flows through the stenosis, but fails to fully opacify the artery beyond.
Grade 2: (Partial reperfusion)	Contrast material flows through the stenosis to opacify the terminal artery segment. Contrast enters the terminal segment perceptibly more slowly than more proximal segments. Alternatively, contrast material clears from a segment distal to a stenosis noticeably more slowly than from a comparable segment not preceded by a significant stenosis.
Grade 3: (Complete reperfusion)	Antegrade flow into the terminal coronary artery segment through a stenosis is as prompt as antegrade flow into a comparable segment proximal to the stenosis. Contrast material clears as rapidly from the distal segment as from as uninvolved more proximal segment.

Addendum A3-3

TIMI Collateral Grades (modified)

Grade 0: (Absent)	No angiographic filling of the distal vessel.
Grade 1: (Minimal)	Faint opacification of the distal vessel only or if only small segments were visualized.
Grade 2: (Well developed)	Entire distal vessel is visualized and densely opacified.

Addendum A3-4

OAT Angiographic Data Sheet

Patient ID: _____ **Initials:** _____ **Site:** _____

Format: Cine film / CD-ROM (DICOM) / S-VHS videotape / Not compatible

A. Ventriculogram:

Acceptable? Y / N ; If not, why not? _____

EF %: _____ Regional Wall Motion SD/Chord: _____
(Infarct Segment)

Mitral Valve Regurg: _____

B. **Qualifying Occlusion:** IRA CASS Code: _____

Film Date: _____ PCI Date: _____

Catheter Size: _____ Brand: _____ Type: _____

	Pre-Intervention	Post-Intervention
TIMI Flow		
TIMI Collateral		
Reference Diameter (mm)		
% DS		
MLD (mm)		
Stent Deployed (Y/N)		

C. Residual Coronary Tree:

		Left Anterior Descending	Circumflex	Right Coronary
CASS Site Code				
% DS (<30, 30-50, 51-70, 71-99, 100)				
Dominant (Y/N)				

(* worst and most proximal lesion)

Technician Signature: _____ Date Received: _____

Date Completed: _____

I have reviewed these analyses and found them to be accurate and complete.

_____ _____
G.B. John Mancini, M.D. Date

_____
C. E. Buller, M.D.

Addendum A3-5

OAT Assessment of Angiographic Quality

Patient ID: _____ **Site:** _____

Scoring System:
1=Unacceptable 2=Marginally acceptable 3=Acceptable 4=Superior

Categories for assessment:

Image quality:	1 / 2 / 3 / 4	Resolution:	1 / 2 / 3 / 4
Framing:	1 / 2 / 3 / 4	Artifacts:	1 / 2 / 3 / 4
Contrast:	1 / 2 / 3 / 4	Documentation:	1 / 2 / 3 / 4
Labeling:	1 / 2 / 3 / 4		

Coronary Views:

Variety of projections:	1 / 2 / 3 / 4
Identification of occluded segment:	1 / 2 / 3 / 4
Documentation of antegrade flow beyond occlusion:	1 / 2 / 3 / 4
Collateral visualization	1 / 2 / 3 / 4

Left Ventriculography:

Sinus or paced rhythm during injection:	1 / 2 / 3 / 4
LV filling:	1 / 2 / 3 / 4

Format: Compatible / Not Compatible

SUMMARY: Acceptable / Unacceptable

Comments:
_____
_____
_____
_____
_____

_____ _____
G.B. John Mancini, MD Date

_____
C.E. Buller, MD

Appendix 4
Policy Matters

OAT Protocol

Appendix 4
Policy Matters

TABLE OF CONTENTS

Appendix 4

POLICY MATTERS

A4.1 Publication Policy

A4.1.1 General Statement of Editorial Policy

It is anticipated that the Occluded Artery Trial (OAT) will generate considerable new data relative to the recruitment, evaluation, and management of patients with occluded IRA's post MI. The purpose of OAT Publications Committee is to foster and guide development of scientific reports originating from data obtained in the OAT project. The scientific integrity of the project requires that all data from all OAT sites be analyzed study wide and reported as such. Thus, an individual site is expected not to report and publish data collected from its site alone under the by-line of the OAT project. Development of substudies or data bank studies dealing with specific analyses is encouraged. All presentations and publications of any type (OAT or related studies) are expected to maintain the integrity of the main objectives of the overall project. By agreement of the Principal Investigators, endpoint data will not be presented prior to release of "mainline" results. The Publications Committee will prepare recommendations concerning the timing of presentation of mainline or endpoint data (including papers on design and methods) and designation of the meetings at which they might be presented and will submit these recommendations to the Executive Committee for approval.

Publications will be grouped into five general types of papers (see Section A4.1.2). Topics for consideration to be developed into publications will be generated from questions or hypothesis that are submitted to the Publications Committee by investigators, study coordinators and other OAT staff. The Operations Committee will prioritize each request. A writing group with a designated Chairperson will be recommended for each topic and this recommendation will be forwarded to the Executive Committee for approval.

The Executive Committee has primary responsibility for the scientific conduct of the study including all endpoint, data bank, ancillary, and independent studies (defined below) as well as for all publications and presentations evolving from OAT.

Investigators at all OAT sites, including the Core Laboratories, the Clinical Coordinating Center (CCC), Data Coordinating Center (DCC), Economics and Quality of Life Coordinating Center (EQOLCC) and NHLBI Program Office have equal status with regard to developing protocols, participating in such studies as approved by the Executive Committee, and collaborating in the development and publication of research papers based on OAT material. With the approval of the Principal Investigator, study coordinators and other OAT staff at the various sites are encouraged to participate in this process. The Publications Committee will develop standards for regular evaluation of the submission and completion of these protocols.
OAT Investigators at Clinical Units or Central Units proposing studies that require the collaboration of one or more of the OAT Central Units (e.g., Core Laboratories the DCC or CCC or EQOLCC) must contact the appropriate individuals prior to submission of a given proposal. The appropriate staff in the Central Units will participate in drafting the proposal, indicate willingness to participate, and identify sources of funding to support the level of effort required for the project.

The DCC Investigators must be consulted in the development and analysis of protocols that require review of accumulated data from the Clinical Units or data on file at the DCC. The members of the DCC, CCC, EQOLCC and NHLBI Program Office are available to collaborate in designing and carrying out all OAT research.

A4.1.2 Types of OAT Research

OAT research and the resulting presentations and publications may be grouped into the following categories:

1. Design paper(s) and reports on methodology,
2. Endpoint studies,
3. Data bank studies,
4. Ancillary studies, and
5. Independent studies.

Distinctions among these types of studies are given in Section A4.2. Research other than endpoint studies may be conducted prior to the end of the OAT investigation and is strongly encouraged, so that the maximum information can be obtained from this trial and so that the methods for evaluating and analyzing secondary endpoints may be refined in preparation for later analyses.

A4.1.3 Authorship

The first publication(s) pertaining to the fundamental goals (endpoints) of OAT involving patients enrolled in OAT will have authorship identified on the byline as "the OAT Investigators." Individuals who contributed specific sections of the publication and members of the ad hoc Writing Committee which prepared the manuscript will be identified in appropriate footnotes. An appendix listing all Principal and Co-Investigators in OAT will be included at the end of the manuscript's text. It is intended that there will be more than one publication concerning the major goals; these publications will list the writing team as the authors on behalf of the OAT Investigators. The same guidelines will apply to reports of OAT studies, in other categories.

A4.1.4 Purpose of Procedural Guidelines

The procedures adopted by the OAT Investigators for utilization of OAT data are intended to protect the interests of all investigators and participants in the trial, to assure that study data conform to the requirements of study design and are accurately presented, that authorship is appropriately acknowledged, that the text of each publication is well-written, that all investigators are aware of ongoing analysis projects, to avoid duplication of analysis projects and to ensure that publication or presentation of OAT data does not occur without the knowledge and approval of the Executive Committee.

A4.1.5 Restrictions on Which Data May be Released

OAT endpoint data or data which might jeopardize the blinding of therapy or continuation of the project will not be released to OAT Investigators or the public until the end of the study, at a time deemed appropriate by the OAT Data and Safety Monitoring Board, the NHLBI Project Office, and the Study Chair.

A4.2 Design and Methods Reports, Endpoint, Data Bank, Ancillary, and Independent Studies

A4.2.1 Design Papers and Reports on Methodology

Manuscripts concerning the Study's overall design, protocol, procedures, or organizational structure which do not involve endpoint data or data collected on OAT patients may be published prior to the end of the study. Such major publications will be developed and reviewed according to the same guidelines used for endpoint studies.

Many public presentations or publications about OAT which involve no endpoint, data bank or ancillary study data (e.g., grand rounds talks concerning the study's general design and objectives) will not require formal preliminary review and approval by the Publications Committee. However, if there is any doubt, investigators are asked to first consult with the OAT Chair or Co-Chair Committee indicating their intention to publish or present the material, in order to avoid the premature release of OAT data or the inappropriate publication of confidential information.

A4.2.2 Endpoint Studies

An endpoint study is a study that addresses the fundamental goals of OAT or that involves data (such as treatment assignment, success rates of revascularization or differences in event rates by treatment assignment) which cannot be released prior to the end of the study. These studies will summarize the findings based on the entire study population and will be written at the conclusion of the project.

Endpoint studies from OAT will generally involve the collaboration of many investigators. Proposals for endpoint studies may be introduced and developed by any member of the Executive Committee. Some Writing Subcommittees will be designated by the Operations Committee on an ad hoc basis for preparation of these abstracts and manuscripts on behalf of the OAT Study Group and others on the basis of submission of an investigator-initiated proposal.

A4.2.2.1 Conduct of This Research

After approval of a proposed endpoint study, members will be elected or invited to serve on an ad hoc Writing Committee and a Chairperson will be chosen. These investigators will work with the CCC, DCC, EQOLCC and NHLBI staff to conduct the data analysis needed to investigate the question at hand and prepare a manuscript based on these findings. Every effort will be made by the Subcommittee to consider and incorporate comments and suggestions from the Executive Committee in this manuscript. Often the Subcommittee members may meet with staff from the CCC, DCC, EQOLCC or other OAT Clinical Sites for development of these papers.

A4.2.3 Data Bank Studies

A data bank study uses data, specimens, or recordings, which are routinely collected on patients who are logged, screened for entry into, or randomized into OAT. Analysis of these data are used to answer specific scientific questions. Data used in this research are not directly related to the fundamental goals of the study (e.g., the efficacy of OAT experimental strategies). Data bank studies must be approved by the Publications Committee and ratified by the Executive Committee. All presentations or publications are to be reviewed following the procedures outlined below.

A4.2.3.1 Conduct of This Research

After approval is given by the Publications Committee, the Investigators proposing the data bank study will work with the CCC, DCC and NHLBI staff to conduct the data analysis.

A4.2.3.2 Priorities for Work

Because of the routine workload at the DCC, it will be necessary to establish priorities for data processing and analysis. Therefore, the DCC will, as necessary, conduct analyses on data bank studies in the order in which they have been approved or seek guidance from the Operations Committee for determining priorities for analysis.

A4.2.3.3 Authorship

After a data bank study proposal is approved by the Publications Committee, its research and development are the responsibility of the identified investigators on the project. Authorship decisions on OAT data bank studies will take into account the unique cooperative effort that has produced the results. For clinical papers in particular, authorship should be offered to individuals fom Clinical Sites, Core Laboratories, CCC, DCC, EQOLCC and NHLBI staff when their contributions are appropriate. On the other hand, there will be papers of more limited scope which probably do not warrant a large number of authors. The following mechanism will be utilized to determine authorship:

a. The lead author will propose a list of co-authors, based on the above guidelines.
b. The Chairperson of the Publications Committee, and the OAT Study Chair or Co-Chair, will review and approve, or make recommendations regarding alterations in the proposed list of authors.

The names of these investigators will be followed by the designation "and the OAT Investigators" on the byline.

A4.2.4 Ancillary Studies

An ancillary study uses supplementary data that are collected on patients who are logged, screened for entry into, or randomized into OAT, over and above the data collection required by the OAT protocol. Such studies are restricted to consideration of a specific test, technique or involve only supplemental data collected on OAT patients. Ancillary studies must be reviewed and approved by the OAT Publications Committee and ratified by the Executive Committee prior to initiation to ensure that they do not conflict with the main protocol. Review by the OAT Publications and Operations Committees is required for presentation or publication of an ancillary study.

A4.2.5 Independent Studies

Independent studies of concern to OAT are studies conducted in patients with an occluded IRA post MI who enter an OAT Clinical Site but are not enrolled in OAT and not entered into the OAT Registry.

It is understood that each Clinical Site has the right to conduct studies which are independent of OAT in patients with an occluded IRA post MI who do not meet criteria for randomization into OAT. Independent studies of patients who meet any of the OAT eligibility criteria must be reviewed by the Publications Committee. OAT investigators agree not to conduct independent studies which would compete with or have a detrimental effect on the conduct of the OAT during the period of recruitment and follow-up of patients.

Results of independent studies which are approved as acceptable within OAT may be published or presented at the discretion of investigators initiating the independent study.

A4.3 Procedures for Initiation and Approval of Studies

A4.3.1 Submission of Proposals

Before beginning an endpoint, data bank, or ancillary study, a proposal initiated by one or more of the OAT Investigators and/or their associates should be submitted for consideration by the Publications Committee. Each proposal should include the following:

a) Background,
b) Clear statement of objectives or research hypothesis,
c) Brief description of data to be used,
d) Description of methods of analysis, and
e) Proposed collaborators, and
f) Plans for presentation and/or publication.

Full details should be given concerning any procedures to be carried out on study patients such as laboratory tests, radiological procedures, etc. Any substances to be injected or otherwise administered to the patients should be identified. Any observations to be made or procedures to be carried out on a patient outside of the Clinical Site should be described. The extent to which the data bank or ancillary study will require extra clinic visits by the patient or will prolong the patient's usual telephone interviews should be described. Information should be given concerning the extent to which the ancillary study will require blood specimens in addition to those presently required for main study. If blood specimens are to be obtained from the patients, all procedures to be carried out on these specimens should be specified. If additional procedures or blood specimens are required, the study will require a consent form.

Two copies of each proposal should be submitted to the Clinical Coordinating Center for inventory and transmission to the Publications Committee Chairperson. The Chairperson of the Publications Committee will notify the Investigator, the Study Chair, the DCC, EQOLCC and CCC whether the project is approved, disapproved or additional information is needed before a decision can be made.

After a proposal has been approved, analysis requests may be submitted to the DCC. Analysis requests for planned abstracts should be submitted to the DCC at least 90 days before the abstract deadline.

A4.4 Review and Approval of Manuscripts and Abstracts Prior to Presentation and Publication

The Publications Committee and the Study Chair's Office, on behalf of the Executive Committee and NHLBI, will review all data bank study abstracts and manuscripts prior to submission for publication or presentation. All abstracts must be received by the Publications Committee members, all co-authors, and CCC at least two weeks prior to the submission deadline. Manuscripts produced by data bank studies must be received by these reviewers at least one month (30 days) before the scheduled submission date.

Every study manuscript considered suitable for publication will be submitted by the Chairperson of the Writing Committee to the OAT CCC for distribution to the OAT Publications Committee Chairperson, who will be responsible for arranging and implementing review according to the following procedures.

1. The manuscript will be forwarded promptly to at least two reviewers selected from the members of the Publications Committee or their associates, with the request to respond within two weeks with a detailed critical review of the manuscript. Outside reviewers may be selected when appropriate.
2. Reviews will be forwarded to all members of the ad hoc Writing Committee without the reviewers being identified, with a request for appropriate revision and response.
3. The Writing Committee will be expected to respond to the review in a reasonable period of time, forwarding to the Publications Committee Chair, the CCC, and DCC the revised manuscript and a letter commenting in detail on the points raised by the reviewers.
4. After review, the Publications Committee will decide, in consultation with the CCC, DCC and NHLBI, if release for publication is appropriate.
5. The Chairperson of the Publications Committee will then notify the authors, the OAT Study Chair's Office, DCC and NHLBI Program Office of its decision within one month of the receipt of a manuscript, within one week for abstracts. Approved manuscripts or abstracts may then be submitted.

A4.5 Conflict of Interest

A4.5.1 Introduction

The Occluded Artery Trial (OAT) is a multicenter study which compares two strategies of treatment for patients with occluded IRA's post MI, including currently approved medical treatments and revascularization with percutaneous transluminal coronary angiography (PTCA) and stent, when possible. Since the findings of this investigation may have implications for future clinical practice, potential conflicts of interest will be addressed.

The OAT Investigators recognize that bias is a concern for any clinical trial, and the study design has incorporated a number of safeguards against the introduction of bias. These include randomization into one of the two treatment groups, the management and analysis of data by a DCC, central and blinded interpretation of angiograms by a Core Laboratory, and the use of an independent Mortality and Morbidity Classification Committee for determination of clinical endpoints, and an independent Data and Safety Monitoring Board to monitor the study and evaluate the safety and efficacy of the treatments. This study will compare different treatments for patients with occluded IRA's post MI and the results will reflect the comparison of these treatment groups. The study is not designed to test efficacies of individual diagnostic methods, medications or revascularization procedures.

Nevertheless and despite these safeguards, the OAT Investigators realize that concerns about real or potential conflicts of interest may arise. In a broad study comparing strategies of treatment using common medications and therapies, 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 exist, the OAT Investigators have endorsed the rational management of these potential conflicts according to pre-agreed guidelines and principles. The OAT Investigators have agreed to a policy on conflict

of interest which has few specific restrictions, but a broad indication for disclosure of potential conflicts of interest. The OAT Investigators also endorsed the spirit and content of the 21st Bethesda Conference: Ethics in Cardiovascular Medicine[1] dealing with these issues, and have agreed to make the OAT policy consistent with the record of that conference.

To address actual or perceived conflicts of interest, the participating OAT Investigators voluntarily agree to abide by the guidelines described in this policy statement.

A4.5.2 Individuals to be Governed by These Guidelines

Members of the OAT Research Group who will be governed by these guidelines include the Study Chair, Co-Chair, the Principal Investigator at each Clinical Unit, professional staff in the CCC, DCC, EQOLCC, and the Principal Investigators of the Core Laboratories. Co-Investigators and other staff who have major responsibility for enrollment, recruitment, follow-up or collection of data for OAT at Clinical Units, affiliated hospitals or Core Laboratory will also be governed by these guidelines. The Principal Investigator of each participating unit will review the guidelines with all appropriate staff prior to the start of patient recruitment and will review the guidelines at least annually thereafter.

A4.5.3 Time Period of the Policy

The guidelines set forth in this policy commenced at the start of patient recruitment and will terminate at the time of initial public presentation or publication of the principal results. Investigators not privy to endpoint data who discontinue participation in the trial during recruitment will be subject to these guidelines until their departure from the study.

A4.5.4 Financial Guidelines

CCC will maintain conflict of interest statements updated annually from each site principal investigator and study leadership.

Activities not explicitly prohibited, but to be reported annually to the Study Chair and maintained by the CCC include:

1. Stock or stock option in any of the pharmaceutical companies or medical equipment companies who have provided financial support for the study.
2. Retainer-type consultant positions with these companies for the time period defined above.
3. An ad hoc consultant relationship to companies providing drug devices or financial support to the trial.
4. Participation of investigators in any educational activities sponsored by the companies.
4. Participation of investigators in other research projects supported by the companies.

Financial interests in these companies, over which the investigator has no control, such as mutual funds or blind trusts do not need to be reported.

A4.5.5 Reporting of Financial Disclosures and Other Activities

The OAT Investigators agree to update their financial disclosures and related activities as described above on an annual basis and submit these data to the CCC for storage. The CCC will maintain the confidentiality of these records and present them to a review committee, to be constituted by the Study Chair. 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 and Safety Monitoring Board to discuss whether an individual should be eligible for certain study activities such as membership on policy making committees or writing groups for study manuscripts. .

A4.5.6 Review of Policy Statement

The OAT Investigators agree to review these guidelines on an annual basis and take any additional steps to insure the scientific integrity of the trial.

A4.5.7 Relationship to Institutional Policies on Conflict of Interest

Since existing policies on conflict of interest may vary between participating institutions, in addition to the above policy, it is expected that investigators will comply with the policies on conflict of interest which exist within their individual participating institutions (i.e., medical schools and hospitals). This is the responsibility of each individual investigator.

A4.6 Acknowledgment of Non-Federal Funding

In the reports on endpoint, data bank and ancillary studies, the financial support of all non-federal groups will be acknowledged at the end of each manuscript.

A4.7 Required Education in the Protection of Human Subject Research Participants

The investigators and coordinators of all participating OAT sites are required to comply with the NIH policy that requires education on the protection of human subject participants for all investigators and "key personnel" who are responsible for the design and conduct of research under NIH grant and contract awards for the research involving human subjects. Most academic institutions have developed educational programs on the protection of research participants and have made attendance at such programs a requirement for their investigators. If the institution has not provided this training, an educational program on the NIH web at http://ohsr.od.nih.gov/ will be taken. This training module was originally developed for NIH staff, but it can be used by other personnel to meet training requirements. Each Principal Investigator was requested to submit a list of key personnel who will be asked to have training and to forward this list to the Data Coordinating Center (DCC) for inventory. Also, each investigator and staff on the list will forward to the Data Coordinating Center documentation indicating that training has been completed.

A4.8 Reference

1. Frommer P.L., Ross J., Benson J.A., et al. Task Force IV: Scientific responsibility and integrity in medical research. JACC A490;16:1-36.

Occluded Artery Trial

Appendix 5

Rationale for November 1, 2000 modification of time window for enrollment

Appendix 5

RATIONALE FOR NOV 1, 2000 MODIFICATION OF TIME WINDOW FOR ENROLLMENT

The time window for eligibility into OAT is changed to allow enrollment of patients one calendar day earlier than the original OAT Protocol dated November 12, 1999. Because of confusion regarding the definition of date of index MI this was accomplished by redefining the date of index MI from day 0 to day 1 . The rationale for this protocol change appears below.

Rationale:

The practice in the US includes coronary angiography relatively early post MI and potentially eligible OAT patients have been lost because angiography was performed on day 2 post-MI. There was discussion about whether the time window for enrollment could be changed from a minimum of 3 days post MI (Day 0 is the calendar day of the MI) to 2 days post MI without substantially affecting the primary endpoint analysis of the study. Changing the boundary will have the effect of including patients into the study whose arteries would have opened spontaneously between day two and day three. The clinical reason for changing the time window is that it will be possible for study investigators to approach patients about the study before a routine coronary angiography and PTCA are performed (on day two). Using this new rule and based on enrollment and registration of patients to date, approximately 15% of the patients would be enrolled on day two if the new plan were adopted. A literature review indicated that approximately 8% of the patients enrolled on day two would have arteries that spontaneously reopen by day three. This would have made them ineligible under the old rules. The question is what impact does this have on the study design?

Study Impact Estimates:

A simple model has been assembled to address this question. The OAT study is designed to detect a *25% reduction* of a primary endpoint that is hypothesized to have a 25% event rate over three years.

Additional assumptions are:

- The percent of day 2 enrollments will comprise 15% of the study population.
- The spontaneous reopening rate for these patients will be 8%.
- An open artery (no matter what the means) will convey a 25% reduction to the risk of a primary endpoint (i.e., the risk of the primary endpoint is 25 % if the artery is closed on day 3 and 18.75 % if the coronary stenting is performed or if the artery has spontaneously reopened on day 3.
- The incidence of the primary endpoint between Day 2 and Day 3 is negligible.

Under these assumptions the risk of a primary endpoint event in the invasive group would remain at 18.75% since the only way that the procedure would not be attempted (which would lower the risk to 18.75%) would be if the artery were open spontaneously in which case the rate has already been reduced to 18.75%.
The risk in the control group will change. The magnitude of the change can be addressed by using conditional probability statements. The following probabilities are assumed:

P(en day 2) = .15	Probability a patient enrolls (en) on day two.
P(reopen| en day 2) = .08	Probability that an artery reopens given enrollment in day2.
P(ep | open on day 3) = .1875	Probability that a conservative patient suffers an endpoint by three years given an open artery on day three.
P(ep | closed on day 3) = .25	Probability that a conservative patient suffers an endpoint

by probability that a conservative patient suffers an endpoint three years given a closed artery on day three.

Using the law of total probability:

*P(ep) = P(ep | en day 2) * P(en day 2) + P(ep | en day 3) * P(en day 3).*

The first part of the sum can be further partitioned by whether the artery is open on day 3 or not.

This yields the following calculation for a conservative patient:

*P(endpoint by year 3) =(0.92*0.25+0.08*0.1875)*0.15 + 0.25*0.85 = 0.24925.*

This result is not substantially different from the hypothesized endpoint incidence in the conservative group of 0.25. The factors leading to the small difference are the low percentage admitted into the study on the second day (15%) and the very low probability that a patient's artery will reopen between day two and day three (8%).

Tables 1 and 2 show how varying the proportion of patients recruited on day 2 and the proportion of conservative strategy patients whose arteries reopen in day 2 can affect the three-year endpoint incidence in the Conservative Group and the percent reduction in the endpoint due to treatment. We compared these numbers to the power tables generated for the OAT study. Even if the proportion of patients enrolled on Day 2 increased to 30% (15% is hypothesized) and 30%in conservative strategy patients reopened in Day 2 (8% is hypothesized), OAT power would remain at 80% after accounting for crossovers and lost to follow-up.

Conclusion:
There will be a loss of power associated with the introduction of Day 2 patients, but the overall impact is *small. Therefore, the time window will be changed in order to enhance recruitment and reflect current clinical practice.*

The DSMB approved the protocol and consent revisions on September 11, 2000 and November 1, 2000.

Table 1

Three-year event rate (in the Conservative Group)
as a function of Day 2 Reopening Rate
and the Proportion Recruited on Day 2

Day 2 Reopening Rate	Proportion Recruited on Day 2 **0.1**	**0.2**	**0.3**	**0.4**	**0.5**
0.10	0.249	0.249	0.248	0.248	0.247
0.20	0.249	0.248	0.246	0.245	0.244
0.30	0.248	0.246	0.244	0.243	0.241
0.40	0.248	0.245	0.243	0.240	0.238
0.50	0.247	0.244	0.241	0.238	0.234
0.60	0.246	0.243	0.239	0.235	0.231
0.70	0.246	0.241	0.237	0.233	0.228
0.80	0.245	0.240	0.235	0.230	0.225
0.90	0.244	0.239	0.233	0.228	0.222

Table 2

Percent Reduction (Invasive Group Compared to Conservative Group)
based upon the changes in the Conservative Event Rates Listed Above

Day 2 Reopening Rate	Proportion Recruited on Day 2 **0.1**	**0.2**	**0.3**	**0.4**	**0.5**
0.10	24.81	24.62	24.43	24.24	24.05
0.20	24.62	24.24	23.86	23.47	23.08
0.30	24.43	23.86	23.27	22.68	22.08
0.40	24.24	23.47	22.68	21.88	21.05
0.50	24.05	23.08	22.08	21.05	20.00
0.60	23.86	22.68	21.47	20.21	18.92
0.70	23.66	22.28	20.84	19.35	17.81
0.80	23.47	21.88	20.21	18.48	16.67
0.90	23.27	21.47	19.57	17.58	15.49